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A Difluoromethylene Linchpin/Synthon: Application in Conjunction with Anion Relay Chemistry (ARC) Permits Ready Access to Diverse Difluoromethylene Scaffolds

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ABSTRACT: Organodifluorine synthons, in conjuction with three-component diastereoselective anion relay chemistry (ARC), permit ready access to diverse difluoromethylene scaffolds. Initiated via [1,2]-addition of an organolithium reagent to a β-difluoromethylene silyl aldehyde, an alkoxide intermediate is formed, which is capable of undergoing a [1,4]-Brook rearrangement to generate a stabilized α-difluoromethylene carbanion, which, upon electrophile capture, affords a three-component adduct. This three component synthetic tactic represents a novel one-pot divergent strategy for the construction of diverse organodifluorine containing compounds.

Organofluorine compounds are ubiquitous in modern society, with polytetrafluoroethylene (PTFE) polymers and hydrofluorocarbon (HFC) refrigerants seeing widespread use.[1] Over the last several decades, the role of fluorine in small molecule therapeutics has gained significant attention, with ∼20% of approved active pharmaceutical ingredients and 35% agrochemicals containing at least one F atom.[2] The strong polarization of the C−F bond, in conjunction with the short bond length and small van der Waals radius of the F atom, results in a variety of useful properties.[3] In medicinal chemistry, these properties manifest in a myriad of ways, permitting fluorine to serve as a bioisostere,[4] to modify the basicity and acidity of adjacent functional groups,[5] to effect the solubility of compounds,[6] to alter metabolism,[7] and/or to control the conformation of structures,[8] among other attributes.

Accordingly, numerous methods for the incorporation of F atoms into organic compounds have been developed, which utilize either direct or indirect fluorination tactics, either adding a single F atom (for instance, employing DAST or SelectFluor) or an activated organofluorine reagent, such as the Ruppert−Prakash reagent (TMS-CF_3).[9] However, most existing fluorination methods employ monovalent synthons, which generally permit only linear syntheses (Figure 1a). Ideally, fluorination could be performed as a convergent synthetic step, permitting the reaction to serve as a point of diversification, which is often desirable from the perspective of the medicinal chemist. Recently, Dilman has exploited divalent difluoromethylene synthons for use in multicomponent coupling tactics (Figure 1b).[10] While highly effective, this method lacks a broad scope of coupling partners and requires multiple steps to achieve.

We reasoned that a one-pot three-component union (Figure 1c) could be achieved by employing an ambiphilic linchpin in

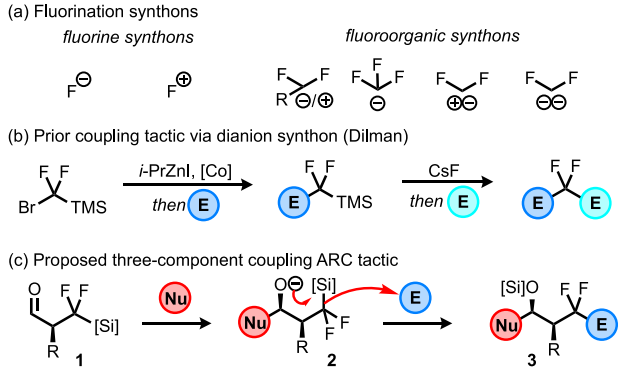

Figure 1. (a) Fluorination synthons; (b) prior coupling tactic employing a dianion synthon; and (c) fluoro-organic synthon and three-component coupling tactic via Type II anion relay chemistry (ARC).

which the anionic carbon is stabilized by geminal fluorine substituents, in a tactic comprising [1,2]-addition of an organolithium reagent to aldehyde linchpin **1** to afford an alkoxide intermediate (**2**). Subsequent [1,4]-Brook rearrangement of alkoxide **2** with electrophile capture could then afford a three-component adduct (**3**), with the relative stereochemistry of the anion relay chemistry (ARC) adduct under Felkin−Anh stereocontrol.[11] Such a method would hold great promise if (a) the scope of each component is broad, (b) the

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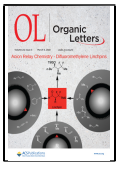

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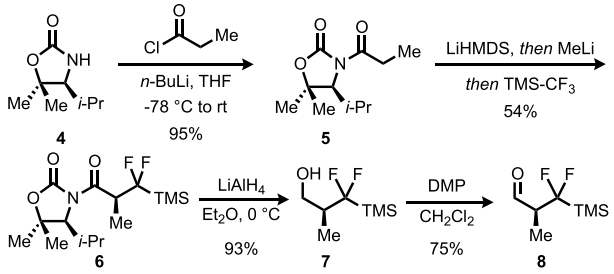
Org. Lett. 2021, 23, 1521−1524

diastereoselectivity is high, (c) the reaction is performed in a single pot, and (d) the linchpin is readily constructed.

We first set out to validate a synthetic route to access diverse difluoro-linchpins (**1**), which would be amenable to varied substitution at the α-position. Drawing inspiration from the work of Mikami and co-workers,[12] we sought to construct β-difluoro-linchpins via a direct α-silyldifluoromethylation of an oxazolidinone-derived lithium enolate. Initially, oxazolidinone **4** was acylated with an acid chloride to afford **5** (Scheme 1).

Scheme 1. Linchpin Synthesis



Next, the lithium enolate of **5** was generated with LiHMDS and subsequently α-silyldifluoro-methylated, to furnish **6** as a single diastereomer. The absolute stereochemistry of **6** was determined unambiguously using X-ray crystallography (see the Supporting Information). The desired linchpin was then obtained via reduction of oxazolidinone **6** with $LiAlH_4$ to provide **7**, followed by oxidation with Dess–Martin periodinane (DMP) to afford **8** in good yield.

With the desired linchpin **8** in hand, we next sought to validate the proposed reaction sequence (see Figure 2). High

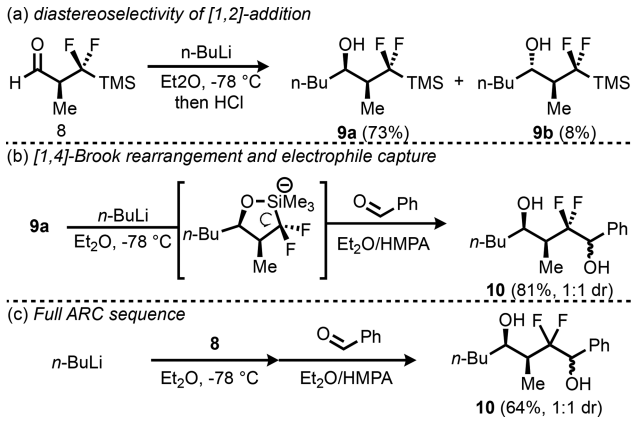
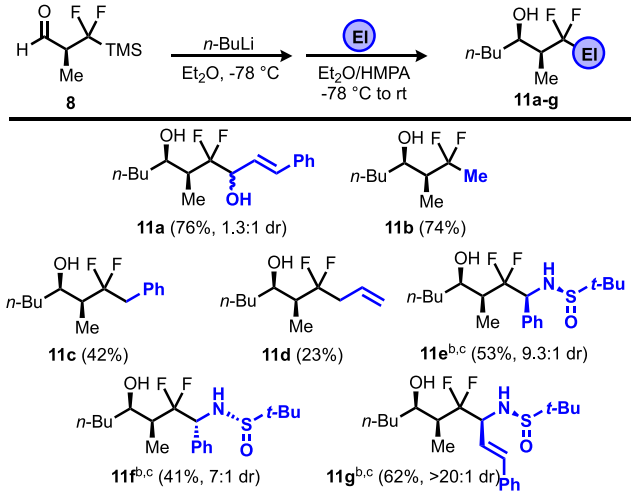


Figure 2. Stepwise evaluation of ARC sequence.

diastereoselectivity of the initial [1,2]-addition was deemed critical for the utility of this transformation. Therefore, we first performed the initial [1,2]-addition of *n*-BuLi to linchpin **8** at −78 °C in Et_2O, with subsequent reaction with HCl in Et_2O to arrive at alcohols **9a** and **9b** as separable diastereomers. High diastereoselectivity was observed (9:1 by ^1H NMR analysis), with the absolute configuration of **9a** determined by Mosher ester analysis, demonstrating that Felkin–Anh diastereoselectivity was operative.[13] Next, deprotonation of **9a** was achieved with *n*-BuLi at −78 °C in Et_2O, and benzaldehyde was added. The envisioned [1,4]-Brook rearrangement was then triggered via the use of the polar additive HMPA. Pleasingly, tricomponent adduct **10** was obtained in 72% yield as an expected 1:1 mixture of diastereomers at the benzylic position. Having demonstrated the proof-of-concept via a two-pot ARC sequence utilizing **9a**, we next turned our attention to validation of the one-pot, three-component coupling ARC tactic. To this end, employing the defined conditions, three-component adduct **10** was observed as the major product from the one-pot sequence in 64% yield.

Having validated the ARC sequence, we turned to explore the electrophile scope. Reactions were performed using *n*-BuLi as the nucleophile and linchpin **8**, with a variety of electrophiles (Scheme 2). Evaluation of (*E*)-cinnamaldehyde

Scheme 2. Electrophile Scope[a]



[a]Conditions: *n*-BuLi (1.0 equiv), linchpin (1.0 equiv), electrophile (2.0 equiv), TBAF deprotection of crude product. [b]Diastereomeric ratio pertains to the α-position of amine. [c]Absolute configuration assigned by the transition-state model (see the Supporting Information).

as an electrophile demonstrated that α,β-unsaturated aldehyde electrophiles are amendable to the ARC sequence to provide allyl alcohol **11a**. Next, a series of alkyl halide electrophiles were employed with MeI, affording **11b** in good yield, and with benzyl and allyl bromide, affording three-component adducts **11c** and **11d** in modest yield. Pleasingly, enantioenriched sulfonyl imine electrophiles also served as successful electrophiles in the ARC sequence, providing β-difluoroamine substrates as three-component adducts as single diastereomers; both (*S*)- and (*R*)-phenyl sulfonyl amine furnished ARC adducts **11e** and **11f** with high diastereoselectivity in moderate yield. In addition, employing the (*R*)-α,β-unsaturated sulfonyl imine of cinnamaldehyde permitted access to β-difluoro-allyl amine **11g** in 62% yield. Thus, this ARC tactic holds the promise of a viable method for the construction of enantioenriched β-difluoroamines, for which limited methods are currently available.[14]

At first glance, it may appear that the three-component adducts obtained from aldehyde electrophiles are less than ideal, as there is no diastereoselectivity in the second [1,2]-addition. However, such diol products can be used to access difluorocyclopentyl ketals (see Scheme 3). Similar pseudo-pentose structural motifs are found in many bioactive compounds, such as the approved drug Gemcitabine (Gemzar). For example, benzylic oxidation of **10** with MnO_2 spontaneously leads to ketal formation to arrive at **12**, as a 4:1

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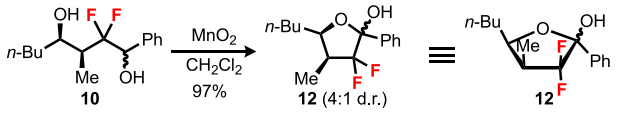
Scheme 3. Difluorocyclopentyl Ketal Synthesis



mixture of diastereomers in excellent yield. A similar strategy may be adapted to permit the synthesis of other difluorocyclopentyl ketals from the corresponding aldehyde adducts.

Next, our attention turned to the scope of organolithium reagents that could be employed as initiating nucleophiles in this ARC sequence. Standard reaction conditions were employed, utilizing linchpin **8** to evaluate a variety of organolithium reagents (Figure 3). Having demonstrated that

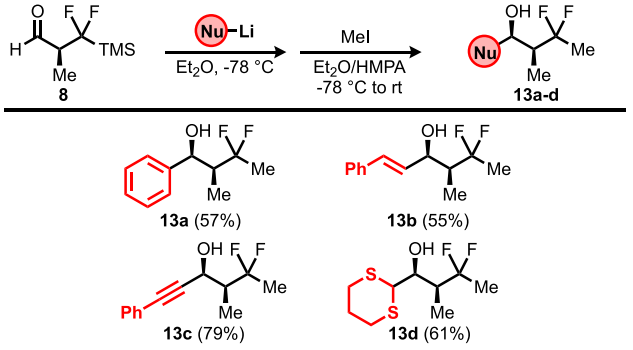


Figure 3. Nucleophile scope. [Conditions: Nu-Li (1.0 equiv), linchpin (1.0 equiv), MeI (2.0 equiv), TBAF deprotection of the crude product.]

n-butyllithium with methyl iodide as the electrophile is amenable to the ARC tactic, we attempted commercially available PhLi. Accordingly, the three-component adduct **13a** was obtained as a single diastereomer in moderate yield. Vinyl lithium and alkynyl lithium reagents were also successfully employed to afford allyl and propargyl alcohols **13b** and **13c** in moderate to good yield. Equally pleasingly, lithiated 1,3-dithiane can be utilized successfully in the ARC sequence, permitting the incorporation of this versatile functionality in adduct **13d**. Thus, alkyl, vinyl, alkynyl, aryl, and dithianyl lithium reagents comprise viable nucleophiles in this three-component ARC coupling tactic.

Another significant aspect of this coupling tactic would be the tolerance on variability of the linchpin. At this juncture, we had examined exclusively the viability of linchpin **8**, bearing an α-Me substitution. While this substitution is useful for polyketide synthetic targets, larger substituents or functional handles would serve to provide access to a more diverse pool of difluoromethylene scaffolds. Therefore, we set out to examine several linchpins with varied α-substitution. 9See Figure 4.) For the evaluation of linchpins **8a**−**8d**, standard reaction conditions were employed, utilizing *n*-BuLi as the nucleophile and MeI as the electrophile. Increasing the size of the substituent from Me to Et had a slightly negative effect on yield, arriving at the three-component adduct **14a** in 63% yield. Olefin moieties were well-tolerated at the α-position, affording homoallyl and allyl products **14b** and **14c**. Pleasingly, Ph and vinyl α-substitutions were also well-tolerated, despite the expected increased acidity of the corresponding linchpins. Furthermore, the synthesis of three-component adduct **14d**

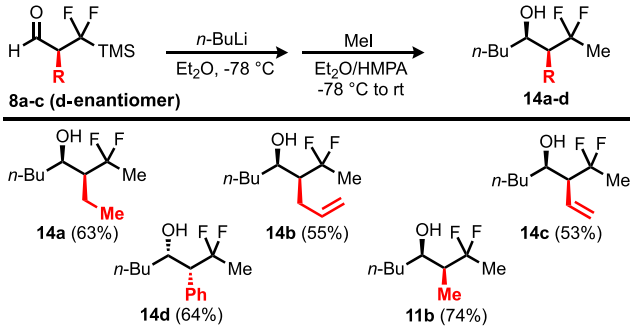
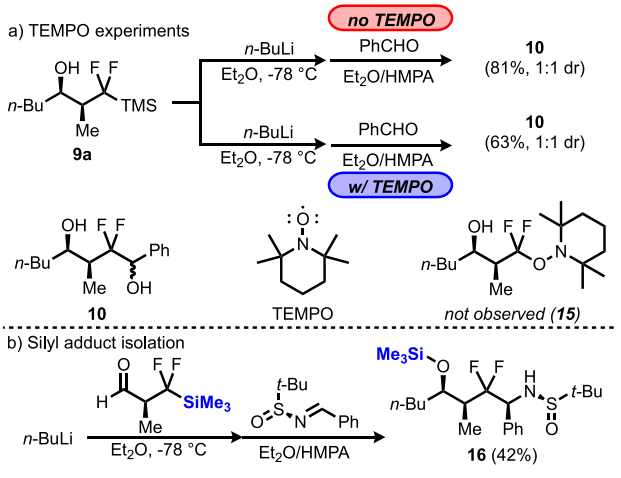


Figure 4. Scope of linchpin substrates. [Conditions: *n*-BuLi (1.0 equiv), linchpin (1.0 equiv), MeI (2.0 equiv), and TBAF deprotection of crude product; linchpins: R = Et (**8a**), allyl (**8b**), vinyl (**8c**), Ph (**8d**), and Me (**8**).]

demonstrates that this ARC methodology is amenable to both epimers of the linchpins.

Many synthetic methods are predicated on the manipulation of difluoromethyl radicals.[15] The σ-withdrawing, π-donating properties of the F atom permit access to difluoromethyl radicals, anions,[16] and carbenes.[17] Mechanistic studies were performed to provide support in this case for an anionic reaction mechanism for the [1,4]-Brook rearrangement with alkylation (Scheme 4). Here, the principle concern was the

Scheme 4. Mechanistic Studies



[1,4]-Brook rearrangement, rather than the [1,2]-carbonyl addition. Thus, the ARC sequence was entered via the deprotonation of alcohol **9a**. Next, the [1,4]-Brook rearrangement was triggered via the addition of a solution of benzaldehyde in Et_2O/HMPA, with or without an equivalent of TEMPO. In both cases, three-component adduct **10** was obtained in good yield. In addition, TEMPO adduct **15** was not identified in the trapping experiment. Next, to offer support for a [1,4]-Brook rearrangement, we demonstrated the isolation of silyl ether ARC product **16**. The labile nature of TMS ethers led us to remove this group prior to purification for simplicity. However, isolation of **16** here demonstrates that C−Si to O−Si migration indeed occurs.

In summary, we disclose here a new ambiphilic organo-difluoromethylene synthon that can be employed in a three-component ARC coupling tactic to afford a variety of difluoromethylene adducts with high diastereoselectivity. Moreover, we have disclosed a synthetic route that permits

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Org. Lett. 2021, 23, 1521−1524

access to these β-difluorosilyl aldehyde linchpins in which the α-substituent and absolute stereochemical configuration can be readily achieved by selecting the appropriate acid chloride and oxazolidione substrates, respectively, many of which are commercially available. The value of this synthon and the corresponding three-component coupling tactic is also apparent in the great variety of nucleophiles, linchpins, and electrophiles that can be employed. Thus, one can envision numerous difluoromethylene scaffolds that can be prepared by employing this tactic as a key disconnection, which may otherwise be laborious to construct.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03508.

General experimental procedures; characterization data; ^{1}H NMR/^{13}C NMR/^{19}F NMR spectra (PDF)

Accession Codes

CCDC 2040145 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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