Advanced Synthesis & Catalysis

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201900464

Link to VoR: http://dx.doi.org/10.1002/adsc.201900464

10.1002/adsc.201900464

UPDATE

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Asymmetric Vinylogous Mukaiyama-Mannich Reactions of Heterocyclic Siloxy Dienes with Ellman's Fluorinated Aldimines

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. Vinylogous Mukaiyama Mannich reactions of furan and pyrrole based dienoxy silanes with α-fluoroalkyl sulfinyl imines provide a powerful synthetic access to a variety of amino fluoroalkyl γ-butenolide-type and butyrolactams frameworks with high regio- and diastereoselectivity. *Anti*-configured adducts were obtained in all cases, independent of the nature of the heteroatom (*O* or *N*) present in the dienoxy silane. The absolute configuration of the adducts prepared was unequivocally established by X-ray crystallographic analysis. It is noteworthy that the introduction of substituents at the γ-position of the heterocyclic partner allows the generation of adducts bearing chiral quaternary centers.

Keywords: siloxy dienes; asymmetric vinylogous Mukaiyama-Mannich; fluorinated sulfinyl imines; chiral butenolide; chiral butyrolactam.

Introduction

Amines are extremely important functional groups in bioorganic chemistry. This functionality is present in many natural products and drugs, where, in most cases, the biological activity correlates with intrinsic basic properties. [1] Fluorine-containing amino derivatives, especially those bearing fluoroalkyl moieties near the amino group, can modify their physicochemical properties, and more specifically basicity. Consequently, biological activity[2] can be modulated by a straightforward tactic based on the incorporation of fluoroalkyl groups. In this context, strategies for introduction of fluorinated moieties in amino-derivative compounds are of particular interest. [3] Among the different existing approaches for the preparation of amines, the addition reaction of nucleophiles to imines represents a simple and relevant approach. Against that backdrop, the addition reaction of an enolizable alkylidene [4],[5] to an imine—known as vinylogous Mukaiyama Mannich-type reactions (VMMnR)—constitutes a fertile methodology, since this kind of reaction allows functionalization beyond the regular α or β positions and can give rise directly to versatile unsaturated synthetic intermediates. Among the various donors available, siloxydiene heterocycles are a useful subset of preformed enolates that afford δ-amino-α,β-unsaturated carbonyls. These frameworks are shared by many natural products and exhibit a variety of biological activities (Figure 1). [6],[7] Furan-based siloxy dienes provide access to the corresponding nitrogen-containing γ-butenolides and γ-butyrolactones, substructures which have a high

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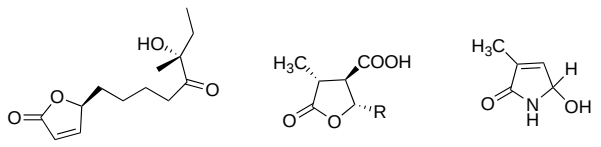
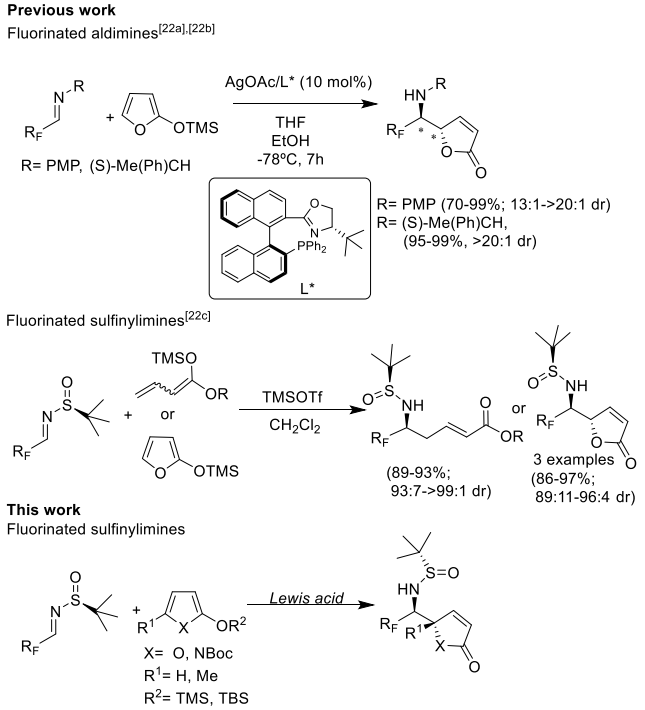


Figure 1. Biorelevant compounds containing the γ-butyrolactam and γ-butenolide-type frameworks.

prevalence in Nature[7] and therefore represent attractive reference substrates in the context of drug discovery. The first catalytic asymmetric versions of VMMnRs based on these starting



Scheme 1. Vinylogous Mukaiyama Mannich-type reactions (VMMnRs) with fluorinated imines.

materials were described by Martin providing the corresponding adducts in moderate enantioselectivity and chemical yields. [8] Later, Carretero, [9] Shi, [10] and more recently Hoveyda, [11] reported the preparation of valuable δ-amino γ-butenolide fragments with high chemical and optical efficiency, although each of them employed different catalytic conditions. Expansion of the scope of the catalytic asymmetric VMMnRs encompasses the use of pyrrole-based silicon dienolates, first developed by Casiraghi and coworkers. [12] The efficiency of the VMMnRs of siloxy pyrroles and aldimines as a key step of a designed reaction sequence has been shown by DeGoey, [13] McLaughlin[14] and Huang, [15] who reported the synthesis of valuable γ-butyrolactam derivatives such as anti-influenza compound A-315675 or 1-aminopyrrolizidine alkaloids.

In the context of asymmetric VMMnRs, Ellman's *N-tert*-butanesulfinimines [16] should be taken into account as versatile chiral amine templates. In fact, the synthetic potential of the combination of a powerful methodology based on a *d4* donor and a chiral sulfinimine acceptor has already been recognized, [15],[17] albeit scarcely explored. So far, only a few examples of the synthesis of highly functionalized non-fluorinated heterocycles have been reported by Huang [15],[17] by means of a sequence in which the VMMnR was the key step, using imines bearing a *tert*-butyl sulfinyl group as a chiral auxiliary acting as acceptors. The possibility of the introduction of substituents at the γ-position of the heterocyclic partner is noteworthy, allowing the generation of adducts bearing chiral quaternary centers, a structural feature that is not easily accomplished. [18] Furthermore, the strategy can easily be extended to the preparation of nitrogen-containing fluorinated compounds such as fluorine-containing imines. [19] It is now well established that the incorporation of fluorine in target molecules can positively modify their biological activities, [2] and consequently the development of an efficient asymmetric method for the synthesis of these compounds is highly desirable.[20] Nevertheless, only a few examples of the use of fluorinated imines in VMMn reactions are found in the literature. [21],[22] In a communication, Crousse and Bonnet-Delpon briefly studied the vinylogous Mannich reaction involving fluorinated aldimines.[21] However, only trifluoromethyl aldimines were explored, and although the corresponding butenolides were obtained in high yields and good diastereoselectivities, the reaction was conducted in a non-asymmetric manner. Thereafter, Shi[22a] described a catalytic asymmetric version using a wide range of aldimines that included various difluorinated derivatives. The combination of chiral phosphine-oxazolidine ligands and silver(I)-catalysis afforded the corresponding adducts in moderate enantioselectivities (66-81% *ee*). The additional incorporation of the (*S*)-Me(Ph)CH grouping as a chiral auxiliary under the aforementioned catalytic conditions allowed the synthesis of fluorine-containing butenolides in >95% *ee* (Scheme1). [22b] The requirement of both the chiral complex catalyst and the chiral

auxiliary to obtain fluorinated butenolides with high optical purity illustrates the difficulty of this goal perfectly well. On the other hand Qing reported the use of several α-fluoroalkyl sulfinylimines in Lewis acid catalyzed diastereoselective additions with different acyclic siloxydienes. This procedure was also applicable to trimethylsiloxyfurane as an example of a cyclic dienolate (Scheme 1). [22c]

Results and Discussion

Herein, we report our findings in the preparation of chiral γ-monosubstituted and γ,γ-disubstituted butenolides and butyrolactams through a diastereoselective Mukaiyama-Mannich reaction between heterocyclic silyloxy dienes **1a-c** and fluorinated aldimines **2a-g** bearing an *N-tert*-butanesulfinyl group as the chiral auxiliary.

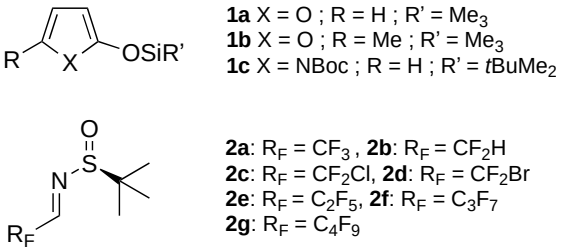
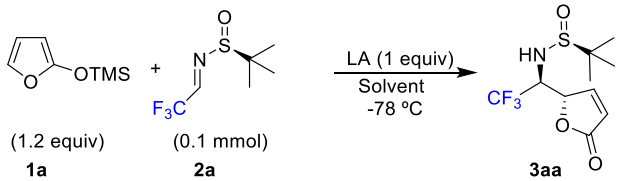


Figure 2. Starting materials used in the VMMnRs.

Siloxy furan **1a** and imine **2a** were selected as model substrates for the initial catalyst and solvent screening (Table 1). First, we assayed

Table 1. Optimization of the reaction conditions of siloxy furan **1a** and imine **2a**. [a],[b]



entry	solvent	Lewis acid	*t* (h)	*dr* (*anti/syn*)	yield (%)
1	THF	AgOAc	1	85:15	53
2	THF	TMSOTf	1	88:12	57
3	THF	TMSOTf	2	93:7	52
4	DCM	TMSOTf	2	96:4	70

[a] All reaction yields are isolated yields.

[b] Dr values were determined by ^{19}F NMR spectroscopy.

silver acetate as a Lewis acid catalyst and THF as solvent at low temperatures (-78 °C). The reaction took place with complete regioselectivity at the γ-position, moderate yield and acceptable *anti* diastereoselectivity (entry 1, Table 1). [21],[23] Switching the Lewis acid to TMSOTf in the same solvent and temperature slightly improved the diastereoselectivity, while the yield was comparable (entries 2 and 3, Table 1). Dichloromethane gave an improved asymmetric induction (96:4 *dr*), possibly due to its non-coordinating nature, when compared to the coordinating THF (93:7 *dr*). Reaction times of more than 2 hours notably eroded the diastereoselectivity, suggesting the formation of an equilibration of isomers under the reaction conditions. Since an acceptable yield (70%) and excellent *dr* (96:4) were attained when the reaction was conducted at -78 °C for 2 hours in dichloromethane and TMSOTf as Lewis acid, we selected these conditions as appropriate for our method (entry 4, Table 1).

With suitable reaction conditions in hand, the scope of the reaction with respect to the optically active fluorinated aldimines was subsequently examined (Table 2 (R=H)). The size of the substituent on imine **2** slightly influenced the yields that ranged from moderate to good for the set of imines tested. Conversely, the diastereoselectivity was better with the less sterically-demanding substituents of imine **2**. The configuration of the major diastereoisomer obtained was established as *anti* by X-ray analysis (Figure 4) (see SI for details). [24]

A plausible interpretation of the simple diastereoselectivity (4,5-*anti*) found in **3a** could be that it might be governed by transition state TS1 (Figure 3) where the carbon-carbon bond forming

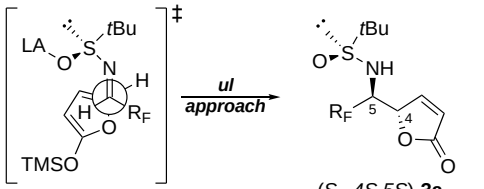


Figure 3. Suggested TS1 accounting for *anti* diastereoselectivity of **3a**.

trajectory (*ul approach*, *re* face of the dienolate *vs si* face of imine) would seemingly be preserved due to favorable stereoelectronic requirements. On the other hand, for facial diastereoselection, a monocoordinated species with a preferred conformation—where the *re* face of the imine is shielded by the *O*-LA group—can be supposed.

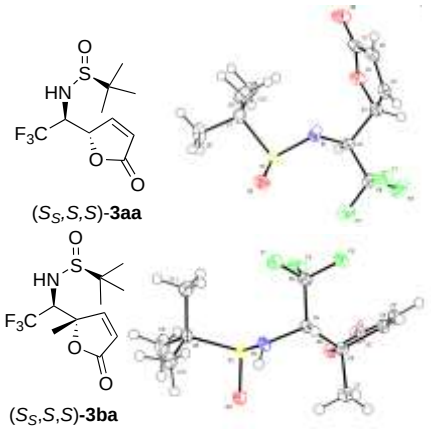


Figure 4. Absolute configuration of compounds **3aa** and **3ba**.

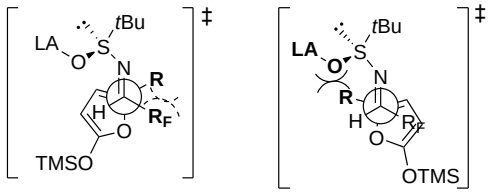
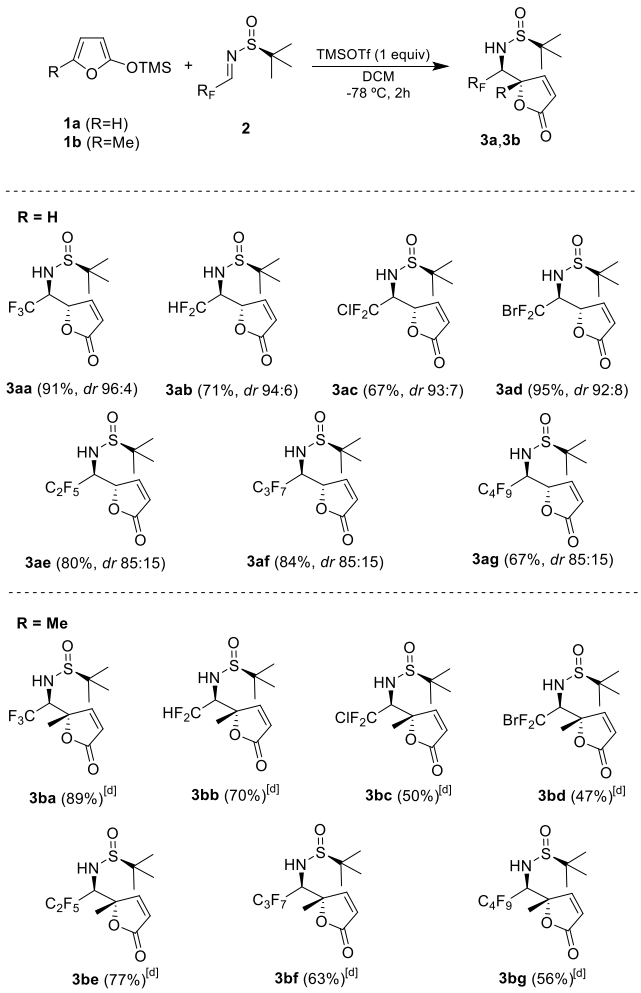


Figure 5. Postulated transition states for the VMMnR of **3a** and **3b**.

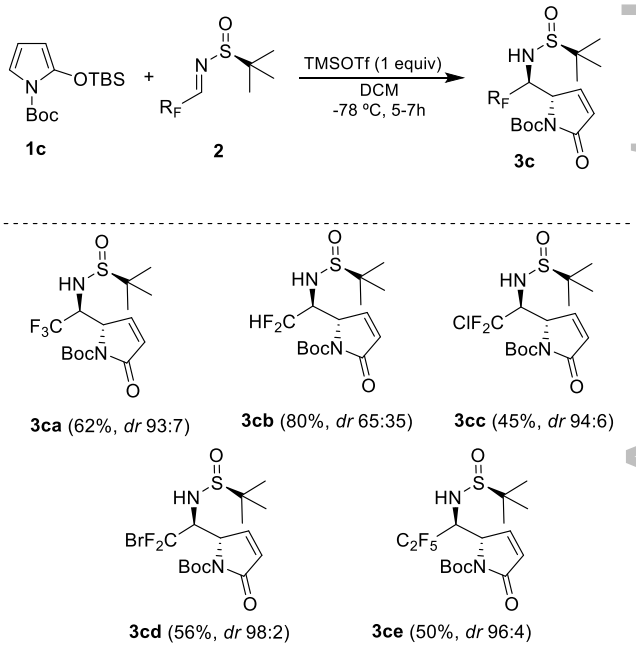
Subsequently, γ-substituted dienol silane **1b** was tested. The corresponding 5,5-disubstituted butenolides **3ba-3bg** possessing a quaternary chiral center at the γ-position were obtained with moderate to good yields and excellent diastereoselectivities (*dr* > 99%) in all cases (Table 2). The absolute *anti*-configuration of the single diastereoisomer obtained was unequivocally determined by X-ray crystallographic analysis of butenolide **3ba** as *S*s,4*S*,5*S* (Figure 4) (see SI for details). [24]

Table 2. Scope of the reaction of siloxy furans **1a-b** and imines **2**.[a],[b],[c]



[a] Reaction conditions: **1a** and **1b** (0.5 mmol), **2** (0.6 mmol), TMSOTf (0.5 mmol), DCM (2.5 mL). [b]All reaction yields were isolated yields. [c] Dr values were determined by ^{19}F NMR spectroscopy.[d] Dr>99:1

Table 3. Reaction of siloxy pyrrole **1c** and imines **2**. [a],[b],[c]



[a] Reaction conditions: **1c** (0.5 mmol), **2** (0.6 mmol), TMSOTf (0.5 mmol), DCM (2.5 mL). [b]All reaction yields were isolated yields. [c] Dr values were determined by ^{19}F NMR spectroscopy.

Comparison of the results obtained with unsubstituted furan derivative **1a** and methyl substituted **1b** shows that the increase of the steric demand of the butenolide precursor slightly decreases the yields, most likely as a consequence of the decreased nucleophilicity at the γ-carbon due to the steric effect of the substituent.

Regarding the asymmetric induction, the effect of the substitution is markedly positive and the *anti*-adduct clearly predominates despite the major steric hindrance between methyl (R=Me) and the R_F substituent found in TS3 compared with the equivalent interaction existing in TS1 (*ul approach*) (Figure 5). Assuming that adducts **3a** do not equilibrate under the reaction conditions, the observed increase in diastereoselectivity when switching from unsubstituted siloxy furan **1a** to substituted analog **1b** would be a consequence of the major difference between TS4 and TS3 compared with TS2 and TS1 (*lk approach vs ul approach*) (Figure 5). Given the less favorable interaction existing in TS4 between the methyl group and the *O*-LA grouping, the *anti*-approach through TS3 would be more favored, thus explaining the greater diastereoselectivity.

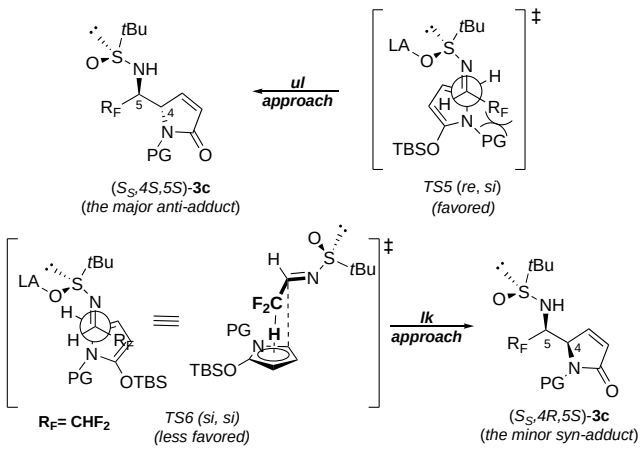


Figure 6. Plausible transition states for the VMMnR of diene **1c** and imines **2**.

Next, we extended the vinylogous Mukaiyama Mannich-type reaction (VMMnR) to the pyrrole-based siloxy diene **1c** aiming at the preparation of functionalized butyrolactams derivatives **3c** (Table 3).

In sharp contrast with the furan dienes **1a** and **1b**, siloxy pyrrole **1c** was very sensitive to the substitution at the imine, and a progressive decline in the yields was observed with the increase of the steric hindrance in the imine substituent. No reaction was observed in the case of imines **2f** and **2g**, bearing perfluorinated propyl and butyl groups respectively.

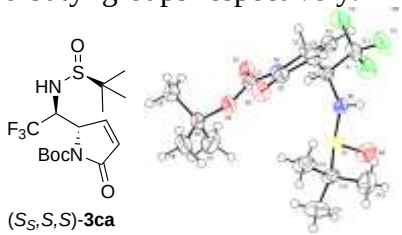


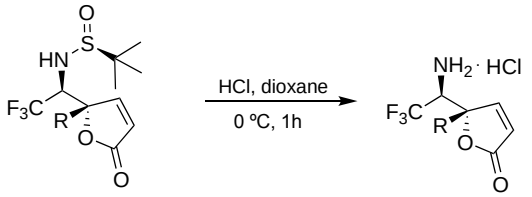
Figure 7. Absolute configuration of compound **3ca.**

By contrast, the diastereoselectivity remained high, around 90% *dr*, with the sole exception of the difluoromethyl adduct **3cb**. The declined reactivity of the pyrrole derivative **1c** with respect to the furan analogs **1a** and **1b** could be explained by steric interactions in the corresponding transition state (TS5, Figure 6) between the voluminous protective Boc group present in diene **1c** and the R_F substituent of the imine **2** (*ul approach*) in agreement with the model proposed by Huang for related substrates. [17]

Scheme 2. Hydrogenation of unsaturated lactam **3ca**.

On the other hand, the abnormal diastereoselectivity obtained in the case of the reaction of imine **2b** bearing a difluoromethyl group and diene **1c** could be related to the weak hydrogen-bond donating character of the difluoromethyl group. [25] As a consequence, a possible secondary interaction between the hydrogen donor of the difluoromethyl group and the pyrrole heterocyclic moiety, acting as an acceptor [26] could occur in the corresponding transition state (TS6, Figure 6), making the approach to the *si* face of the dienolate (*lk approach*) more competitive and thereby increasing the percentage of the *syn* adduct.

The absolute *anti*-configuration of the major diastereoisomer of derivative **3ca** was also determined by X-ray diffraction analysis, exhibiting three consecutive stereocenters (Figure 7).[27] Furthermore, unsaturated lactam **3ca** could



3aa (R= H)
3ba (R= Me)

5a (>99 %)
5b (90 %)

Scheme 3. Removal of the chiral sulfoxide auxiliary on compounds **3aa a**nd **3ab**.

be efficiently transformed into the diamine protected derivative **4** by catalytic hydrogenation (Scheme 2).

Finally, we were able to successfully remove the *tert*-butylsulfinyl chiral auxiliary from representative substrates simply by treating adducts **3aa** and **3ba** with HCl in dioxane at low temperature with good yield and without loss of optical purity, rendering the free amines **5** as the corresponding hydrochloride salts (Scheme 3). [28]

Conclusion

α-Fluoroalkyl sulfinyl imines behave as excellent acceptors in Mukaiyama Mannich-type reactions with furan or pyrrole based dienoxy silanes as *d4* donors. The method provides facile access to α,β-unsaturated lactones and lactams bearing different amino fluoroalkyl moieties at the γ-position. The reaction was highly regio- and diastereoselective for both furan dienes **1a** and **1b**, and siloxy pyrrole **1c**. When furan-based dienoxysilanes substituted at the γ-position were used, the corresponding disubstituted butenolides bearing a quaternary chiral center at this position were obtained with moderate to good yields and excellent diastereoselectivities. *Anti*-configured adducts were obtained in all cases and their absolute configuration was unequivocally established by single-crystal X-ray crystallographic analysis. Cleavage of the chiral auxiliary in butenolides **3aa** and **3ba** was easily accomplished under mild conditions allowing preservation of the stereochemical integrity of the two newly-generated chiral centers.

Experimental Section

All reactions were carried out in oven-dried resealable test tubes under an atmosphere of argon. Dichloromethane (DCM) was distilled from CaH_2. All reactions were monitored by gas chromatography. GC analyses were performed on an Agilent 6950 GC system equipped with a HP5-MSI column (length 30 m, internal diameter 0.25 mm, film thickness 0.25 μm) and flame ionization detection under a constant flow 1 mL/min helium carrier gas. GC-MS analyses were performed on an Agilent 6890N GC system equipped with a (5%-phenyl)-methylpolysiloxane capillary column (length 30 m, internal diameter 0.25 mm, film thickness 0.25 μm) coupled to a Agilent 5973N MS low resolution quadrupole. Commercial aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F254 were used for analytical thin layer chromatography. Visualization was carried out with UV light. Product purification by flash chromatography was performed using Silica gel (230-400 mesh). ^{1}H (300, 400 and 500 MHz), and ^{13}C NMR (75, 100 and 126 MHz) spectra were recorded with a Bruker instrument. Chemical shifts are reported in δ ppm relative to TMS (δ ^{1}H= 0.0 ppm) and $CDCl_3$ (δ ^{13}C= 77.16 ppm) and coupling constants (*J*) are given in Hertz (Hz). Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), septet (sept), multiplet (m), and broad (br). High Resolution Mass Spectra were determined on a TripleTOF™ 5600 (ABSciex, USA) spectrometer by using electrospray in positive mode (ESI+). Melting points were recorded on a Cambridge Instruments apparatus and are uncorrected.

Starting materials.

Siloxy diene **1a** is commercial available. Siloxy dienes **1b**[29] and **1c**[30] and fluorinated aldimines **2a-g**[19] were prepared according described procedures.

General Procedure for Vinylogous Mukaiyama Mannich Reactions (VMMnR)

An oven-dried resealable test tube was filled with a solution of optically active fluorinated aldimine **2** (**2a-2g**) (0.5 mmol) in CH_2Cl_2 (2.5 mL), and the solution was allowed to cool to -78 ºC. At the same temperature, siloxydiene **1** (**1a-1c**) (0.6 mmol, 1.2 equiv) was added, and then TMSOTf (0.5 mmol, 1.0 equiv) was slowly added in a dropwise manner to the solution. After the appropriate reaction time, a saturated aqueous

solution of $NaHCO_3$ was added, and the aqueous layer was washed with EtOAc (3 x 5 mL), dried over anhydrous $MgSO_4$; the volatiles were removed under reduced pressure and the residue was purified by flash column chromatography on silica gel.

Acknowledgements

The authors are grateful to the Spanish MINECO (CTQ2017-84249-P) for financial support and the SCSIE (Universidad de Valencia) for access to instrumental facilities. Technical and human support provided by SGIker (UPV/EHU, MINECO, GV/DJ, ERDF, and ESF) is gratefully acknowledged).

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10.1002/adsc.201900464

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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