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Fluorine-induced diastereodivergence discovered in an equally rare enantioselective *syn*-aza-Henry reaction†

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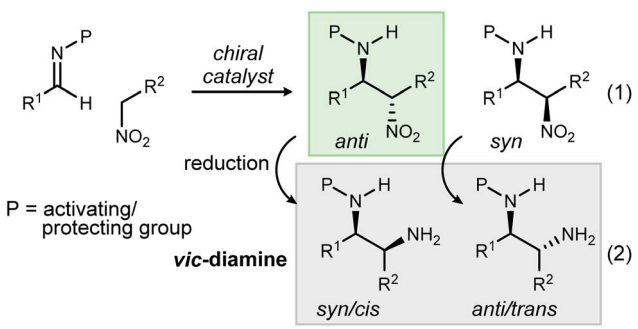
Attention to the aza-Henry reaction, particularly over the past two decades, has resulted in a wide range of effective catalysts for the enantio- and diastereoselective versions, driven by the versatility of the β-amino nitroalkane products as precursors to secondary amines and *vic*-diamines. Despite this broad effort, *syn*-diastereoselective variants are exceedingly rare. We have discovered a subset of α-fluoro nitroalkane additions that are characterized by an unusual crossover in diastereoselection, often delivering the products with high selectivities. We report here a rigorous comparative analysis of non-fluorinated and α-fluoro nitroalkanes in their additions to azomethines. Both homogeneous and heterogeneous catalysis were applied to probe the possibility that this phenomenon might be more widely operative in the enantioselective additions of fluorine-substituted carbon nucleophiles. A complete correlation within four categories is described that uncovered a clear trend, while revealing a dramatic and distinct reversal of diastereoselection that would normally go undetected.

Introduction

The addition of nitroalkanes to imine azomethines is often referred to as the aza-Henry or nitro-Mannich reaction (Scheme 1, eqn (1)). It has been successfully developed into a leading method for the stereocontrolled synthesis of *vic*-diamines[1] owing to the ease of subsequent nitro reduction (Scheme 1, eqn (2)).[2] The discovery of a wide array of Lewis acid and metal-free chiral catalysts that accelerate the aza-Henry reaction has greatly expanded the amine products readily accessed, in particular diamine and secondary amine precursors to small molecules with relevance to therapeutic development.[3,4] Despite these advances, nearly all aza-Henry reactions promoted by chiral catalysts favor the *anti*-diastereomer.[5,6] Simultaneous observation of high *syn*-diastereoselection and high enantioselection (up to 98% ee) has been achieved only once[7] with α-alkyl or α-aryl nitromethane derivatives, and twice[8,9] with α-nitro ester derivatives.[10] The absence of general *syn*-selective aza-Henry reactions reflects a gap in our understanding of the factors responsible for selectivity, while diminishing the reaction's otherwise broad utility as a source of diamines for therapeutic development and asymmetric synthesis.[1]



Scheme 1 The aza-Henry reaction as a source of enantioenriched β-amino nitroalkanes (eqn (1)) and *vic*-diamines (eqn (2)).

We have discovered an unusual reversal of diastereoselectivity, favoring the *syn*-aza-Henry product, that arises within a subset of α-fluoro nitroalkane pronucleophiles. A notable feature is that the reversal is mediated, but not determined by the catalyst, leading to the discovery of an example of fluorine-based diastereodivergence.[11] This behavior is outlined by a methodical investigation of this substrate control using aryl and aliphatic aldimines, combined with aryl and aliphatic α-fluoro nitromethane derivatives. An underlying hierarchy has been uncovered in these additions whereby fluorine reverses the inherent *anti*-selectivity of nitroalkane additions in cases not including aryl nitromethanes. These nitronates, bearing geminal aryl and fluorine, remain unaffected when changing from hydrogen to fluorine at nitronate carbon, suggesting a dominant directing effect provided by the aromatic ring. As

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† Electronic supplementary information (ESI) available: Complete experimental details (PDF); NMR and HPLC trace data (PDF); data for *anti*-**6d**, *syn*-**6f**, *anti*-**6g**, *anti*-**6h**, and *syn*-**6h** (CIF). CCDC 2118052–2118056. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc05910f

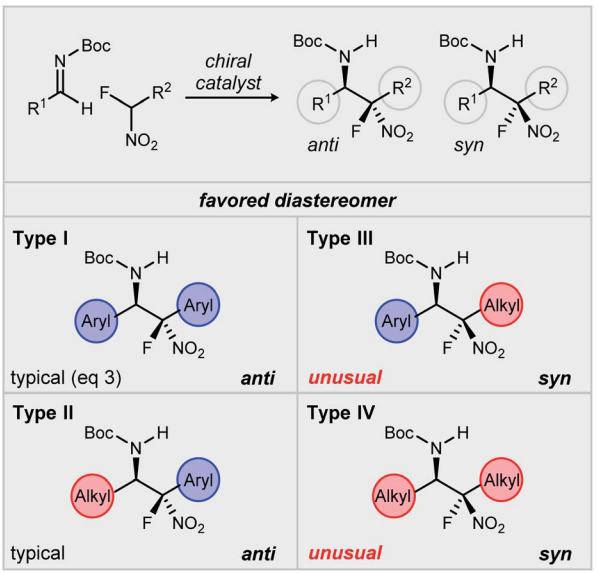
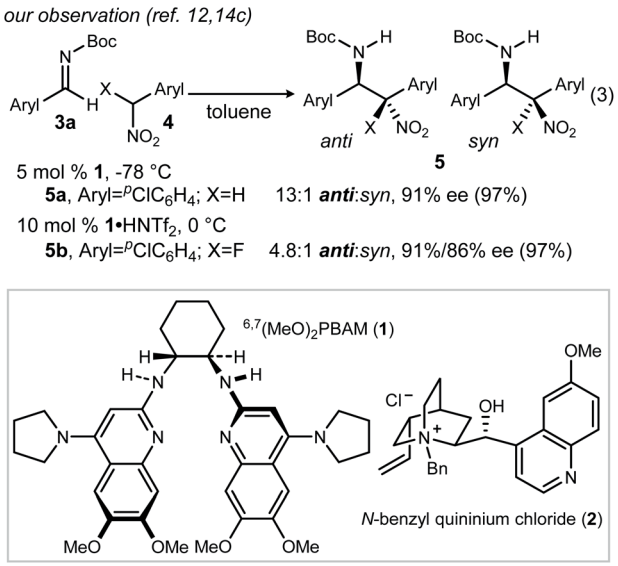


Fig. 1 Proposed classification system for catalyzed enantioselective aza-Henry reactions studied (this work), highlighting the substituent-dependence of *syn*-selectivity.



Scheme 2 The aza-Henry reaction: typical *anti*-selective reactions.

a result of our observations, a classification system (Fig. 1, Types I–IV) is proposed by which to organize these behaviors, one that might be adaptable to future studies.

Results

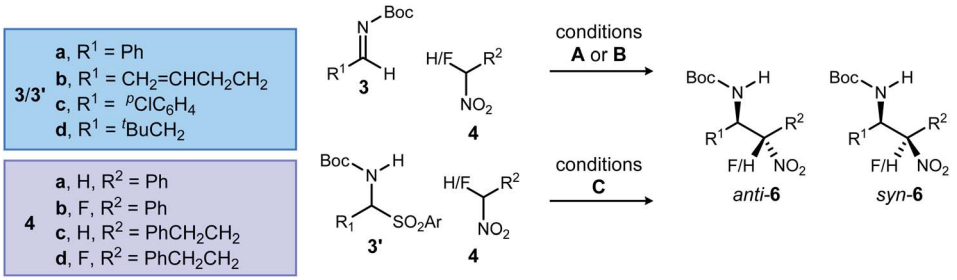
We recently reported the catalyzed addition of α-fluoro nitroalkanes to *N*-Boc aldimines using chiral bis(amidine) [BAM] catalyst **1** (Scheme 2, eqn (3)).[12] The inclusion of fluorine in the nitroalkane pronucleophile attenuated the overall rate relative to its nonfluorinated counterpart, but otherwise provided for the synthesis of β-fluoro amino stilbenes (after reduction).[13–16] The relative configuration of the β-amino nitroalkanes (Fig. 1, Type I)[17] was assigned by X-ray diffractometry, establishing that the fluorine's effect on rate blunted but did not reverse *anti*-selectivity in this case. Other cases exhibited similarly high selectivity, encouraging a tentative assignment of configuration by analogy.

During our pursuit of applications requiring Type IV additions, we continued to observe high diastereo- and enantioselectivity. These studies provided an additional opportunity to rigorously determine absolute and relative stereochemistry by X-ray diffraction. In doing so, we made the surprising discovery that selectivity favored the *syn*-β-amino-α-fluoro nitroalkane. This led us to launch a comprehensive study of each category of aza-Henry, with the objective to identify the control element(s) leading to *syn*-selectivity, and ultimately an understanding of this phenomenon of diastereodivergence.[18]

Standard conditions were established using **3b**, phenyl nitromethane (**4a**), and **1** as the catalyst (Table 1, entry 1). As previously reported, the product (**6a**) is produced with high *anti*-selectivity (>20 : 1 dr) and 78% ee. The use of heterogeneous catalysis was examined, specifically phase transfer catalysis (PTC) with *N*-benzyl quininium chloride (**2**, 12 mol%) and cesium hydroxide. When this protocol was applied to the α-amido sulfone precursor to *N*-Boc imine, the addition product was formed with high diastereoselectivity, but low enantioselection for the major (*anti*) diastereomer (Table 1, entry 2: **6a**, 15 : 1 dr, 39% ee). Catalysts **1** (homogeneous) and **2** (heterogeneous) not only exhibited similar behavior with phenyl nitromethane, but also α-fluoro phenyl nitromethane (**4b**) (Table 1, entries 3–4). This suggested a robust correlation between nitronate-azomethine orientation during activation by catalyst, and relative insensitivity of this stereochemistry-determining arrangement to the presence of fluorine at a reacting carbon. It should be noted, however, that fluorine notably slowed the aza-Henry additions relative to those of non-fluorinated aryl nitromethanes. This is a phenomenon already noted for BAM catalyst **1** (including the effects of ligand protonation), consistent with a combination of rate-limiting nitroalkane deprotonation, and the higher effective pK_a exhibited by α-fluoronitroalkanes.[19] In summary, homogeneous catalyst **1** is superior to heterogeneous catalyst **2** in Type I additions, but both favor *anti*-diastereoselectivity, and the same absolute configuration for the major and minor diastereomers.

We next investigated an alkyl aldimine electrophile (Table 1, entries 5–8) with the same pair of nitroalkanes (**4a–b**), observing varying levels of selectivity. Catalysts **1** and **2** favored the same relative and absolute configurations for the products of these reactions. The level of diastereoselection during formation of **6c** was highest using BAM catalysis (Table 1, entry 5 *vs.* entry 6), but enantioselection was higher using phase transfer catalyst (PTC) **2** (89% ee *vs.* 60% ee). Extending this examination to α-fluoronitroalkane **4b** conversion to **6d**, both catalysts **1** and **2** featured *anti*-selective additions for α-fluoro aryl nitromethane additions to aliphatic aldimines. For example, α-fluoro phenyl nitromethane provided the β-amino-α-fluoro-nitroalkane in 5.2 : 1 *anti* : *syn*, 83% ee (Table 1, entry 7). Temperature in this

Table 1 Catalyzed aza-Henry reactions varying aromatic/aliphatic substituents of azomethine and nitronate/fluoronitronate (Types I–IV)[a]



Entry	Type	R^1 3/3′	Conditions	R^2	H/F	4 → 6	Temp. (°C)	Catalyst	*anti* : *syn*[b]	ee[b] (%) *anti*	ee[b] (%) *syn*	Yield[c] (%) NMR	Yield[c] (%) Isol
1	I	Ph (**a**)	B	Ph	H	**4a**/**6a**	−55	**1**	>20 : 1	78	99	79	—
2	I	Ph (**a**)	C	Ph	H	**4a**/**6a**	−50	**2**	15 : 1	39	99	30	—
3[d]	I	Ph (**a**)	B	Ph	F	**4b**/**6b**	0	**1**·$HNTf_2$	3.5 : 1	94	84	—	88
4	I	Ph (**a**)	C	Ph	F	**4b**/**6b**	−55	**2**	4.2 : 1	52	31	60	—
5	II	CH_2=$CHCH_2CH_2$ (**b**)	A	Ph	H	**4a**/**6c**	−55	**1**	>20 : 1	60	99	35	35
6	II	CH_2=$CHCH_2CH_2$ (**b**)	C	Ph	H	**4a**/**6c**	−35	**2**	11 : 1	89	99	33	31
7[e]	II	CH_2=$CHCH_2CH_2$ (**b**)	A	Ph	F	**4b**/**6d**	−20	**1**·$HNTf_2$	5.2 : 1	83	99	—	53
8	II	CH_2=$CHCH_2CH_2$ (**b**)	C	Ph	F	**4b**/**6d**	−35	**2**	2.7 : 1	91	93	—	43
9	III	$^pClC_6H_4$ (**c**)	B	$PhCH_2CH_2$	H	**4c**/**6e**	−20	**1**·$HNTf_2$	20 : 1	87	51	—	49
10	III	$^pClC_6H_4$ (**c**)	C	$PhCH_2CH_2$	H	**4c**/**6e**	−55	**2**	3 : 1	33	7	86	—
11[d]	III	$^pClC_6H_4$ (**c**)	B	$PhCH_2CH_2$	F	**4d**/**6f**	25	**1**·$HNTf_2$	1 : 5.0	99	93	—	85
12	III	$^pClC_6H_4$ (**c**)	C	$PhCH_2CH_2$	F	**4d**/**6f**	−35	**2**	1 : 2.5	24	60	89	79
13	IV	$^tBuCH_2$ (**d**)	A	$PhCH_2CH_2$	H	**4c**/**6g**	−55	**1**	1 : 1	20	11	—	21
14	IV	$^tBuCH_2$ (**d**)	C	$PhCH_2CH_2$	H	**4c**/**6g**	−55	**2**	>20 : 1	99	—	94	90
15	IV	$^tBuCH_2$ (**d**)	A	$PhCH_2CH_2$	F	**4d**/**6h**	0	**1**·$HNTf_2$	1 : 2.4	81	80	47	—
16	IV	$^tBuCH_2$ (**d**)	C	$PhCH_2CH_2$	F	**4d**/**6h**	−35	**2**	1 : 7.2	76	91	—	84

[a] Conditions: (A) the α-amido sulfone **3′** is treated with Cs_2CO_3 in toluene to form imine **3**. After filtration, this solution is used directly in the aza-Henry reaction which is carried out in toluene (0.1 M) using the nitro- or fluoronitroalkane (1.2 equiv.) and $^{6,7}(MeO)_2$PBAM (**1**) or $^{6,7}(MeO)_2$PBAM·$HNTf_2$ (**1**·$HNTf_2$, 10 mol%) for 24 hours. (B) Using **3** (neat, preformed from **3′**), the aza-Henry reaction is run in dry toluene (0.1 M) under argon using the nitro- or fluoronitroalkane (1.2 equiv.) with **1** or **1**·$HNTf_2$. (C) Reaction run in dry toluene (0.1 M) under argon using the nitro- or fluoronitroalkane (4.5 equiv.), *N*-benzylquininium chloride (**2**, 12 mol%), and CsOH·H_2O (1.3 equiv.) for 48–72 hours. See ESI for complete details. [b] Diastereomeric ratios measured by ^{1}H NMR analysis of the crude reaction mixture. Enantiomeric excess determined by HPLC using a chiral stationary phase. [c] Yields over 2 steps (from α-amido sulfone). NMR: yield measured using an internal standard when **6** is present at high apparent purity in crude reaction mixture. Isol: isolated yield obtained when impurities are evident alongside **6** in crude reaction mixture. Selected cases analyzed using both methods for comparison. [d] Data from ref. 12. [e] 20 mol% catalyst. Using 10 mol% catalyst provides **6d** with 5.8 : 1 dr, 87/>99% ee, and 43% yield.

and later examples was most often selected to optimize conversion and yield for specific cases, while seeking the lowest functional temperature to favor higher selectivity. Also of note, our desire for rigorous assignment of the major stereoisomer for the non-fluorinated adduct went unfulfilled, since crystalline *anti*-**6c** formed only thin, feathery needles. As a result, the assignment was made by analogy to a similar case examined by Duan.[26] Absolute and relative stereochemistry for the *major* isomer of the fluorinated substrate was assigned by X-ray diffraction (*anti*-**6d**, Fig. 2).

Within Type III additions, non-fluorinated alkyl-substituted nitronates provided addition products with aryl aldimines with good selectivity (20 : 1 dr, 87% ee) when using **1**·$HNTf_2$ (Table 1, entry 9). Dixon[20] and Palomo[21a] have independently assigned *anti*-selectivity to this type of addition. In the formation of **6e** from **4c**, catalyst **2** was not competitive, providing low diastereoselection (3 : 1) and enantioselection (33% ee, Table 1, entry 10) relative to BAM catalysis. Despite the low selectivity, both catalysts favor the same stereoisomer. In Type III cases involving α-fluoro aliphatic nitroalkane additions (**4d**) and aromatic aldimine electrophiles, good diastereo- and enantioselectivity (5.0 : 1 dr, 99% ee: Table 1, entry 11) was observed. This behavior followed the trends outlined for all of the additions described to this point. Fortunately, we did not rely on analogy for stereochemical assignment since it would have predicted conservation of *anti*-selectivity based on all Type I/II additions, and non-fluorinated Type III additions. We instead sought rigorous stereochemical assignment by X-ray diffraction. Single crystals of the *major* diastereomer for **6f** revealed its *syn*-relationship (Fig. 2). Comparison of homo- and heterogeneous catalysis confirmed again that both methods favored the same relative and absolute stereochemistry in the product, albeit with low dr and ee for **2** (Table 1, entry 12).

For Type IV additions, we selected 3-phenyl-1-nitropropane for evaluation in both hetero- and homogeneous catalyst protocols, delivering the product of addition to **3d** with high

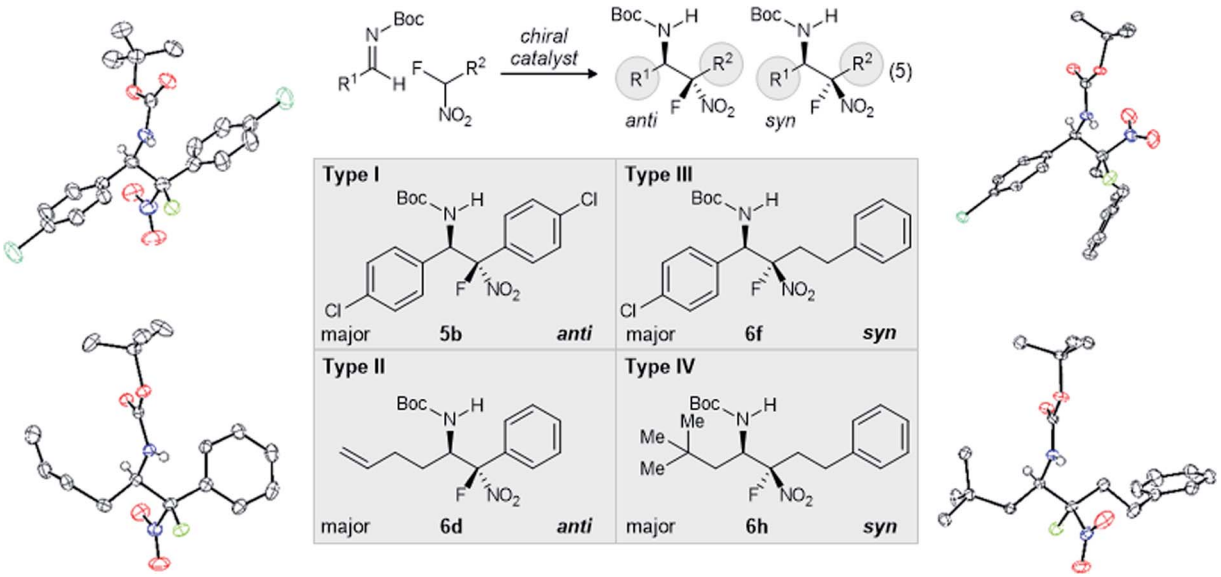


Fig. 2 X-Ray analysis[a] for major (relative and absolute) stereoisomer formed in experiments detailed by Table 1, and categorization of aza-Henry reactions by the type (aryl *vs.* alkyl) of the azomethine electrophile substituent, and the nitromethane substitutent(s). [a] ORTEPs shown at 50% probability.

selectivity only when using **2** (Table 1, entries 13–14). A strength of phase transfer catalysis is the pairing of rates for imine formation and consumption, a feature that is particularly impactful when the imine can tautomerize to the *N*-acyl enamide. In this comparison, catalyst **1** provided **6g** in low yield and with minimal stereoselection. However, PTC **2** delivered **6g** with exceptional selectivity (>20 : 1 dr, 99% ee) and yield (Table 1, entry 14). Rigorous assignment of *anti*-selectivity for this reaction was made by X-ray diffraction analysis of the major product, *anti*-**6g**.

Our examination of the corresponding Type IV additions of α-fluoronitroalkane using either homogeneous BAM catalysis (**1**·$HNTf_2$) or heterogeneous catalysis (**2**) revealed similar selectivity trends again, with the former providing product with low diastereoselection (2.4 : 1) and moderate enantioselection (81% ee) at 0 °C. Catalyst **2** led to the same major diastereomer with high selectivity (7.2 : 1), and moderate enantioselection (76% ee) at −35 °C (Table 1, entry 16). In this case, both the major and minor diastereomers of **6h** formed good quality single crystals that allowed the major to be assigned as *syn*-**6h** and the minor to be assigned as *anti*-**6h**. This also allowed us to further confirm that the stereochemistry at the azomethine carbon is conserved. Once again, the addition of alkyl-substituted α-fluoro nitronates displayed a reversal of diastereoselection, favoring *syn*-selectivity. Notably, this behavior stands in contrast to the *anti*-selectivity observed with non-fluorinated alkyl-substituted nitronates **4c**.

Discussion

An important aspect of this study is the dedicated effort to rigorously assign relative and absolute configuration for each example while placing it in the context of the same efforts by others. In Type I (Ar/Ar) additions, aryl nitromethanes undergo diastereo- and enantioselective addition to *N*-Boc benzaldimines using bis(amidine) [BAM] catalysis, providing *anti*-addition products with high yield and selectivity (Scheme 2, eqn (3), **5a**). In addition to assignment of the favored stereoisomer by X-ray diffraction (R_1=3-Br-4-$MeOC_6H_3$, R_2=C_6H_5), a key analogue (R_1=R_2=4-ClC_6H_4) was converted to the p53/MDM2 inhibitor Nutlin-3a,[14b] and its potency recapitulated *in vitro*.[14,22] Advances for Type I additions have been made by others (Fig. 3). Ooi developed a chiral ammonium betaine (**C1**) that further improves the selectivity of this addition, providing the Type I product (Ph/Ph) in 97% ee. Ooi's investigation of aryl nitromethane, and α-vinyl-α-aryl-nitromethane addition to imines exhibited highly conserved *anti*-selectivity.[23,24] Kozlowski identified cinchonidinium acetate (**C3**·HOAc) as an effective homogeneous catalyst for Type I product (Ph/^{t}BuC_6H_4: 97 : 3 *anti* : *syn*, 70% ee).[25] Finally, Duan used a urea/tetralkyl ammonium bifunctional catalyst (**C4**) to provide **6a** (Ph/Ph) in 99 : 1 *anti* : *syn* and 99% ee.[26,27]

In Type II (Alkyl/Ar) additions, the reaction of aryl nitronates with alkyl aldimines have been established as *anti*-selective. Aliphatic *N*-Boc aldimines are best addressed by phase transfer-catalysis since the formation of *N*-Boc enamide by tautomerization is minimized.[21,28] Duan extended the catalyst effective for Type I additions to a single example involving an aliphatic aldimine, which provided the product in 91% yield ($PhCH_2CH_2$/Ph: 94 : 6 dr, 97% ee). The stereochemical assignment of this example was made by analogy to the associated Type I cases, specifically **6a**.

Our assignment of product configuration (*vide supra*) confirmed that Type II additions exhibit robust *anti*-selectivity regardless of fluorine substitution of the intermediate aryl nitronate. Importantly, these results also establish that this

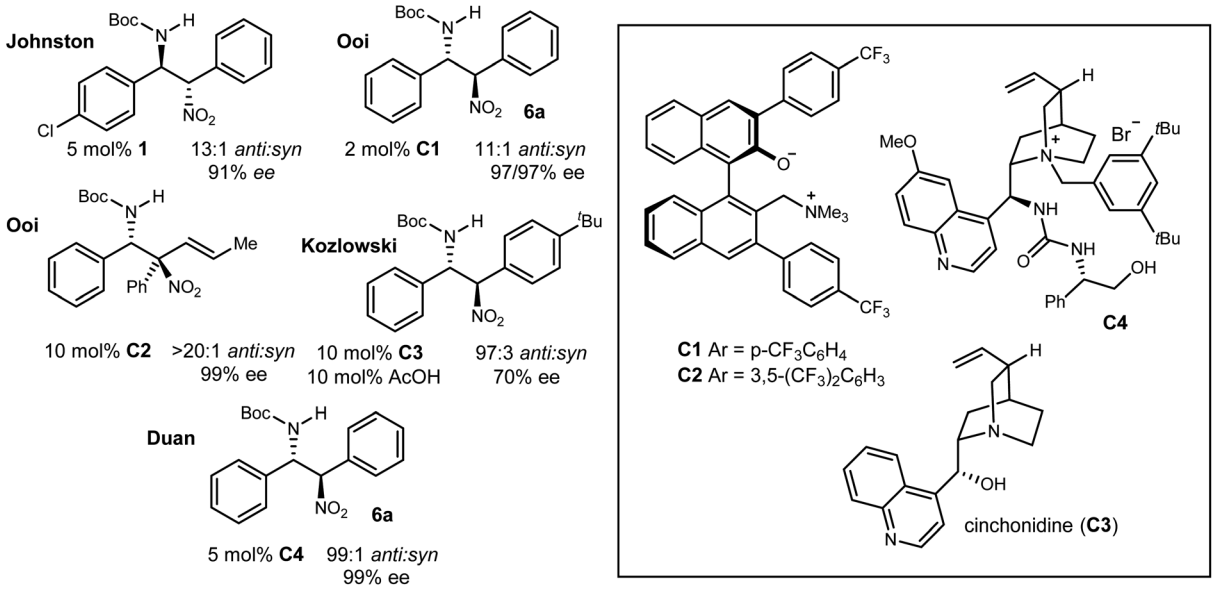


Fig. 3 The aza-Henry reaction of aryl nitromethanes to aryl aldimines: *anti*-selectivity across diverse catalysts.

behavior is independent of catalyst type (homo- *vs.* heterogeneous).

Type III additions are undoubtedly the most studied cases, thereby providing a greater pool of catalysts for comparison. Among these, the catalysts **1**·HNTf$_2$ and **2** have been shown to be highly effective. However, the high degree of consistency exhibited by Type I–II additions using non-fluorinated and fluorinated nitroalkanes **4** did not accurately forecast the behaviors to be uncovered by Type III additions.

Limited literature precedent exists for the favored stereoisomer in additions of alkyl-substituted nitronates to aliphatic aldimines (Type IV). This includes the early examples (2005) by Palomo citing *anti*-selectivity when drawing analogy to Type III additions. This Type IV selectivity was more rigorously established in 2008 using X-ray diffraction.[21b] Shibasaki's singular *syn*-selective Type IV additions featured a Cu(II)/Sm(III) protocol for nitroethane addition to an aliphatic aldimine (65% yield, 20 : 1 dr, 80% ee), and this product was converted to nemonapride, an antipsychotic agent.[7] In other cases, Shibasaki's bimetallic catalyst provided the typical *anti*-selectivity with good enantioselection.[29] Anderson rigorously assigned silyl nitronate addition products within the Type III class for which a copper(II)–bis(oxazoline) system provided high dr/ee. Analogy was then used to assign those belonging to the Type IV class, which included two cases: the product from cyclohexanal *N*-PMP imine (88% yield, >15 : 1 dr, 87% ee) and hexanal imine (88% yield, 1 : 1 dr, 86% ee).[30] Finally, Duan used a phase transfer catalyst equipped with hydrogen bonding ability to report a single example: the addition of nitroethane to the cyclohexyl carboxaldehyde imine, with up to 99 : 1 dr, 97% ee. There is minimal literature related to the effect of fluorine on the diastereo- and enantioselective addition of nitroalkanes bearing alternative activating groups.[31–34]

To summarize, across Types I–IV, *anti*-diastereoselection is observed when using non-fluorinated nitroalkanes. This is observed regardless of catalyst (**1** or **2**), reaffirming reports with PTC,[21] BAM,[35] and a wide range of other catalysts[4,36–38] with alkyl-substituted nitronates, and PTC[24–26] or BAM[14] catalysts applied to aryl-substituted nitronates. Departing from this behavior[39] for enantioselective aza-Henry reactions, Shibasaki's report is a standout. It is the most successful *syn*-diastereo- and enantioselective reaction to-date: using a mixed Cu(II)/Sm(III) complex, excellent *syn*-diastereoselection was achieved, with good enantioselection (43–83% ee). Aliphatic aldimines were less successful, reaching as high as 81% ee, and the scope was also limited to three linear aldimines.[7] The *syn*-selectivity in that work is attributed to reagent control by formation of a samarium(III) nitronate and copper(II)-activated Boc-imine supported simultaneously by the same chiral ligand.

Two basic stereochemistry-determining arrangements of azomethine and nitronate are summarized in Fig. 4: pre-*anti* (**7** or **9**) and pre-*syn* (**8** or **10**). Regardless of catalyst deployed in experiments here, the azomethine Si face is favored. This is evident from the configuration at the aminomethyl carbon for

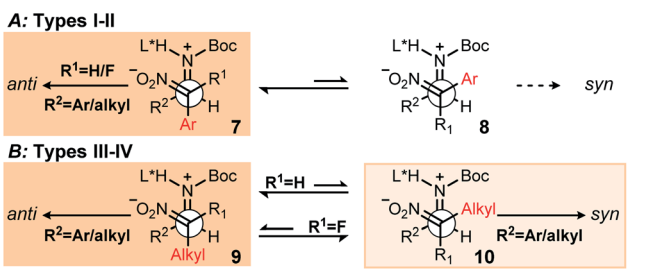


Fig. 4 Working models (*i.e.*, L = **1**) to identify dominant effects present during C–C bond formation as a function of nitronate substituent combination (aryl/alkyl, H/F).

both diastereomers, indicating that the azomethine-catalyst binding is relatively conserved (this was further confirmed in this work by X-ray analysis, see ESI† for details). Therefore, each Newman projection in Fig. 4 illustrates nitronate approach to the azomethine Si face. A second guiding principle is the bifunctional activation of azomethine and nitronate which favors a synclinal arrangement of azomethine nitrogen and nitronate-NO_2 units. This feature has been supported by Dudding's analysis,[40,41] it is consistent with the bifunctional character of BAM catalysis, and it is also invoked elsewhere.[7,21b] Type I–II aza-Henry reactions are *anti*-selective and insensitive to the presence of fluorine (R^1=H *vs.* F). The arrangement in Fig. 4A provides for the first two factors, and placement of the aromatic ring of the nitronate between the smaller aldimine-hydrogen and Ar/Alkyl substituents (*i.e.* R^2) of the azomethine predicts *anti*-selectivity on purely steric grounds. The cases of alkyl-substituted nitronates are more nuanced (Fig. 4B), with the non-fluorinated nitronate (R^1=H) favoring *anti*-selectivity for the same reasons as listed above.

Fluorine-substituted nitronates favor *syn*-selectivity (Fig. 4B) when geminally-substituted with an alkyl substituent, but not aryl. Although fluorine is highly electronegative and a weak hydrogen bond acceptor, the consistent azomethine face-selectivity suggests that the electrostatically-driven hydrogen bonding between ligand and azomethine is not dramatically affected by the presence of fluorine in the nitroalkane.[42] Contemporary models advancing the gauche effect for fluorine[43] align with *anti*-selectivity, wherein iminium and fluorine are gauche (Fig. 4) to allow $\sigma_{CC} \rightarrow \sigma^*_{CF}\sigma CF^*$ overlap involving the aldimine R_2–carbon bond.[44] While this reasoning is consistent with Type I–II (R_1=F) additions, it should also apply to Type III–IV additions (R_1=F), but these lead to *syn*-selectivity instead.

The origin of diastereodivergence may emanate from a secondary interaction between the iminium and the nitronate substituent in an *anti* relationship in the transition state, favoring Ar > F > alkyl. We speculated that the extensive literature describing the Diels–Alder reaction might harbor fluorine-based diastereodivergence, particularly in cases where directing groups compete in a thermal reaction. Indeed, the competition between phenyl and fluorine for *endo*-positioning in Diels–Alder reactions favors slightly (2–3 : 1) *endo*-fluorine with an electron-rich benzoisofuran and α-fluoro styrene.[45] Moreover, (*E*)-β-fluoro styrene is also slightly *endo*-fluorine selective, while (*Z*)-β-fluoro styrene produces only *endo*-product (both Ph and F are positioned *endo*).[46] The substituent effect of fluorine (*vs.* hydrogen) is perhaps most pronounced in enantioselective catalysis with α-fluoro enones and esters. In these cases, fluorine overrides ketone and ester carbonyl for *endo*-positioning by 3 : 1.[47] Computational methods have been applied to thermal and Lewis acid-promoted Diels–Alder cycloadditions of cyclopentadiene with enones, leading to the conclusion that destabilization of the *endo*-pathway for 3-fluorobutenone is primarily responsible for its *endo*-fluorine (*exo*-C=O) selectivity.[48] Overall, these substituent effects follow a hierarchy F > Ph/carbonyl > H consistent across cyclopentadiene and diphenyl isobenzofuran.

Unlike the thermal Diels–Alder reactions where fluorine effected diastereodivergence when competitive with both phenyl (aryl) and carbonyl geminal substituents, the hierarchy here is Ar > F > alkyl. Of course, the transition states for nitronate additions to imines with catalysis are quite different, and the role of fluorine would be expected to be more pronounced than an alkyl group in the transition state. The unusual behavior lies in the contrasting effects when phenyl nitromethane derivatives are involved. We speculate that in these cases the electronic nature of an aryl ring prevails, perhaps through a secondary interaction between *anti*-aryl or *anti*-F and imine π* orbitals: $\pi_{Ar} \rightarrow \pi^*$-imine > $n_F \rightarrow \pi^*$-imine > $\sigma_{C\text{-alkyl}} \rightarrow \pi^*$-imine.

Conclusion

Despite extensive investigation of the aza-Henry reaction using a broad range of chiral catalysts, highly enantio- and *syn*-selective variations are rare.[3] Moreover, with one exception, the only known examples require an α-nitro ester.[8–10] Only one *syn*-selective aza-Henry of a nitroalkane without an additional activating group has been reported, with enantioselection as high as 98%.[7] A thorough study of catalyzed nitronate additions to *N*-Boc imines derived from aliphatic and aromatic aldehydes revealed exceptions to the otherwise common finding of *anti*-selectivity that is broadly observed in enantioselective, catalyzed aza-Henry reactions. This selectivity is particularly characteristic of terminal nitroalkanes lacking activating groups, and we replicated and extended this trend, using X-ray diffraction to rigorously assign product stereochemistry when needed. The exceptions were found among fluorine-substituted nitronates, but only those with an aliphatic substituent. In cases where an aromatic ring substituent was geminal to the C–F bond, *anti*-selectivity prevailed. The fluorine effect, and its compartmentalization into a subset of nitronates is unprecedented. We speculate that a hierarchy of directing effects is responsible for the selectivity, with the nitro group's position conserved among Type I–IV, but a phenyl ring overriding the fluorine's additional effect in Type I–II additions. Remarkable aspects of this discovery include the turnover in diastereoselection to *syn*-selectivity simultaneous with high enantioselection, in some cases setting it apart from prior highs established by others.[7] That these trends are relatively independent of catalysis method (hetero- *vs.* homogeneous) when using α-fluoronitroalkane pronucleophiles suggests that the behavior may be more generally observed. Examples of diastereodivergence associated with substrate control, using a single catalyst, are increasing.[49–51] As solutions to the stereocontrolled aza-Henry reaction increase, so will their impact on concise preparations of small molecules in drug development, and innovative entry to peptides based solely on catalytic, enantioselective methods.[52]

Data availability

All experimental and characterization data in this article are available in the ESI.† Crystallographic data for compounds *anti*-

6d, *syn*-**6f**, *anti*-**6g**, *anti*-**6h**, and *syn*-**6h** have been deposited in the Cambridge Crystallographic Data Centre (CCDC) under accession numbers CCDC 2118052–2118056.

Author contributions

J. B. and J. J. conceived the project, J. B. completed the experimental work, N. S. provided X-ray crystallography support. All authors wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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References

1 D. Lucet, T. Le Gall and C. Mioskowski, The chemistry of vicinal diamines, *Angew. Chem., Int. Ed.*, 1998, **37**, 2580.

2 For reviews on the aza-Henry reaction see: (*a*) M. F. P. Ana, Recent Advances on the Organocatalytic Asymmetric Aza-Henry Reaction, *Curr. Organocatal.*, 2016, **3**, 222; (*b*) E. Marqués-López, P. Merino, T. Tejero and R. P. Herrera, Catalytic Enantioselective Aza-Henry Reactions, *Eur. J. Org. Chem.*, 2009, 2401; (*c*) B. Westermann, Asymmetric Catalytic Aza-Henry Reactions Leading to 1,2-Diamines and 1,2-Diaminocarboxylic Acids, *Angew. Chem., Int. Ed.*, 2003, **42**, 151.

3 A. Y. Sukhorukov, A. A. Sukhanova and S. G. Zlotin, Stereoselective reactions of nitro compounds in the synthesis of natural compound analogs and active pharmaceutical ingredients, *Tetrahedron*, 2016, **72**, 6191.

4 A. Noble and J. C. Anderson, Nitro-Mannich Reaction, *Chem. Rev.*, 2013, **113**, 2887.

5 The use of relative stereochemical terms (*anti*, *syn*) here conforms to the most common convention: the aza-Henry product is drawn in zigzag form using the carbon backbone, and *anti* characterizes this drawing when the nitrogens of amine and nitro reside on opposite sides.

6 Ketimine electrophiles in enantioselective aza-Henry reactions are far less common, but *syn*-selective variants are known: G. Hong, D. Mao, X. Zhu, S. Wu and L. Wang, Metal free access to amide compounds via peroxide-mediated N/N double bond cleavage of azobenzenes, *Org. Chem. Front.*, 2015, **2**, 985.

7 (*a*) S. Handa, V. Gnanadesikan, S. Matsunaga and M. Shibasaki, syn-Selective catalytic asymmetric nitro-Mannich reactions using a heterobimetallic Cu-Sm-Schiff base complex, *J. Am. Chem. Soc.*, 2007, **129**, 4900; (*b*) S. Handa, V. Gnanadesikan, S. Matsunaga and M. Shibasaki, Heterobimetallic Transition Metal/Rare Earth Metal Bifunctional Catalysis: A Cu/Sm/Schiff Base Complex for *syn*-Selective Catalytic Asymmetric Nitro-Mannich Reaction, *J. Am. Chem. Soc.*, 2010, **132**, 4925.

8 A. Singh and J. N. Johnston, A Diastereo- and Enantioselective Synthesis of a-Substituted *syn*-α,β-Diamino Acids, *J. Am. Chem. Soc.*, 2008, **130**, 5866.

9 D. Uraguchi, K. Koshimoto and T. Ooi, Chiral Ammonium Betaines: A Bifunctional Organic Base Catalyst for Asymmetric Mannich-Type Reaction of a-Nitrocarboxylates, *J. Am. Chem. Soc.*, 2008, **130**, 10878.

10 α-Substituted (alkyl or aryl) α-nitroesters are conventionally drawn with the ester in the plane, leading to these summary comments, and interpretations of behavior should consider this. In the current context, therefore, this statement might summarize that *syn*-selective additions of α-nitroesters are common, while there are currently only two *anti*-selective exceptions.

11 H. G. Adolph and M. J. Kamlet, Fluoronitroaliphatics. I. The Effect of α Fluorine on the Acidities of Substituted Nitromethanes, *J. Am. Chem. Soc.*, 1966, **88**, 4761.

12 B. A. Vara and J. N. Johnston, Enantioselective Synthesis of β-Fluoro Amines Via β-Amino α-Fluoro Nitroalkanes and a Traceless Activating Group Strategy, *J. Am. Chem. Soc.*, 2016, **138**, 13794.

13 Some stilbene β-fluoroamines can be prepared by enantioselective phase transfer catalysis of aziridine ring-opening. Leading reference: G. Pupo, A. C. Vicini, D. M. H. Ascough, F. Ibba, K. E. Christensen, A. L. Thompson, J. M. Brown, R. S. Paton and V. Gouverneur, Hydrogen Bonding Phase-Transfer Catalysis with Potassium Fluoride: Enantioselective Synthesis of β-Fluoroamines, *J. Am. Chem. Soc.*, 2019, **141**, 2878.

14 (*a*) B. A. Vara, A. Mayasundari, J. C. Tellis, M. W. Danneman, V. Arredondo, T. A. Davis, J. Min, K. Finch, R. K. Guy and J. N. Johnston, Organocatalytic, Diastereo- and Enantioselective Synthesis of Nonsymmetric cis-Stilbene Diamines: A Platform for the Preparation of Single-Enantiomer *cis*-Imidazolines for Protein–Protein Inhibition, *J. Org. Chem.*, 2014, **79**, 6913; (*b*) T. A. Davis, A. E. Vilgelm, A. Richmond and J. N. Johnston, Preparation of (−)-Nutlin-3 Using Enantioselective Organocatalysis at Decagram Scale, *J. Org. Chem.*, 2013, **78**, 10605; (*c*) T. A. Davis and J. N. Johnston, Catalytic, enantioselective synthesis of stilbene *cis*-diamines: a concise preparation of (−)-nutlin-3, a potent p53/MDM2 inhibitor, *Chem. Sci.*, 2011, **2**, 1076; (*d*) S. V. Tsukanov, M. D. Johnson, S. A. May, S. P. Kolis, M. H. Yates and J. N. Johnston, Continuous Platform to Generate Nitroalkanes on-Demand (In Situ)

Using Peracetic Acid-Mediated Oxidation in a PFA Pipes-in-Series Reactor, *Org. Process Res. Dev.*, 2018, **22**, 971; (*e*) S. V. Tsukanov, M. D. Johnson, S. A. May, M. Rosemeyer, M. A. Watkins, S. P. Kolis, M. H. Yates and J. N. Johnston, Development of an Intermittent-Flow Enantioselective Aza-Henry Reaction Using an Arylnitromethane and Homogeneous Brønsted Acid–Base Catalyst with Recycle, *Org. Process Res. Dev.*, 2016, **20**, 215.

15 The effect of added Brønsted acid to ligand **1** when using non-fluorinated aryl nitromethanes was negligible, owing to the acidity of the nitroalkanes (i.e. the nitroalkane serves as an acid modifier). The activity/selectivity increase of added acid ($HNTf_2$) returned when using less acidic (higher pK_a: ref. 12) α-fluoro aryl nitromethanes. The specific effect can be acid-dependent (c.f. ref. 14*c* (HOTf) and Table 1, entry 1: **1**·$HNTf_2$ provided the product with 42% ee).

16 For a general review of fluorine effects on fluoroalkylation reactions, see: C. Ni and J. Hu, The unique fluorine effects in organic reactions: recent facts and insights into fluoroalkylations, *Chem. Soc. Rev.*, 2016, **45**, 5441.

17 The Type framework is based on the hypothesis that the relative stereoselectivity may be influenced by the nature of the reactive functionality's substituents, organized into four categories, Types I–IV (Fig. 1), determined by the *N*-Boc aldimine and nitroalkane substituents (aryl vs. alkyl). For example, a Type I aza-Henry involves an aryl nitromethane addition to aryl aldimine, while a Type III addition involves a nitroalkane addition to an aryl aldimine.

18 In total, three cases (**7h–j** in ref. 12) must be reassigned as *syn*-diastereomers. See ESI† for complete experimental data.

19 (*a*) F. G. Bordwell and J. E. Bartmess, Taft Equation as Applied to Equilibrium Acidities of Nitroalkanes, $G(CH_2)NO_2$, *J. Org. Chem.*, 1978, **43**, 3101; (*b*) ref. 11; (*c*) V. I. Slovetskii, L. V. Okhobystina, A. A. Feinzil'berg, A. I. Ivanov, L. J. Birynkova and S. S. Novikov, Spectrophotometric determination of the ionization constant of fluorodinitromethane, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1965, 2063.

20 A Type III addition product was assigned by analogy to a Type IV product: K. M. Johnson, M. S. Rattley, F. Sladojevich, D. M. Barber, M. G. Nunez, A. M. Goldys and D. J. Dixon, A New Family of Cinchona-Derived Bifunctional Asymmetric Phase-Transfer Catalysts: Application to the Enantio- and Diastereoselective Nitro-Mannich Reaction of Amidosulfones, *Org. Lett.*, 2012, **14**, 2492.

21 (*a*) A Type III product assigned by optical rotation: C. Palomo, M. Oiarbide, A. Laso and R. Lopez, Catalytic Enantioselective Aza-Henry Reaction with Broad Substrate Scope, *J. Am. Chem. Soc.*, 2005, **127**, 17622; (*b*) E. Gomez-Bengoa, A. Linden, R. Lopez, I. Mugica-Mendiola, M. Oiarbide and C. Palomo, Asymmetric Aza-Henry Reaction under Phase Transfer Catalysis: An Experimental and Theoretical Study, *J. Am. Chem. Soc.*, 2008, **130**, 7955.

22 For use of this material *in vivo*, see: (*a*) A. E. Vilgelm, J. S. Pawlikowski, Y. Liu, O. E. Hawkins, T. A. Davis, J. Smith, K. P. Weller, L. W. Horton, C. M. McClain, G. D. Ayers, D. C. Turner, D. C. Essaka, C. F. Stewart, J. A. Sosman, M. C. Kelley, J. A. Ecsedy, J. N. Johnston and A. Richmond, Mdm2 and Aurora Kinase A Inhibitors Synergize to Block Melanoma Growth by Driving Apoptosis and Immune Clearance of Tumor Cells, *Cancer Res.*, 2015, **75**, 181; (*b*) A. E. Vilgelm, N. Saleh, R. Shattuck-Brandt, K. Riemenschneider, L. Slesur, S.-C. Chen, C. A. Johnson, J. Yang, A. Blevins, C. Yan, D. B. Johnson, R. N. Al-Rohil, E. Halilovic, R. M. Kauffmann, M. Kelley, G. D. Ayers and A. Richmond, MDM2 antagonists overcome intrinsic resistance to CDK4/6 inhibition by inducing p21, *Sci. Transl. Med.*, 2019, **11**, eaav7171.

23 K. Oyaizu, D. Uraguchi and T. Ooi, Vinylogy in nitronates: utilization of [α]-aryl conjugated nitroolefins as a nucleophile for a highly stereoselective aza-Henry reaction, *Chem. Commun.*, 2015, **51**, 4437.

24 D. Uraguchi, K. Oyaizu, H. Noguchi and T. Ooi, Chiral Ammonium Betaine-Catalyzed Highly Stereoselective Aza-Henry Reaction of α-Aryl Nitromethanes with Aromatic *N*-Boc Imines, *Chem.–Asian J.*, 2015, **10**, 334.

25 R. R. Walvoord and M. C. Kozlowski, Cinchonidinium acetate as a convenient catalyst for the asymmetric synthesis of *cis*-stilbenediamines, *Tetrahedron Lett.*, 2015, **56**, 3070.

26 N. Lu, R. Li, Z. Wei, J. Cao, D. Liang, Y. Lin and H. Duan, Enantio- and Diastereoselective Nitro-Mannich Reaction of α-Aryl Nitromethanes with Amidosulfones Catalyzed by Phase-Transfer Catalysts, *J. Org. Chem.*, 2017, **82**, 4668.

27 An immobilized thiourea provided low selectivity (up to 91 : 9 *anti* : *syn*, 42% ee): R. Pedrosa, J. M. Andrés, D. P. Ávila, M. Ceballos and R. Pindado, Chiral ureas and thioureas supported on polystyrene for enantioselective aza-Henry reactions under solvent-free conditions, *Green Chem.*, 2015, **17**, 2217.

28 F. Fini, V. Sgarzani, D. Pettersen, R. P. Herrera, L. Bernardi and A. Ricci, Phase-transfer-catalyzed asymmetric aza-Henry reaction using *N*-carbamoyl imines generated in situ from α-amido sulfones, *Angew. Chem., Int. Ed.*, 2005, **44**, 7975.

29 T. Nitabaru, N. Kumagai and M. Shibasaki, Catalytic Asymmetric Nitro-Mannich Reactions with a Yb/K Heterobimetallic Catalyst, *Molecules*, 2010, **15**, 1280.

30 J. C. Anderson, G. P. Howell, R. M. Lawrence and C. S. Wilson, An Asymmetric Nitro-Mannich Reaction Applicable to Alkyl, Aryl, and Heterocyclic Imines, *J. Org. Chem.*, 2005, **70**, 5665.

31 Y. Pan, Y. Zhao, T. Ma, Y. Yang, H. Liu, Z. Jiang and C.-H. Tan, Enantioselective Synthesis of α-Fluorinated β-Amino Acid Derivatives by an Asymmetric Mannich Reaction and Selective Deacylation/Decarboxylation Reactions, *Chem.–Eur. J.*, 2010, **16**, 779.

32 Enantioselective α-fluoro-α-sulfonyl nitroalkanes additions to isatin-derived ketimines catalyzed by cinchonine are also known: M. Urban, M. Franc, M. Hofmanová, I. Císařová and J. Veselý, The enantioselective addition of

1-fluoro-1-nitro(phenylsulfonyl)methane to isatin-derived ketimines, *Org. Biomol. Chem.*, 2017, **15**, 9071.

33 For enantioselective Michael additions of α-fluoro nitroester to enones, see: H.-F. Cui, P. Li, X.-W. Wang, Z. Chai, Y.-Q. Yang, Y.-P. Cai, S.-Z. Zhu and G. Zhao, Highly enantioselective synthesis of α-fluoro-α-nitro esters via organocatalyzed asymmetric Michael addition, *Tetrahedron*, 2011, **67**, 312.

34 R. Blaszczyk, A. Gajda, S. Zawadzki, E. Czubacka and T. Gajda, *N*-Carbamate α-aminoalkyl-*p*-tolylsulfones-convenient substrates in the nitro-Mannich synthesis of secondary *N*-carbamate protected *syn*-2-amino-1-nitroalkanephosphonates, *Tetrahedron*, 2010, **66**, 9840.

35 (*a*) B. M. Nugent, R. A. Yoder and J. N. Johnston, Chiral proton catalysis: a catalytic enantioselective direct aza-Henry reaction, *J. Am. Chem. Soc.*, 2004, **126**, 3418; (*b*) A. Singh, R. A. Yoder, B. Shen and J. N. Johnston, Chiral Proton Catalysis: Enantioselective Brønsted Acid Catalyzed Additions of Nitroacetic Acid Derivatives as Glycine Equivalents, *J. Am. Chem. Soc.*, 2007, **129**, 3466; (*c*) J. C. Wilt, M. Pink and J. N. Johnston, A Diastereo- and Enantioselective Synthesis of α-Substituted *anti*-α,β-Diaminophosphonic Acid Derivatives, *Chem. Commun.*, 2008, 4177; (*d*) T. A. Davis, J. C. Wilt and J. N. Johnston, Bifunctional Asymmetric Catalysis: Amplification of Bronsted Basicity Can Orthogonally Increase the Reactivity of a Chiral Bronsted Acid, *J. Am. Chem. Soc.*, 2010, **132**, 2880; (*e*) D. J. Sprague, A. Singh and J. N. Johnston, Diastereo- and enantioselective additions of [α]-nitro esters to imines for *anti*-[α],[β]-diamino acid synthesis with [α]-alkyl-substitution, *Chem. Sci.*, 2018, **9**, 2336.

36 G. K. Friestad and A. K. Mathies, Recent developments in asymmetric catalytic addition to C=N bonds, *Tetrahedron*, 2007, **63**, 2541.

37 T. Akiyama, J. Itoh and K. Fuchibe, Recent progress in chiral Bronsted acid catalysis, *Adv. Synth. Catal.*, 2006, **348**, 999.

38 T. Vilaivan, W. Bhanthumnavin and Y. Sritana-Anant, Recent advances in catalytic asymmetric addition to imines and related C=N systems, *Curr. Org. Chem.*, 2005, **9**, 1315.

39 *syn*-Selectivity in aza-Henry additions was also observed in cases where an achiral catalyst and/or racemic product is formed, and in others where a solvent effect was noted: (*a*) D. Kundu, R. K. Debnath, A. Majee and A. Hajra, Zwitterionic-type molten salt-catalyzed syn-selective aza-Henry reaction: solvent-free one-pot synthesis of β-nitroamines, *Tetrahedron Lett.*, 2009, **50**, 6998; (*b*) J. C. Anderson, G. J. Stepney, M. R. Mills, L. R. Horsfall, A. J. Blake and W. Lewis, Enantioselective Conjugate Addition Nitro-Mannich Reactions: Solvent Controlled Synthesis of Acyclic *anti*- and *syn*-β-Nitroamines with Three Contiguous Stereocenters, *J. Org. Chem.*, 2011, **76**, 1961; (*c*) X. Wang, Y.-F. Chen, L.-F. Niu and P.-F. Xu, Diastereo- and Enantioselective Aza-MBH-Type Reaction of Nitroalkenes to N-Tosylimines Catalyzed by Bifunctional Organocatalysts, *Org. Lett.*, 2009, **11**, 3310.

40 L. Belding, S. M. Taimoory and T. Dudding, Mirroring Enzymes: The Role of Hydrogen Bonding in an Asymmetric Organocatalyzed Aza-Henry Reaction—A DFT Study, *ACS Catal.*, 2015, **5**, 343.

41 S. M. Taimoory and T. Dudding, An Evolving Insight into Chiral H-Bond Catalyzed Aza-Henry Reactions: A Cooperative Role for Noncovalent Attractive Interactions Unveiled by Density Functional Theory, *J. Org. Chem.*, 2016, **81**, 3286.

42 P. A. Champagne, J. Desroches and J. F. Paquin, Organic Fluorine as a Hydrogen-Bond Acceptor: Recent Examples and Applications, *Synthesis*, 2015, **47**, 306.

43 (*a*) C. R. S. Briggs, M. J. Allen, D. O'Hagan, D. J. Tozer, A. M. Z. Slawin, A. E. Goeta and J. A. K. Howard, The observation of a large gauche preference when 2-fluoroethylamine and 2-fluoroethanol become protonated, *Org. Biomol. Chem.*, 2004, **2**, 732; (*b*) E.-M. Tanzer, L. E. Zimmer, W. B. Schweizer and R. Gilmour, Fluorinated Organocatalysts for the Enantioselective Epoxidation of Enals: Molecular Preorganisation by the Fluorine-Iminium Ion Gauche Effect, *Chem.–Eur. J.*, 2012, **18**, 11334. For reviews see: D. O'Hagan, Understanding organofluorine chemistry. An introduction to the C–F bond, *Chem. Soc. Rev.*, 2008, **37**, 308 (*c*) L. Hunter, The C–F bond as a conformational tool in organic and biological chemistry, *Beilstein J. Org. Chem.*, 2010, **6**, 38.

44 G. K. S. Prakash, F. Wang, N. Shao, T. Mathew, G. Rasul, R. Haiges, T. Stewart and G. A. Olah, A Persistent α-Fluorocarbanion and Its Analogues: Preparation, Characterization, and Computational Study, *Angew. Chem., Int. Ed.*, 2009, **48**, 5358.

45 T. Ernet and G. Haufe, Diels-Alder reactions of vinyl fluorides with 1,3-diphenylisobenzofuran, *Tetrahedron Lett.*, 1996, **37**, 7251.

46 G. Landelle, M.-O. Turcotte-Savard, L. Angers and J.-F. Paquin, Stereoselective Synthesis of Both Stereoisomers of β-Fluorostyrene Derivatives from a Common Intermediate, *Org. Lett.*, 2011, **13**, 1568.

47 K. Shibatomi, K. Futatsugi, F. Kobayashi, S. Iwasa and H. Yamamoto, Stereoselective Construction of Halogenated Quaternary Stereogenic Centers Via Catalytic Asymmetric Diels–Alder Reaction, *J. Am. Chem. Soc.*, 2010, **132**, 5625.

48 L. Merzoud, A. Saal, R. Moussaoui, O. Ouamerali, C. Morell and H. Chermette, Fluorine substituent effect on the stereochemistry of catalyzed and non-catalyzed Diels–Alder reactions. The case of R-butenone with cyclopentadiene: a computational assessment of the mechanism, *Phys. Chem. Chem. Phys.*, 2018, **20**, 16102.

49 J. Hernández-Toribio, R. Gómez Arrayás and J. C. Carretero, Substrate-Controlled Diastereoselectivity Switch in Catalytic Asymmetric Direct Mannich Reaction of Glycine Derivatives with Imines: From *anti*- to *syn*-α,β-Diamino Acids, *Chem.–Eur. J.*, 2010, **16**, 1153.

50 L. Lin and X. Feng, Catalytic Strategies for Diastereodivergent Synthesis, *Chem.–Eur. J.*, 2017, **23**, 6464.

51 R. Ding, Z. A. De los Santos and C. Wolf, Catalytic Asymmetric Mannich Reaction of α-Fluoronitriles with Ketimines: Enantioselective and Diastereodivergent

Construction of Vicinal Tetrasubstituted Stereocenters, *ACS Catal.*, 2019, **9**, 2169.

52 (*a*) B. Shen, D. M. Makley and J. N. Johnston, Umpolung reactivity in amide and peptide synthesis, *Nature*, 2010, **465**, 1027; (*b*) J. P. Shackleford, B. Shen and J. N. Johnston, Discovery of competing anaerobic and aerobic pathways in umpolung amide synthesis allows for site-selective amide ^{18}O-labeling, *Proc. Natl. Acad. Sci. U. S. A.*, 2012, **109**, 44; (*c*) K. E. Schwieter, B. Shen, J. P. Shackleford, M. W. Leighty and J. N. Johnston, Umpolung Amide Synthesis Using Substoichiometric *N*-Iodosuccinimide (NIS) and Oxygen as a Terminal Oxidant, *Org. Lett.*, 2014, **16**, 4714; (*d*) K. E. Schwieter and J. N. Johnston, Enantioselective synthesis of D-α-amino amides from aliphatic aldehydes, *Chem. Sci.*, 2015, **6**, 2590; (*e*) K. E. Schwieter and J. N. Johnston, Enantioselective Addition of Bromonitromethane to Aliphatic *N*-Boc Aldimines Using a Homogeneous Bifunctional Chiral Organocatalyst, *ACS Catal.*, 2015, **5**, 6559; (*f*) K. E. Schwieter and J. N. Johnston, A one-pot amidation of primary nitroalkanes, *Chem. Commun.*, 2016, **52**, 152; (*g*) V. T. Lim, S. V. Tsukanov, A. B. Stephens and J. N. Johnston, Enantioselective Synthesis of α-Bromonitroalkanes for Umpolung Amide Synthesis: Preparation of *tert*-Butyl((1*R*)-1-(4-(benzyloxy) phenyl)-2-bromo-2-nitroethyl)carbamate, *Org. Synth.*, 2016, **93**, 88; (*h*) M. T. Knowe, S. V. Tsukanov and J. N. Johnston, Preparation of Benzyl((*R*)-2-(4-(benzyloxy)phenyl)-2-((tert-butoxycarbonyl)amino)acetyl)-D-phenylalaninate Using Umpolung Amide Synthesis, *Org. Synth.*, 2017, **94**, 388; (*i*) M. S. Crocker, H. Foy, K. Tokumaru, T. Dudding, M. Pink and J. N. Johnston, Direct Observation and Analysis of the Halo-Amino-Nitro Alkane Functional Group, *Chem*, 2019, **5**, 1248.