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Base-Dependent Stereodivergent Intramolecular *aza*-Michael Reaction: Asymmetric Synthesis of 1,3-Disubstituted Isoindolines

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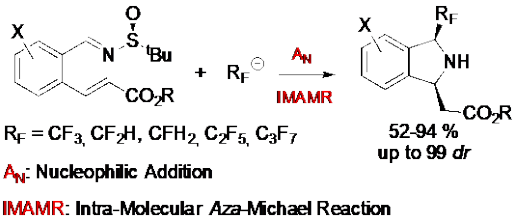
Dedication ((optional))

Abstract: The nucleophilic addition A_N / Intramolecular *aza*-Michael reaction (IMAMR) process on Ellman's *tert*-butylsulfinyl imines bearing a Michael acceptor in the *ortho* position is studied. This reaction affords 1,3-disubstituted isoindolines with a wide range of substituents in good yields and diastereoselectivities. Interestingly, the careful choice of the base for the *aza*-Michael step allows to exclusively obtaining either the *cis* or the *trans* diastereoisomers. This stereodivergent cyclization has enabled us to synthesize C_2-symmetric bisacetate substituted isoindolines. In addition, bisacetate isoindolines bearing two well differentiated ester moieties are also noteworthy as they may allow for the orthogonal synthesis of β,β'-dipeptides using a single *N* atom as linchpin.

Keywords: asymmetric synthesis • chiral auxiliaries • heterocycles • aza-Michael reaction• stereodivergent cyclization

Introduction

Recently, motivated by our group's interest in organofluorine chemistry,[1] on the one hand, and in tandem reactions including an intramolecular aza-Michael reaction as the last step,[2] on the other hand, we described a tandem process nucleophilic addition (AN) / intramolecular aza-Michael reaction (IMAMR) following the cascade design depicted in Scheme 1.[3] The isoindoline core would be formed through an intramolecular aza-Michael addition onto a conveniently placed α,β-unsaturated ester. The isoindoline structures thus obtained constitute a new family of fluorinated β-amino acid derivatives.[1b] The required amine would arise from the diastereoselective addition of a suitable fluorinated nucleophile to an imine. Among the available chiral auxiliaries (CA), we chose Ellman's (*Rs*)-*N*-(*tert*-butanesulfinyl) imines[4,5] as it has successfully been used in this context.[6]



Scheme 1. Tandem nucleophilic addition / intramolecular *aza*-Michael reaction: asymmetric synthesis of fluorinated 1,3-disubstituted isoindolines

Tandem reactions are very attractive since they increase synthetic efficiency by decreasing the number of laboratory operations required and the quantities of solvents and chemicals used, reducing cost and time and allowing for the creation of molecular complexity from simple substrates.[7] Moreover, the synthesis of optically active compounds plays a pivotal role in medicinal chemistry. Therefore, the interest in combining asymmetric processes with tandem reactions is obvious, since multiple stereogenic centers can be created in a single synthetic step. On the other hand, although isoindolines are substructures present in a variety of natural products and pharmaceuticals [8] they still lack general routes for their preparation in a stereoselective manner.[9,10]

This transformation offers several points for the introduction of molecular diversity (Scheme 2), namely: a) the use of ketimines instead of aldimines (Scheme 3), b) the use of non-fluorinated nucleophiles and c) the introduction of Michael acceptors other than acrylates such as enals, enones and others. Finally, the formation of

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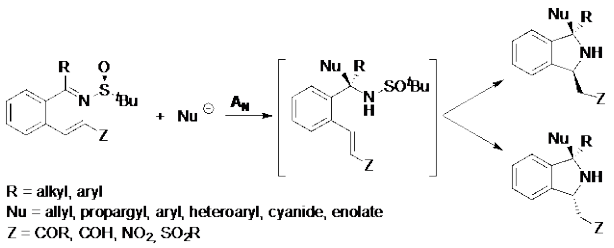
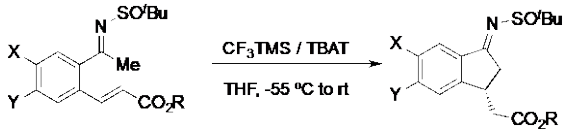
a second stereocenter during the cyclization event makes a stereodivergent cyclization towards either the *cis* or the *trans* isomer possible.



Scheme 2. Molecular diversity scenarios for the AN / IMAMR sequence

Firstly, the corresponding ketimines could be used instead of aldimines, targeting isoindolines featuring a quaternary stereogenic center. Recently, we reported that the reaction of the parent methyl ketimine with the Ruppert-Prakash reagent in the presence of a fluoride source does not yield the expected isoindoline but an indanone derivative arising from a Michael reaction through the C_α (Scheme 3).[11]



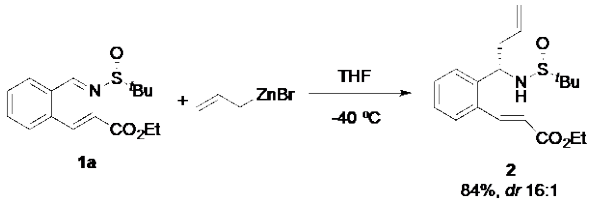
Scheme 3. Intramolecular diastereoselective Michael addition with (*R*)-*N*-(*tert*-butanesulfinyl) ketimines

Moreover, given the versatility of *tert*-butylsulfinylimines as acceptors for virtually any nucleophile, we decided to further explore the scope of our strategy. Herein, we describe the results obtained with respect to the diastereoselective addition of a variety of nucleophiles to *tert*-butylsulfinylimines followed by intramolecular cyclization giving rise to 1,3-disubstituted isoindolines. In addition, the stereodivergent cyclization-giving rise to each diastereoisomer selectively by means of the careful choice of the base is also described.

Results and Discussion

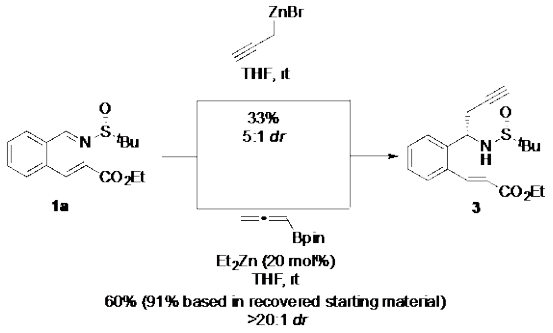
Among the vast number of nucleophiles, which are known to add diastereoselectively to Ellman's imines, we selected some representative ones, such as allyl, propargyl, cyanide, enolate and trichloromethyl groups. In most of the cases, several methodologies are available for the diastereoselective addition of a given nucleophile. Therefore, the reaction conditions had to be optimized independently for each case.

1,2-Addition of allyl reagents: the addition of allylmagnesium bromide was one of the first distereoselective nucleophilic additions to *tert*-butylsulfinylimines reported by Ellman in his seminal report in 1999.[12,13] Many other methodologies have been reported since, including the use of other allylmetal species, mainly organozinc[14] and organoindium[15,16] derivatives, but also allyltrifluoroborates[17] or silanes[18] for the diastereoselective synthesis of homoallylic amines. Most of these methods were tried on our *ortho*-Michael acceptor substrate **1a**, resulting in the use of allylzinc bromide in THF at -40 ºC under the best conditions (Scheme 4).[19]



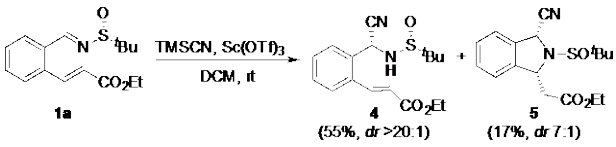
Scheme 4. Allylzinc bromide addition to **1a**

1,2-Addition of propargyl reagents: unlike allyl reagents, the addition of propargyl reagents is almost limited to the use of preformed organozinc derivatives.[20,21] Recently, Fandrick and co-workers reported a zinc catalyzed propargylation of aldehydes[22] and *tert*-butylsulfinylimines[23] with propargyl or allenylboronic acid derivatives. Both, the reaction with the preformed propargylzinc bromide and the zinc-catalyzed addition of allenylboronic pinacol boronic ester were tested on our model substrate **1a**. The results obtained clearly show the superiority of the zinc-catalyzed process over the stoichiometric preformed reagent (Scheme 5) both in terms of chemical yield and diastereoselectivity. Actually, despite the moderate isolated yield, the zinc-catalyzed process is almost quantitative as up to 33% of the starting material can be recovered unaltered from the crude reaction mixture.



Scheme 5. Optimization of the propargylation reaction on substrate **1a**

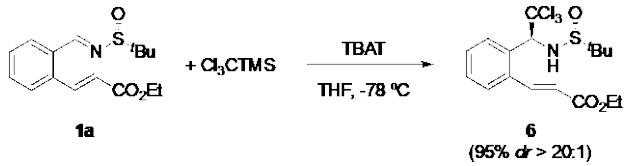
Strecker reaction: the Strecker reaction is among the most longstanding and reliable methods for the stereoselective synthesis of α-amino acids.[24] Regarding the use of *tert*-butylsulfinylimines[25] as electrophilic counterparts in this reaction, two sets of reaction conditions have been described: Et_2AlCN / ^{i}PrOH in THF or TMSCN / Lewis acid in DCM.[26,27] Among the Lewis acids, $Sc(OTf)_3$ was reported to give the best balance between chemical yield and diastereoselectivity. Both methodologies were carried out on our model substrate. Thus, the $Sc(OTf)_3$ catalyzed addition of TMSCN under optimized conditions affords the desired addition product **4** in moderate yield along with a small amount of the isoindoline arising from the tandem process **5** (Scheme 6).[19]



Scheme 6. Strecker reaction on substrate **1a**

Trichloromethylation: stereoselective introduction of a trichloromethyl group is an important task in organic synthesis, as this subunit can be found both in natural products and

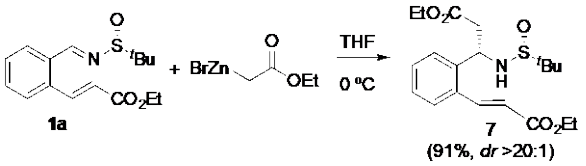
pharmaceutically relevant compounds.[28] Recently, Li and Sun reported the first general method for the asymmetric synthesis of α-trichloromethylamines by using the chlorinated analogue of the Ruppert-Prakash reagent (Cl_3CTMS) and an appropriate fluoride source.[29] In view of our own experience with the Ruppert-Prakash reagent in the tandem AN / IMAMR,[3] we decided to study the use of its chlorinated analogue. A minimal optimization [19] showed that a slight modification of the reported reaction conditions, *i.e.* lowering the reaction temperature to -78 ºC, suppressing the use of 4Å MS (which proved deleterious for our process) and using freshly sublimed Cl_3CTMS[30] enabled us to obtain the desired product **6** in excellent yield (95%) as a single diastereoisomer (Scheme 7).



Scheme 7. Trichloromethylation Reaction on Substrate **1a**

***Aza*-Reformatsky reaction**: the addition of an enolate or an enolate analogue to an imine and the conjugate addition of a nitrogen centred nucleophile onto an α,β-unsaturated carbonylic compound (aza-Michael reaction) are the most common methods for the synthesis of β-amino carbonylic compounds. Amongst them, β-amino acids (β-AAs) are, unarguably, the most important due to their significant role in medicinal chemistry [31] as well as their presence as structural units of β-peptides, compounds with better pharmacological profiles than natural peptides, displaying highly stable secondary structures and being more resistant to proteolytic degradation.[32]

Thus, by coupling an aza-Reformatsky reaction [33] with an aza-Michael process two β-amino acid units could be assembled on a single *N* atom. We were delighted to find that the addition of the Reformatsky reagent derived from ethyl bromoacetate to our model substrate **1a** proceeded in very high yield and with complete diastereoselectivity (Scheme 8).



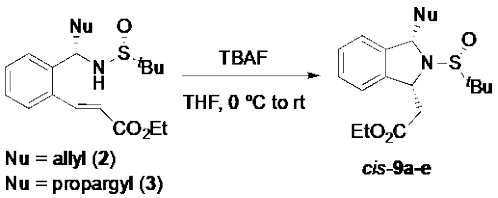
Scheme 8. Aza-Reformatsky reaction on substrate **1a**

Stereochemical outcome during the nucleophilic addition step: for the addition of allyl, propargyl, cyano and zinc enolate a chelated transition state is assumed to control the diastereoselectivity as proposed in the original reports (for detailed TS structures, see SI). [15,24,28,33] On the contrary, the trichloromethylation is reported to take place through an open transition state, which accounts for the opposite configuration at the α-stereocenter (for detailed TS structures, see SI). [29] The configuration of this stereocenter is crucial in the stereochemical outcome during the intramolecular *aza*-Michael reaction (*vide infra*).

Both, the allylation and the propargylation with the corresponding organozinc reagents take place *via* a well-established six membered chair-like transition state. [34] Very similar transition states can be invoked for the Reformatsky reactions. In the latter case, the same relative configuration would be obtained regardless of whether the C- or the O-enolate is formed. [35] Finally, a related five-membered transition state explains the diastereoselectivity observed in the Strecker reaction. On the other hand, the Cram product arising from a non-chelation-controlled transition state accounts for the stereochemical outcome in the trichloromethylation (and trifluoromethylation [3]) reaction. In this case, either the conformation in which the *tert*-butyl group adopts an antiperiplanar arrangement with respect to the C=N bond or the s-*cis* arrangement favoured by an intramolecular hydrogen bond between the oxygen of the sulfinyl group and the iminic hydrogen give rise to the observed diastereoisomer.

Stereodivergent intramolecular aza-Michael reaction (IMAMR) on substrates 2, 3, 4, 6, 7 and 8: with a small library of addition products available (trifluoromethylated product **8** has previously been reported by us, see ref 3), we turned to study the IMAMR. Cyclization with an inorganic base such as fluoride (TBAF) affords the *cis* products *cis*-**9a-e** [36] in good yields and as single diastereoisomers, in most of the cases (Table 1, entries 1,2,4-6). Substrate **4** leads to decomposition, starting material **1a** arising from a *retro*-Strecker reaction being the only identifiable product (Table 1, entry 3).

Table 1. IMAMR on substrates **2**, **3**, **4**, **6**, **7** and **8**

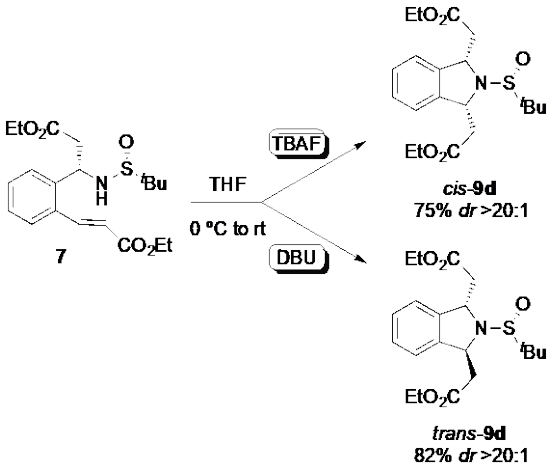


Nu = allyl (2)
Nu = propargyl (3)
Nu = CN (4)
Nu = CCl_3 (6)
Nu = CH_2CO_2Et (7)
Nu = CF_3 (8)

Entry	Substrate	*cis*-**9** (%)[a]	*dr* [b]
1	**2**	*cis*-**9a** (84)	> 20:1
2	**3**	*cis*-**9b** (88)	> 20:1
3	**4**	-	-
4	**6**	*cis*-**9c** (76)[c]	> 20:1
5	**7**	*cis*-**9d** (75)	> 20:1
6	**8**	*cis*-**9e** (81) [c]	> 20:1

[a] Yield of the isolated product. [b] Determined by ^{1}H NMR on the crude reaction mixture. [c] Reactions performed at -60º C

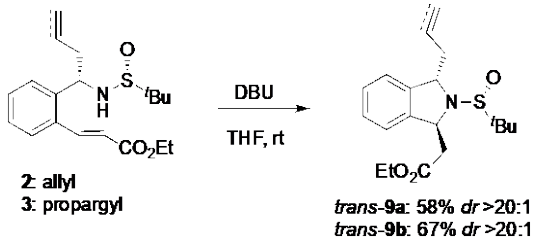
Isoindoline *cis*-**9d** arising from the Reformatsky substrate **7** renders a *meso* compound after elimination of the chiral auxiliary, resulting in loss of the chiral information (Table 1, entry 7). Therefore, we decided to evaluate other bases in order to obtain the diastereodivergent cyclization leading to *trans*-**9d**. After an extensive screening of both inorganic and organic bases, we found that the use of DBU at room temperature affords *trans*-**9d** with complete diastereoselectivity and good yield (Scheme 9).[37]



Scheme 9. Stereodivergent cyclization of substrate **7** giving rise to C2 symmetric isoindoline *trans*-**9d**

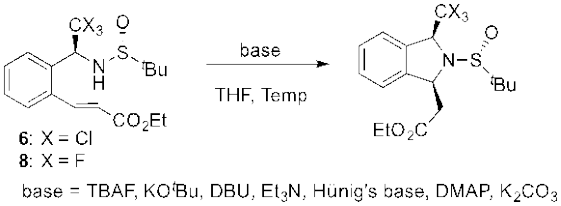
Besides the inherent importance of diastereodivergent transformations,[38] which make the selective synthesis of different diastereoisomers from a single chiral precursor possible, in this example we were able to switch from a synthetically uninteresting *meso* compound to an unprecedented *C2-symmetric*[39] isoindoline core, which can be transformed into promising scaffolds for asymmetric synthesis (*vide infra*).

Subsequently, we investigated the generality of this stereodivergent process with the rest of the substrates and found that *trans*-**9a,b** could be obtained in good yields and complete diastereoselectivities from substrates **2** and **3** (Scheme 10).



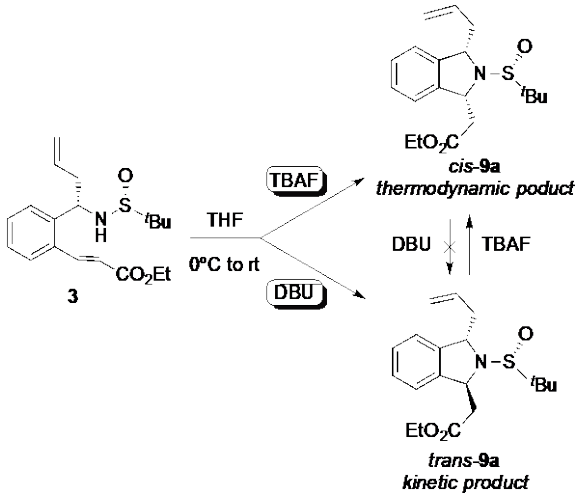
Scheme 10. *Anti* cyclization of substrates **2** and **3**

Once again, substrate **4** was reluctant to cyclization, the *retro*-Strecker pathway being preferred, presumably due to the superior leaving group ability of the cyano group. Trihalomethylated substrates **6** and **8** afforded the corresponding *cis*-isoindolines regardless of the base used (Scheme 11).



Scheme 11. *Syn* cyclization of substrates **6** and **8**

Stereochemical outcome during the cyclization step: a series of experiments were then carried out in order to rationalize the stereochemical outcome observed in each case. First of all, complete epimerization to *cis*-**9a** was observed when *trans*-**9a** was treated with TBAF, while *cis*-**9a** remained unaltered upon treatment with DBU (Scheme 12).



Scheme 12. Investigation on the thermodynamic/kinetic origin of *cis*- and *trans*-**9a**

These observations indicate that *cis*-products would be the thermodynamically more stable. In this sense, others as well as our group have reported [3,10] that placing both substituents *anti* to the bulky SO^{t}Bu group (thus, *syn* to each other) renders the most stable product (Figure 1). The inherent reversibility of the process would account for the formation of the thermodynamically most stable product when a strong enough base is used (see Scheme 15).

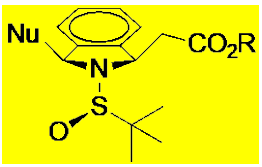
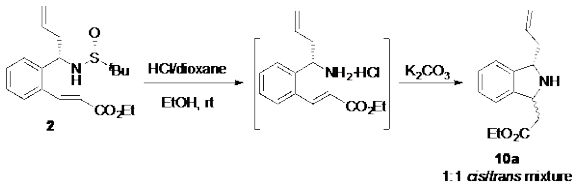


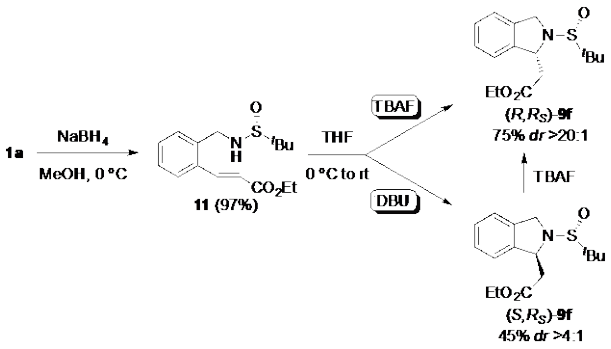
Figure 1. Thermodynamically favoured 1,2-*trans*-2,3-*trans* (1,3-*cis*) arrangement in 1,2,3-trisubstituted isoindolines.

In a further step, the origin of the kinetic stereoinduction in the TBAF mediated reaction was investigated. As the intramolecular *aza*-Michael process is performed on substrates bearing two stereocenters (the chiral auxiliary plus the newly created upon nucleophilic addition) a double stereoinduction effect has to be considered: either one of the stereocenters might be exerting the stereocontrol while the other would merely be a spectator or both exert their own stereoinduction in a classical match / mismatch scenario. Hence, experiments in the presence of only one of the stereocenters were conducted independently. Removal of the chiral auxiliary on intermediate **2** spontaneously afforded, upon basification, an equimolecular mixture of diastereoisomeric isoindolines *cis*- and *trans*-**10a** suggesting lack of stereoinduction attributable to the stereocenter formed upon nucleophilic addition (Scheme 13).



Scheme 13. Non-selective IMAMR

Finally, reduction product **11** was obtained in excellent yield and submitted to cyclization mediated by the two bases: TBAF and DBU (Scheme 14).



Scheme 14. Evaluation of the stereoinduction of the chiral auxiliary

Once again, stereodivergent reaction pathways were observed for each base. The TBAF mediated reaction affords (1*R*,*RS*)-**9f**, while the reaction with DBU gives rise to *pseudo*-enantiomeric (1*S*,*RS*)-**9f** which evidences the stereocontrol exerted by the chiral auxiliary.

The relative configuration of the newly created stereocenter in (1*R*,*RS*)-**9f** has been assigned by means of X-ray crystallography to be *R* (Figure 2). Suitable crystals were obtained by slow evaporation of a solution of (1*R*,*RS*)-**9f** in hexane at room temperature.[40]

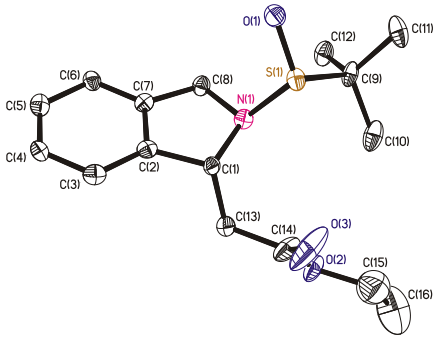


Figure 2. ORTEP diagram of (*R*,*RS*)-**9f**

All these data suggest that the kinetic stereoinduction can mainly be attributed to the chiral auxiliary giving rise, under kinetic conditions, to a 1*S* stereocenter during the ring-forming event regardless of the stereochemistry of the previously set chiral center. However, the moderate diastereoselectivity observed in the absence of a second stereocenter indicates some reinforcement under double stereoinduction conditions (*match* case). A tentative transition state that would account for the observed stereochemical outcome has been proposed (Figure 3).

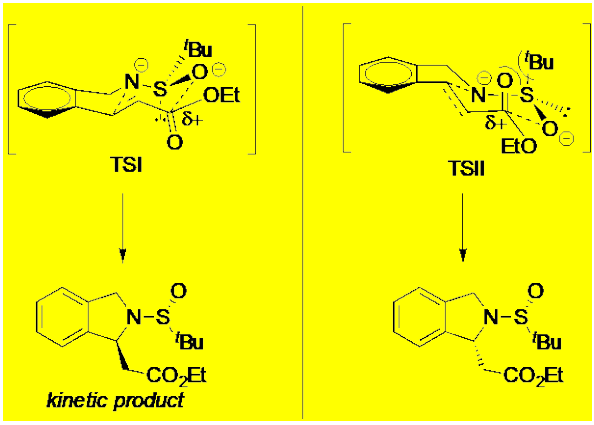
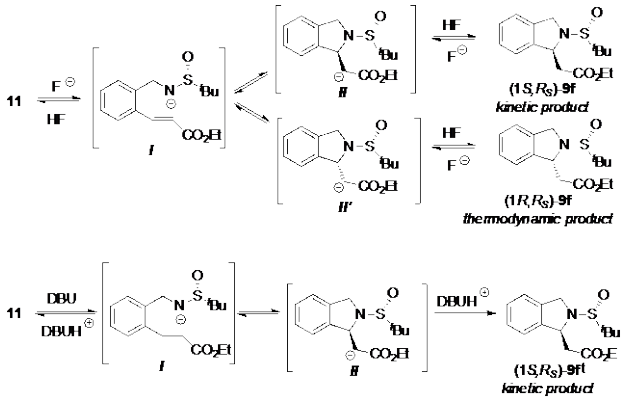


Figure 3. Possible origin of the kinetic stereocontrol during the cyclization step

A stabilizing electrostatic interaction between the negatively charged oxygen of the sulfinamide group and the electrophilic ester carbonyl carbon leading to a rigid six-membered chair-like transition state could explain the high diastereoselectivities observed.[41] Hence, in TSI, responsible of the observed stereocontrol, the bulky *tert*-butyl group occupies a pseudo-equatorial position while it would destabilize diastereotopic TSII by 1,3-diaxial interations.

A rationale for the selective switch from the thermodynamic product to the kinetic control products by the careful choice of the base is depicted in Scheme 15.

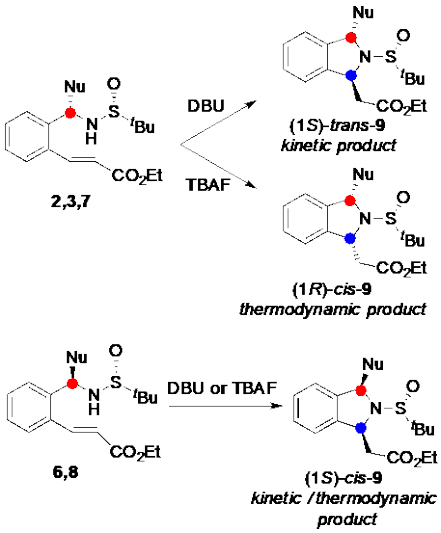


Scheme 15. Reaction pathways towards the kinetic and the thermodynamic control products

The use of a stronger base, such as F^-, gives rise to the thermodynamic product (1*R*,*RS*)-**9f**, while a weaker base affords the kinetic product (1*S*,*RS*)-**9f**. Presumably, the use of a weaker base renders the protonation step irreversible, thus preventing the equilibration (1*R*,*RS*)-**9f** /(1*S*,*RS*)-**9f** through the common open chain intermediate ***I***. [42]

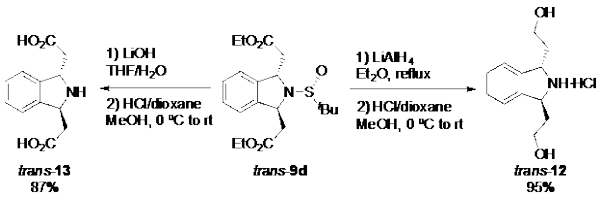
Regarding the 1,3-disubstitued products, depending on the stereochemistry of the addition product the thermodynamic and kinetic controlled products would fit in or not. The addition products arising from a cyclic transition state (**2**, **3**, **7**) display the same configuration (Scheme 16, stereocenter highlighted in red). Cyclization under kinetic conditions (DBU) affords the 1*S* products (Scheme 16, stereocenter highlighted in blue), which, in these cases, display a *trans* relative configuration; therefore, they undergo epimerization to the more stable *cis* product under thermodynamic conditions (TBAF). On the other hand, trihalomethylation products

(**6**, **8**) are formed through an open chain transition state and, hence, display the opposite configuration (Scheme 16, stereocenter highlighted in red). Once again, 1*S* products (Scheme 16, stereocenter highlighted in blue) are obtained upon cyclization under kinetic conditions. In these cases, the relative configuration is *cis* and, therefore, the kinetic and thermodynamic products are coincident preventing the formation of the *anti* isomer regardless of the base used (Scheme 16).



Scheme 16. Differences between the thermodynamic and kinetic products depending on the nucleophile used

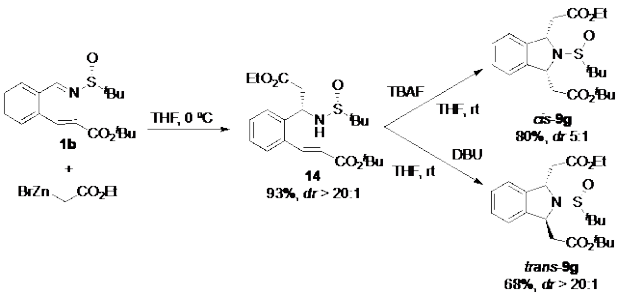
Structural modifications on *C2*-symmetric isoindoline *trans*-9d: among the 1,3-disubstituted isoindolines obtained, *trans*-**9d** deserves special attention as it can be regarded as a *C2*-symmetric benzo-fused analogue of bis-β-proline. This structural motif may find applications in two main fields, *i.e.* asymmetric catalysis and synthesis of modified peptides. With these two possible applications in mind, a few structural modifications have been carried out as depicted in Schemes 17-19.



Scheme 17. Reduction and hydrolysis of *trans*-9d

Double ester reduction with $LiAlH_4$ or basic hydrolysis, respectively, afforded diol *trans*-**12** or diacid *trans*-**13** in excellent yields, after removal of the *tert*-butanesulfinyl group in methanolic HCl.

Orthogonal manipulation of both ester ends would be highly desirable with regard to asymmetric catalysis and, specially, for the independent elongation of the *C*-terminus in modified peptides. Therefore, we decided to repeat the Reformatsky / IMAMR sequence on substrate **1b** containing a *tert*-butyl acrylate moiety (Scheme 18). In this case, isoindoline products *cis*- and *trans*-**9g** are selectively obtained in good overall yields. The lower diastereoselectivity observed during the cyclization of **14** using TBAF as base can be explained by the diminished thermodynamic stability of the *syn* product due to the presence of a bulky *tert*-butyl group. This result further supports the thermodynamic origin of the diastereoselectivity in this case. Once again, cyclization with DBU affords the isomeric isoindoline *trans*-**9g**, in good yield and complete diastereoselectivity.



Scheme 18. Reformatsky / IMAMR sequence on substrate **1b**

Products **9g** feature two well-differentiated ester groups, which allow for chemoselective manipulation of both molecule ends. Thus, two independent β-amino acid subunits have been attached to a single *N*-atom making use of two complementary approaches, *i.e.* a C-C bond forming aza-Reformatsky reaction and an *N*-heterocyclic ring formation by an IMAMR (Figure 3). In this case, both diastereoisomers keep their chirality due to the desymmetrization of the ester ends rendering synthetically useful scaffolds.

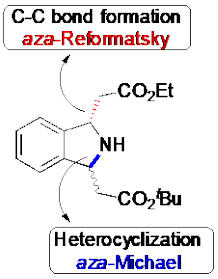
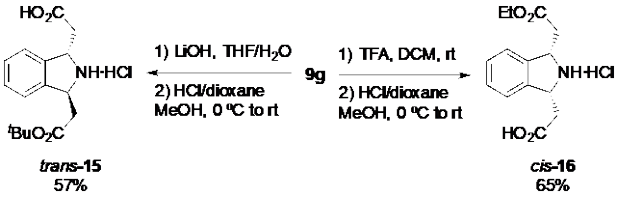


Figure 3. Modular introduction of a bis β-Amino Acid unit

Orthogonal hydrolysis of the ester functionalities were performed under basic and acidic conditions affording monoacids *trans*-**15** and *cis*-**16** starting from diesters *cis*-**9g** and *trans*-**9g**, respectively (Scheme 19).



Scheme 19. Orthogonal hydrolysis of the ethyl and *tert*-butyl esters

Finally, Ellman's auxiliary was removed from all final products by treatment with anhydrous HCl in methanol affording the corresponding hydrochlorides in good yields (for details, see SI).

Conclusion

The AN / IMAMR sequence has been generalized to some representative non-fluorinated nucleophiles giving rise to a family of 1,3-disubstituted isoindolines from readily available starting

materials. Products are obtained in good chemical yields and as single diastereoisomers.

Moreover, we have found that the appropriate choice of the base enables the development of a stereodivergent intramolecular *aza*-Michael reaction affording either *cis*- or *trans*-isoindolines, selectively. Remarkably, C_2-symmetric isoindoline *trans*-**9d** can be obtained through a convenient reaction route in good overall yield and diastereoselectivity. In addition, some structural modifications have been carried out resulting in a small library of C_2-symmetric isoindolines.

Among the 1,3-disubstituted isoindolines synthesized, products *cis*- and *trans*-**9g** noteworthy, displaying two orthogonally protected β-amino acid subunits attached to a single *N* atom. Orthogonal hydrolysis of both ester moieties enables the selective synthesis of the corresponding monoacids.

Experimental Section

General methods: Reactions were carried out under a nitrogen atmosphere unless otherwise indicated. Solvents were purified prior to use: THF and PhMe were distilled from sodium and CH_2Cl_2 from calcium hydride. The reactions were monitored with the aid of TLC on 0.25 mm precoated silica-gel plates. Visualization was carried out with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size: 0.040–0.063 mm). ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents. Coupling constants (*J*) are given in Hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. The abbreviation br indicates a broad signal.

Reaction of compound 1a with allylzinc bromide: a 1M solution of allylzinc bromide in THF was prepared by stirring 0.4 mL of allyl bromide and 1g of activated Zn in 2.5 mL of anhydrous THF at 50 ºC. 0.22 mL of this freshly prepared solution were added to a solution of substrate **1a** (61 mg, 0.20 mmol) in 2 mL of dry THF at 0 ºC. After stirring for 10 min at 0 ºC the reaction mixture was quenched with saturated NH_4Cl aqueous and extracted three times with AcOEt. Flash chromatography afforded compound **2** as a colourless oil (59 mg, 84%).

(*E*)-Ethyl 3-{2-[1-((1*S*)-*N*-(*R*$_S$)-*tert*-butanesulfinylamino)but-3-enyl]phenyl}acrylate (2): $[\alpha]^{25}_D$ = -82.0 (*c* = 1.0 in $CHCl_3$) ^{1}H NMR (300 MHz,$CDCl_3$): 1.19 (s, 9H), 1.33 (t, *J* = 7.1 Hz, 3H), 2.48 (dt, *J* = 14.1, 8.3 Hz, 1H), 2.57-2.65 (m, 1H), 3.72 (d, *J* = 2.4 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.81 (ddd, *J* = 8.2, 5.5, 2.5 Hz, 1H), 5.15.5.20 (m, 2H), 5.71 (dddd, *J* = 16.6, 10.3, 8.3, 5.9 Hz, 1H), 6.31 (d, *J* = 15.8 Hz, 1H), 7.27-7.43 (m, 3H), 7.53 (dd, *J* = 7.6, 1.3 Hz, 1H), 8.18 (d, *J* = 15.8 Hz, 1H) ; 13C NMR (75.5 MHz, CDCl3): 14.2 (CH_3), 22.5 (3 x CH_3), 42.5 (CH_2), 53.9 (CH), 55.7 (C), 60.5 (CH_2), 119.6 (CH_2), 120.8 (CH), 127.2 (CH), 127.8 (CH), 128.2 (CH), 129.8 (CH), 133.4 (C), 133.7 (CH), 140.0 (C), 141.6 (CH). 166.5 (C). HRMS (EI): m/z calcd for $C_{19}H_{28}NO_3S$: 350.1784 [M^+ + 1]; found: 350.1780.

Zinc-catalyzed propargylation of substrate 1a: to a solution containing **1a** (31 mg, 0.10 mmol) and allenylpinacolboronic ester (27 µL, 15mmol, 1.5 equiv) in 1 mL of dry THF Et_2Zn (1.1M in toluene, 36 µL, 0.02 mmol) was added subsurfacely. When no further conversion was observed, as judged by TLC, the reaction was quenched by the addition of water (1 mL) and extracted with AcOEt (3x 1mL). Flash chromatography afforded compound **3** as a colourless oil (21 mg, 60%) along with 11 mg of unreacted starting material (35%).

(*E*)-Ethyl 3-{2-[1-((1*S*)-*N*-(*R*$_S$)-*tert*-butylsulfinamido)but-3-ynyl]phenyl}acrylate (3): $[\alpha]^{25}_D$ = -57.3 (*c* = 1.0 in $CHCl_3$) ^{1}H NMR (300 MHz,$CDCl_3$): 1,24 (s, 9H), 1.34 (t, *J* = 7.1 Hz, 3H), 2.13 (t, *J* = 2.7 Hz, 1H), 2.70 (ddd, *J* = 2.7, 7.5, 16.8 Hz, 1H), 2.79 (ddd, *J* = 2.7, 5.7, 16.8 Hz, 1H), 4.06 (d, *J* = 4.0 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.94 (ddd, *J* = 4.0, 5.7, 7.5, 1H), 6.33 (d, *J* = 15.8 Hz, 1H), 7.31-742 (m, 2H), 7.48 (dd, *J* = 1.5, 7.6 Hz, 1H), 7.55 (dd, *J* = 1.6, 7.5, 1H), 8.15 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (75.5 MHz, CDCl3): 14.2 (CH_3), 22.5 (3 x CH_3), 27.8 (CH_2), 53.7 (CH), 56.0 (C), 60.5 (CH_2), 72.5 (CH), 79.3 (C), 121.3 (CH), 127.3 (CH), 127.9 (CH), 128.3 (CH), 129.8 (CH), 133.6 (C), 138.6 (C), 141.2 (CH), 166.3 (CH). HRMS (EI): m/z calcd for $C_{19}H_{26}NO_3S$: 348.1628 [M^+ + 1]; found: 348.1635.

Scandium (III) triflate catalyzed Strecker reaction on substrate 1a: to a solution of **1a** (62 mg, 0.20 mmol) in dry DCM (2 mL) $Sc(OTf)_3$ (20 mg, 20 mol%) was added followed by the dropwise addition of TMSCN (53µL, 0.40 mmol, 2 equiv.). The reaction mixture was stirred at room temperature for 3 days. The solvent was removed under reduced pressure and the crude reaction mixture purified by flash chromatography affording **4** (37 mg, 55%) and **5** (11mg, 17%), both as colourless oils.

(*E*)-Ethyl 3-{2-[((*R*)-*N*-(*R*$_S$)-*tert*-butylsulfinamido)(cyano)methyl]phenyl}acrylate (4): $[\alpha]^{25}_D$ = +84.9 (*c* = 1.0 in $CHCl_3$) ^{1}H NMR (300 MHz,$CDCl_3$): 1.19 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.60 (d, *J* = 8.2 Hz, 1H), 5.61 (d, *J* = 8.2 Hz, 1H), 6.37 (d, *J* = 15.0 Hz, 1H), 7.41-7.44 (m, 2H), 7.60-7.63 (m, 1H), 7.68-7.71 (m, 1H), 7.95 (d, *J* = 15.0, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 14.1 (CH_3), 22.3 (3 x CH_3), 48.0 (CH), 57.1 (C), 60.6 (CH_2), 117.7 (C), 122.1 (CH), 127.7 (CH), 128.8 (CH), 130.1 (CH), 130.4 (CH), 131.9 (C), 133.5 (C), 139.8 (CH), 166.0 (C). HRMS (EI): m/z calcd for $C_{17}H_{23}N_2O_3S$: 335.1424 [M^+ + 1]; found: 335.1440.
For complete characterization of minor product **5**, see SI.

Trichloromethylation of substrate 1a: to a suspension of **1a** (61 mg, 0.20 mmol) and TBAT (113 mg, 0.20 mmol, 1 equiv) in 1.5 mL of dry THF, a solution of Cl_3CTMS (57 mg, 0.30 mmol, 1.5 equiv) in dry THF (1 mL) was added dropwise at -78ºC. Upon completion, the reaction was quenched with saturated NH_4Cl_{aq} (1 mL) and extracted with AcOEt (3 x 1 mL). Flash chromatography afforded **6** (81 mg, 95%) along with a small amount of unreacted starting material (4 mg, *ca*. 5%).

(*E*)-Ethyl 3-{2-[1-((1*S*)-*N*-(*R*$_S$)-*tert*-butylsulfinamido)-2,2,2-trichloroethyl]phenyl} acrylate (6): $[\alpha]^{25}_D$ = -99.5 (*c* = 1.0 in $CHCl_3$) ^{1}H NMR (300 MHz,$CDCl_3$): 1.27 (s, 9H), 1.32 (t, *J* = 7.1 Hz, 3H), 4.20 (d, *J* = 8.3 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 5.43 (d, *J* = 8.3 Hz, 1H), 6.35 (d, *J* = 15.6 Hz, 1H), 7.32-7.48 (m, 2H), 7.51-7.52 (m, 1H), 7.66-7.69 (m, 1H), 8.16 (d, *J* = 15.6, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 14.1 (CH_3), 22.5 (3 x CH_3), 57.5 (C), 60.6 (CH_2), 68.9 (CH), 102.5 (C), 123.1 (CH), 126.8 (CH), 127.8 (CH), 129.5 (CH), 130.4 (CH), 129.7 (CH), 135.3 (2 x C), 141.4 (CH), 166.1 (C). HRMS (EI): m/z calcd for $C_{13}H_{15}Cl_3NO_2$: 322.0163 [M^+ + 1 - SO^{t}Bu]; found: 322.0162.

***Aza*-Reformatsky reaction:** the required Reformatsky reagent was prepared as follows: to a suspension of activated Zn (200 mg, 1.3 equiv) in refluxing Et_2O (5mL) ethyl bromoacetate (0.30 mL) was added dropwise. After refluxing the reaction mixture for 1h a light green solution was obtained. This solution was titrated with iodine and its concentration was always found to be around 0.4M. 0.42 mL of this solution (0.17 mmol, 1.7 equiv) were added dropwise at 0 ºC to a solution of **1a** (31 mg, 0.1 mmol) in dry THF (1 mL). After stirring for 15 min. at this temperature the reaction was allowed to reach room temperature and further stirred for 1h. The reaction was quenched with saturated NH_4Cl_{aq} (1mL) and extracted with AcOEt (3 x 1mL). Flash chromatography afforded **7** as a colourless oil (36mg, 91%).

(*E*)-Ethyl 3-{2-[1-((1*S*)-*N*-(*R*$_S$)-*tert*-butylsulfinamido)-3-ethoxy-3-oxopropyl]phenyl} acrylate (7): $[\alpha]^{25}_D$ = -67.2 (*c* = 1.0 in $CHCl_3$) ^{1}H NMR (300 MHz,$CDCl_3$): 1.13 (t, *J* = 7.1 Hz, 3H), 1.15 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H), 2.69 (s, 1H), 2.82 (d, *J* = 2.1 Hz, 1H), 4.04 (q, *J* = 7.1 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.70 (d, *J* = 4.7 Hz, 1H), 5.04 (dd, *J* = 11.3, 6.5 Hz, 1H), 6.26 (d, *J* = 15.8 Hz, 1H), 7.21-7.30 (m, 2H), 7.32-7.37 (m, 1H), 7.47 (dd, *J* = 7.5 1.6 Hz, 1H), 8.10 (d, *J* = 15.8, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 13.9 (CH_3), 14.2 (CH_3), 22.4 (3 x CH_3), 41.3 (CH_2), 52.6 (CH), 55.6 (C), 61.0 (CH_2), 61.4 (CH_2), 121.1 (CH), 127.3 (CH), 127.9 (CH), 128.2 (CH), 129.8 (CH), 133.4 (C), 138.8 (C), 141.2 (CH), 166.3 (C), 170.9 (C). HRMS (EI): m/z calcd for $C_{20}H_{30}NO_5S$: 396.1839 [M^+ + 1]; found: 396.1838.

IMAMR: to a solution of the substrate (0.1 mmol) in dry THF (1 mL) the indicated base was added at room temperature. Upon completion (typically *ca*. 30 min), the reaction was quenched with saturated NH_4Cl_{aq} (1 mL) and extracted with AcOEt (3 x 1 mL). Flash chromatography afforded the indicated products.

Ethyl 2-{(1*R*,3*S*)-*N*-[(*R*$_S$)-*tert*-butylsulfinyl]-3-(prop-2-en-1-yl)-isoindolin-1-yl} acetate (*cis*-9a): $[\alpha]^{25}_D$ = -23.5 (*c* = 1.0 in $CHCl_3$) ^{1}H NMR (300 MHz,$CDCl_3$): 1,28 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H), 2.38 (ddd, *J* = 14.0, 9.2, 8.6 Hz, 1H), 2.70 (dd, *J* = 15.7, 6.2 Hz, 1H), 2.73-2.81 (m, 1H), 2.78 (dd, *J* = 15.7, 8.0 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 1H), 5.05 (dtd, *J* = 17.1, 1.8, 1.1 Hz, 1H), 5.10-5.14 (m, 1H), 5.39 (dd, *J* = 8.0, 6.2 Hz, 1H), 5.76 (dddd, *J* = 17.0, 10.2, 8.4, 5.9 Hz, 1H), 7.16-7.23 (m, 4H); ^{13}C NMR (75.5 MHz, CDCl3): 14.2 (CH_3), 23.6 (3 x CH_3), 42.7 (CH_2), 44.3 (CH_2), 57.1 (CH), 57.6 (C), 60.6 (CH_2), 69.1 (CH), 118.4 (CH_2), 122.0 (CH), 123.0 (CH), 127.4 (CH), 127.4 (CH), 133.9 (CH), 140.7 (C), 142.7 (C), 170.6 (C). HRMS (EI): m/z calcd for $C_{19}H_{28}NO_3S$: 350.1784 [M^+ + 1]; found: 350.1780.

$NaBH_4$ reduction of substrate 1a: 11 mg of $NaBH_4$ (3 equiv) were added to a stirred solution of **1a** (31 mg, 0,1 mmol) in 1 mL of anhydrous MeOH at 0 ºC. After consumption of the starting material (20 min), the reaction was quenched with saturated $NaHCO_3$ aqueous and extracted twice with AcOEt. Flash chromatography using a 1:1 mixture of hexanes and AcOEt afforded compound **11** as a colourless oil (30 mg, 97%).

(*E*)-Ethyl 3-(2-[*N*-(*R*$_S$)-*tert*-butanesulfinylaminomethyl]phenyl)acrylate (11): $[\alpha]^{25}_D$ = +45.0 (*c* = 1.0 in $CHCl_3$) ^{1}H NMR (300 MHz,$CDCl_3$): 1.18 (s, 9H), 1.30 (t, J = 7.2 Hz, 3H), 3.48 (dd, J = 4.8, 7.4 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 4.35 (dd, J = 7.4, 13.3 Hz, 1H), 4.41 (dd, J = 4.8, 13.3 Hz, 1H), 6.34 (d, J = 15.8 Hz, 1H), 7.29-7.35 (m, 3H), 7.57-7.59 (m, 1H), 7.98 (d, J = 15.8 Hz, 1H) ; 13C NMR (75.5 MHz, CDCl3): 14.2 (CH3), 22.4 (3 x CH3), 47.2 (CH2), 55.8 (C), 60.4 (CH2), 120.1 (CH), 126.8 (CH), 128.4 (CH), 129.9 (CH), 130.0 (CH), 133.8 (C), 136.8 (C), 141.3 (CH), 166.4 (C). HRMS (EI): m/z calcd for $C_{16}H_{24}NO_3S$: 310.1471 [M^+ + 1]; found: 310.1455.

$LiAlH_4$ reduction of substrate *trans*-9d: to a suspension of $LiAlH_4$ 29 mg (0.76 mmol, 2 equiv) in dry Et_2O (2mL), a solution of *trans*-**9d** (151 mg, 0.38 mmol) in dry Et_2O (2ml) was added dropwise. The mixture was refluxed until complete consumption of the starting material was observed by TLC (*ca.* 2h). After addition of $Na_2SO_4{\cdot}10H_2O$ and stirring for 30 minutes, water (5mL) and AcOEt (5 mL) were added. The organic layer was separated and the aqueous layer was extracted with AcOEt (2 x 5mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography on SiO_2 using hexane:AcOEt (1:1) as the eluent afforded *trans*-**12** as a yellowish foam (112 mg, 0.36 mmol, 95%).

2,2'-{(1*S*,3*S*)-*N*-[(*R*$_S$)-*tert*-Butylsulfinyl)]isoindoline-1,3-diyl}diethanol hydrochloride (*trans*-12): white foam; $[\alpha]^{25}_D$ = -13.1 (*c* = 1.0 in EtOH) ^{1}H NMR (300 MHz, MeOH): 2.07-2.19 (m, 2H), 2.25-2.31 (m, 2H), 3.78-3.90 (m,4H), 5.16 (dd, *J* =

8.6, 3.3 Hz, 2H), 7.40-7.47 (m, 4H); ^{13}C NMR (75.5 MHz, CD_3OD): 24.22 (CH), 59.31 (CH_2), 128.31 (4 xCH). HRMS (EI): m/z calcd for $C_{12}H_{18}NO_2$: 208.1332 [M^+ + 1]; found: 208.1333.

Basic hydrolysis of substrate *trans*-9d: to a solution of *trans*-**9d** (144 mg, 0.36 mmol) in 3mL of THF:H_2O (5:1), LiOH (86 mg, 3.6 mmol, 10 equiv.) was added portionwise at 0 ºC. Upon completion (TLC, *ca.* 24h), water (5 mL) and AcOEt (5 mL) were added and the layers separated. The aqueous layer was acidified with HCl conc and extracted with DCM (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford *trans*-**13** as a white solid (106 mg, 0.31 mmol, 87%)

2,2'-{(1*S*,3*S*)-*N*-[(*R*$_S$)-*tert*-Butylsulfinyl)]isoindoline-1,3-diyl}diacetic acid (*trans*-13):
$[\alpha]^{25}_D$ = -74.7 (*c* = 0.5 in MeOH) ^{1}H NMR (300 MHz, MeOH): 3.07 (dd, J = 17.9, 8.8 Hz, 2H), 3.23 (dd, J = 17.9, 4.4 Hz, 2H), 5.38 (dd, J = 8.5, 4.4 Hz, 2H), 7.44 (m, 4H) ; ^{13}C NMR (125.8 MHz, D_2O): 24.22 (CH), 59.31 (CH_2), 128.31 (4 xCH). HRMS (EI): m/z calcd for $C_{12}H_{18}NO_2$: 208.1332 [M^+ + 1]; found: 208.1333.

Selective basic hydrolysis of substrate *trans*-9g: to a solution of *trans*-**9g** (60 mg, 0.14 mmol) in 1.2 mL of THF:H_2O (5:1), LiOH (20 mg, 0.84 mmol, 6 equiv) was added portionwise at 0 ºC. Upon completion (TLC, *ca.* 24h), water (2 mL) and AcOEt (2 mL) were added and the layers separated. The aqueous layer was acidified with HCl_{conc} and extracted with DCM (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was dissolved in anhydrous ethanol (1mL) and treated with 10 equiv of dry HCl in dioxane (4M). Upon disappearance of the starting material, most of the solvent was removed in vacuum and diethylether was added to afford *cis*-**15** as a white solid (26 mg, 0.08 mmol, 57%).

2-((1*S*,3*R*)-3-(2-*tert*-Butoxy-2-oxoethyl)isoindolin-1-yl)acetic acid hydrochloride (*trans*-15): $[\alpha]^{25}_D$ = +6.3 (*c* = 1.0 in $CHCl_3$) ^{1}H NMR (300 MHz, MeOH): 1.47 (s, 9H), 2.94-3.27 (m, 4H), 5.27-5.42 (m, 2H), 7.42-7.44 (m, 4H);^{13}C NMR (75.5 MHz, CD_3OD): 28.3 (3xCH_3), 38.1 (CH_2), 39.2 (CH_2), 61.6 (CH), 61.7 (CH), 83.3 (C), 123.9 (CH), 124.0 (CH), 130.7 (CH), 137.8 (CH), 137.9 (C), 138.0 (C), 170.8 (C), 172.0 (C). HRMS (EI): m/z calcd for $C_{16}H_{21}NO_4$: 291.1387 [M^+]; found: 290.1384.

Selective acidic hydrolysis of substrate *cis*-9g: to a solution of *cis*-**9g** (60 mg, 0.14 mmol) in 2 mL of DCM, TFA (0.11 mL, 1.40 mmol, 10 equiv) was added dropwise at 0 ºC. Upon completion (TLC, *ca.* 3h), water (2 mL) and DCM (2 mL) were added and the layers separated. The organic layer extracted with saturated Na_2CO_{3q} (3 x 10 mL), the combined aqueous layers acidified with HCl_{conc} and extracted with DCM (3x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was dissolved in anhydrous ethanol (1mL) and treated with 10 equiv of dry HCl in dioxane (4M). Upon disappearance of the starting material, most of the solvent was removed in vacuum and diethylether was added to afford *cis*-**16** as a white solid (27 mg, 0.09 mmol, 65%).

2-((1*R*,3*S*)-3-(2-Ethoxy-2-oxoethyl)isoindolin-1-yl)acetic acid hydrochloride (*cis*-16): $[\alpha]^{25}_D$ = -34.7 (*c* = 1.0 in $CHCl_3$)^{1}H NMR (300 MHz, MeOH): 1.30 (t, *J*=7.1 Hz, 3H), 2.97-3.10 (m, 2H), 3.36-3.46 (m, 2H), 4.21-4.29 (m, 2H), 5.23-5.30 (m, 2H), 7.37-7.48 (m, 4H); ^{13}C NMR (75.5 MHz, CD_3OD): 14.5 (CH_3), 37.8 (CH_2), 38.0 (CH_2), 61.4 (CH), 61.5 (CH), 62. 5 (CH_2), 123.7 (2xCH), 130.7 (CH), 130.8 (CH), 137.8 (C), 137.9 (C),171.5 (C), 171.6 (C). $C_{14}H_{18}NO_4$: 264.1230 [M^++*1*]; found: 264.1240.

Removal of the chiral auxiliary from the final products: dry HCl (4M in dioxane) was added dropwise to a solution of substrate (0.1 mmol) in dry EtOH (1 mL) at 0 ºC. Upon completion, the reaction was concentrated to *ca*. 0.1 mL and the corresponding hydrochloride was precipitated by the addition of Et_2O. The supernatant was removed and the solid washed with Et_2O and dried under vacuum.

Ethyl 2-((1*R*,3*S*)-3-allylisoindolin-1-yl)acetate hydrochloride (*cis*-17a): white solid m. p. 199-200 ºC; $[\alpha]^{25}_D$ = +24.8 (*c* = 1.0 in EtOH) ^{1}H NMR (300 MHz,CD_3OD): 1.30 (t, *J* = 7.1 Hz, 3H), 2.73 (ddd, *J* = 15.1, 8.8, 7.6 Hz, 1H), 3.04-3.13 (m, 1H), 3.07 (dd, *J* = 17.8, 9.7 Hz, 1H), 3.30 (dt, *J* = 3.3, 1.6 Hz, 1H), 3.46 (dd, *J* = 17.9, 4.0 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 1H), 4.99 (dd, *J* = 8.9, 4.9 Hz, 1H), 5.21 (dd, *J* = 9.7, 3.9 Hz, 1H), 5.32 (dd, *J* = 10.3, 1.3 Hz, 1H), 5.39 (ddd, *J* = 17.1, 2.9, 1.4 Hz, 1H), 5.93-6.07 (m, 1H), 7.38-7.40 (m, 1H), 7.45-7.46 (m, 3H); ^{13}C NMR (75.5 MHz, CD_3OD): 14.5 (CH_3), 37.2 (CH_2), 37.6 (CH_2), 60.9 (CH), 62.6 (CH_2), 64.5 (CH), 120.5 (CH_2), 123.7 (CH), 124.0 (CH), 130.6 (CH), 130.7 (CH), 133.5 (CH), 137.9 (C), 138.6 (C), 171.7 (C). HRMS (EI): m/z calcd for $C_{15}H_{20}NO_2$: 246.1489 [M^+ + 1]; found: 246.1490.

For complete characterization, NMR spectra of all new compounds and crystallographic details of compound (*R*,*R*$_S$)-**9f** see Supporting Information.

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Asymmetric Synthesis

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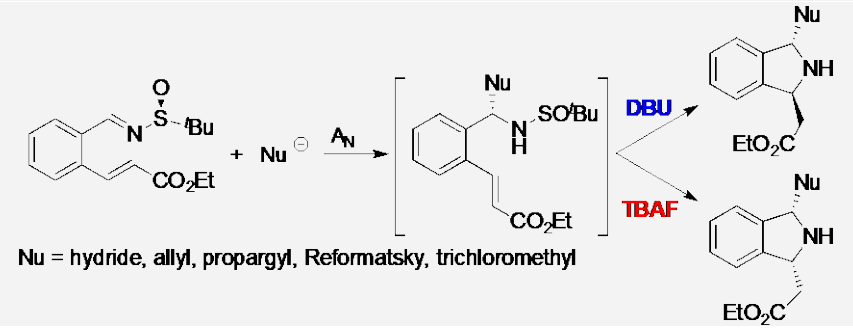
Title Text

Base-Dependent Stereodivergent Intramolecular *aza*-Michael Reaction: Asymmetric Synthesis of 1,3-Disubstituted Isoindolines



A series of 1,3-disubstituted isoindolines with a wide range of substituens have been prepared in good yields and diastereoselectivities from Ellman's imines bearing a Michael acceptor in the *ortho* position.

The careful choice of the base for the *aza*-Michael step allows to exclusively obtaining either the *cis* or the *trans* diastereoisomers.