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Synthesis of Enantiomerically Enriched Indolines and Tetrahydroisoquinolines from (*S*)-Amino Acid-Derived Chiral Carbocations: An Easy Access to (3*S*,4*R*)-Demethoxy-3-isopropyl Diclofensine

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Enantiomerically enriched indolines and tetrahydroisoquinolines were synthesized within 5 min to 2 h in high yields from easily accessible (*S*)-amino acids derived chiral carbocations. The diastereoselective Friedel-Crafts reaction is promoted by Lewis acid ($AlCl_3$) offering *trans*-diastereoselectivity. The rate of the reaction and diastereoselectivity of the product are significantly influenced by steric hindrance of substituents of amino acids and aryl groups. The methodology can be applied for the synthesis of enantiomercally enriched bioactive scaffold (3*S*, 4*R*)-demethoxy-3-isopropyl diclofensine.

Introduction:

About 70% of the new chemical entities (NCEs) introduced in the past 25 years were directly or indirectly derived from natural products.[1,2] Due to the presence of two chiral centers, substituted indoline and tetrahydroisoquinoline moiety leads to four possible stereoisomers. Therefore, the development of efficient stereoselective method to synthesize chiral indolines and tetrahydroisoquinoline continues to be a highly demanded goal. Optically active disubstituted indolines and tetrahydroisoquinolines include the acetyl cholinesterase inhibitors physovenine (**1a**) and physostigmine (**1b**),[3,4] communesin B,[5] aspidophylline A (**1c**),[6] and the anticancer agents diazonamide A (**1e**),[7] bipleiophylline (**1f**),[8] echitamine chloride (**1g**)[9], Figure 1. Benzastatin E (**1d**) and its congeners are a family of indoline alkaloids that were isolated from *Streptomyces nitrosporeus* 30643 in 1997.[10] They showed neuronal cell protecting activity that can be used to prevent brain ischemia injury.[11] Benzastatin E, another indoline alkaloid, is the most potent inhibitor of glutamate toxicity using neuronal hybridoma N18-RE-105 cells among the benzastatin family.[10]

The 4-aryl-*N*-methyl-1,2,3,4-tetrahydroisoquinolines[12-14] are present in many bioactive natural products like cherylline (**2a**) and latifine (**2b**) which are isolated from Amaryllidaceae plants,[15] nomifensine[16] (**2c**) and diclofensine[17a] (**2d**), hexahydropyrrolo[2,1-*a*]isoquinolines (**2e**).[17b,c] Many approaches such as Pictet-Spengler and Pommeranz-Fritsch-Bobbit reaction for substituted tetrahydroisoquinolines have been developed.[18-20] More recently, a two-step processes, involving palladium catalyzed α-arylation between dihydroisoquinolinones and aryl halides followed by BH_3 reduction of the carbonyl group, have been reported by Hu *et al*.[21]

Literature survey revealed that the indoline containing architectures can rapidly be accessed through catalytic hydrogenation[22] or hydrosilylation of the corresponding indoles,[23] non-enzymatic kinetic resolution of indolines[24] and a broad range of convergent methodologies such as free radical promoted aryl aminations,[25] intra-molecular shifting of sulfonyl groups,[26] diastereoselective electrophilic cyclization processes[27] or palladium catalyzed coupling reactions.[28] Diastereoselective protonation of chiral lactam enolates[29] and radical mediated cyclization are common routes for synthesizing

tetrahydroisoquinoline type of architectures.[30] Though these processes are new in this field, for cost effective, atom economic and thus effective preparation of this motif, diastereoselective Friedel-Crafts cyclization remains the mainstay. The use of π-activated alcohols, producing water as the by product,[31,32] as a replacement of the less widely available and more toxic organohalides is really a major breakthrough in this field. Recently Lautens *et al*. disclosed asymmetric benyzylic arylation for the preparation of tetrahydrotetralins.[33a-b]

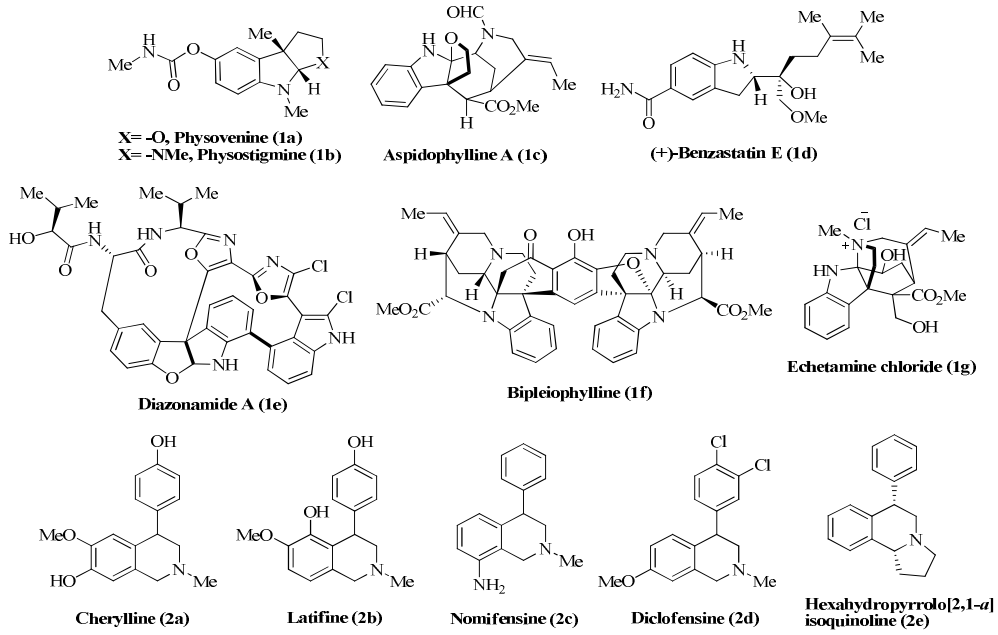


Figure 1: Important representative indoline and isoquinoline core containing natural products

The trivalent carbocation[33c] with three different substituents is prostereogenic. In the absence of any control from the medium, solvent or catalyst attack from both faces of the plane leading to 1:1 mixture of the enantiomers. However, this situation is changed if one of the substituents is chiral, as the two faces can no longer remain equivalent. Chiral benzyl carbocation with α-substituents preferentially remain in the conformation drawn below to avoid the allylic strain between the sterically more demanding substituent and the aryl ring and hence there is a facial control in the nucleophilic substitution of the benzylic systems (Figure 2). This concept has efficiently been used by Bach *et al.*[34] and Chung *et al.*[35a] We envisioned that N-Aryl benzylic carbocations derived from (*S*)-amino acids[36] can take part in the intra-molecular Friedel-Crafts alkylation furnishing stereoselective synthesis of indolines and tetrahydroisoquinolines.

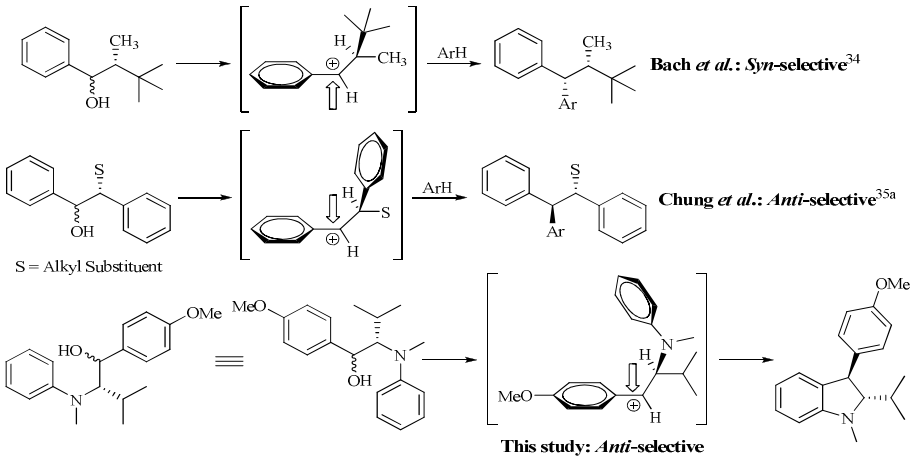


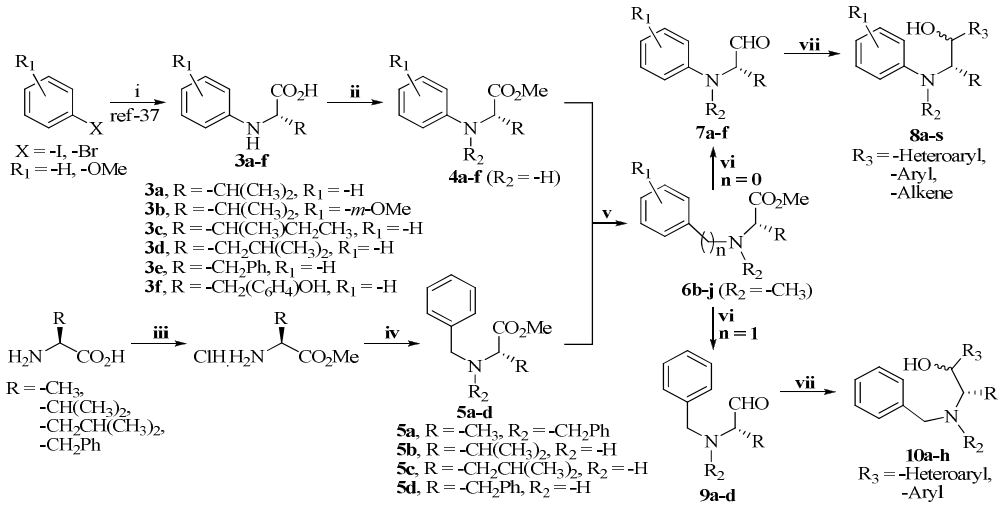
Figure 2: Friedel-Crafts acylation through chiral carbocations

Results and Discussion:

Synthesis of amino acids derived aryl, heteroaryl and alkene substituted carbinols (**8a-s**, **10a-h**) were prepared in good yields from naturally abundant (*S*)-amino acids following synthetic steps, involving Ullmann coupling, esterification of acids, benzylation/methylation of amines, LAH reduction of ester groups, Parikh-Doering oxidation (Scheme 1). After Parikh-

Doering oxidation, the crude product was used for Grignard reaction without further purification (due to unstability of substituted aldehydes).

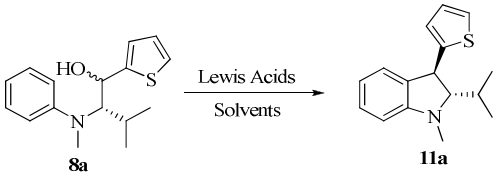
To find the most advantageous reaction condition for diastereoselective Friedel-Crafts cyclization of amino acids derived aryl, heteroaryl and alkene substituted carbinols (**8a-s**, **10a-h**), we tested several Lewis acids [$SnCl_2$, $Sc(OTf)_3$, $SnCl_4$, $BF_3{\cdot}OEt_2$, $FeCl_3{\cdot}6H_2O$, $AuCl_3{\cdot}3H_2O$, $AlCl_3$, AgOTf, $Cu(OTf)_2$ and $In(OTf)_3$] under different conditions (solvent, temperature and Lewis acid amount). A solution of the carbinol **8a** was refluxed with 0.5 equiv $SnCl_2$ in dry benzene, which did not provide the required product. Changing the solvent to dichloroethane (DCE) gave trace amount of desired indoline while increasing the catalyst loading to 1 equiv in dry dichloromethane (DCM) at room temperature furnished the desired indoline in 45% yield at 70% conversion after 5 h (Entry 3, Table 1). Further increase in the reaction time, catalyst loading and the reaction temperature didn't improve the reaction yield.



Scheme 1: *Reagents and conditions:* (i) Amino Acids, CuI, K_2CO_3, DMA, 48 h; (ii) K_2CO_3, MeI, DMF, 2 h; (iii) $SOCl_2$, MeOH, 6 h; (iv) BnBr, K_2CO_3, DMF, 4-5 h; (v) Ag_2O, MeI, dry DMF, 6 h; (vi)(a) LAH, dry THF, 1 h; (b) $Py{\cdot}SO_3$, DCM:DMSO (1.6:2 mL per mmol), Et_3N, 1 h; (vii) R_1-Br, Mg/I_2, dry THF, rt, 1 h.

Thus we screened stronger Lewis acid for this diastereoselective transformation. When the $SnCl_4$ loading was 1.2 equiv, the 80% starting material was consumed after 3-5 h and **11a** was obtained in 50% yields. Milder Lewis acids like $Sc(OTf)_3$, $FeCl_3$, $AuCl_3{\cdot}3H_2O$, AgOTf gave desired **11a** in 25-52% yield. Subsequently, various other catalytic systems (Lewis acids as well as protic acids) were screened, Table 1 (see Supporting Information). With increase in catalyst $AlCl_3$ loading (from 0.5 to 1.0 to 1.5 equiv) in the same solvent, the yield of **11a** improved from 65% to 74% to 82%. In some entries of table 1, desired yield of **11a** was low (25-52%), thus the diastereoselectivity was not measured.

Table 1: Optimization studies for the diastereoselective Friedel-Crafts reaction of **11a**



Entry	Lewis Acids	Solvents	Conditions	Yield(%)[a]
1	$SnCl_2$ (0.5 equiv)	Dry benzene	Reflux, 30 min	NR
2	$SnCl_2$ (0.5 equiv)	DCE	Reflux, 2 h	Trace
3	$SnCl_2$ (1.0 equiv)	Dry DCM	RT, 1-5 h	45[b]
4	$Sc(OTf)_3$ (5 mol%)	Dry DCM	RT, 1 h	Trace
5	$Sc(OTf)_3$ (10 mol%)	Dry DCM	Reflux, 1-3 h	33[b]
6	$SnCl_4$ (1.2 equiv)	Dry DCM	RT, 3-5 h	50[c]
7	$BF_3{\cdot}OEt_2$ (10 mol%)	Dry DCM	RT, 1 h	38[b]
8	$FeCl_3{\cdot}6H_2O$ (5 mol%)	Dry DCM	RT, 1 h	NR
9	$AuCl_3{\cdot}3H_2O$ (10 mol%)	Dry DCM	RT, 1 h	NR
10	$AuCl_3{\cdot}3H_2O$ (10 mol%)	DCE	Reflux, 1-2 h	25[b]

11	$AlCl_3$ (0.5 equiv)	Dry DCM	RT, 1 h	65
12	$AlCl_3$ (1.0 equiv)	Dry DCM	0 °C-RT, 1 h	74
13	$AlCl_3$ (1.5 equiv)	Dry DCM	0 °C-RT, 5 min	82
14	$FeCl_3 \cdot 6H_2O$ (1.5 equiv)	Dry DCM	Reflux, 1 h	52

[a]Isolated yield of indoline (**11a**) after silica gel column chromatography, [b]70% and [c]80% starting material consumed and unreacted portion has been recovered, NR = no reaction.

It is noteworthy that most of the reactions with Lewis acids were performed under strictly inert atmosphere, as these catalysts immediately react with water or moisture rather than substrates. Coordination of the amine and eliminated water with Lewis acid might increase the required amount of Lewis acid, making the use of an extra equivalent of Lewis acid necessary in the reaction. Based on these facts and the above optimization results, we then turned our attention to explore the scope of $AlCl_3$ catalyzed diastereoselective Friedel-Crafts cyclization of amino acids derived electron-rich aryl, heteroaryl and alkene substituted carbinols (**8a-s**, **10a-h**). A series of carbinols (**8a-s**, **10a-h**) were used in dry DCM at 0 °C-rt, using 1.5 equiv $AlCl_3$ under inert atmospheric conditions, furnishing desired indolines (**11a-s**) and tetrahydroisoquinolines (**12a-h**) in 48-84% yields and in high diastereoselectivity (Figure 3).

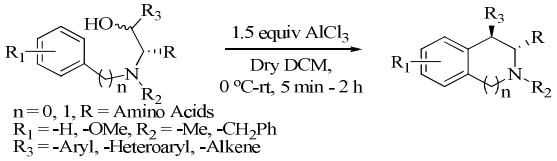
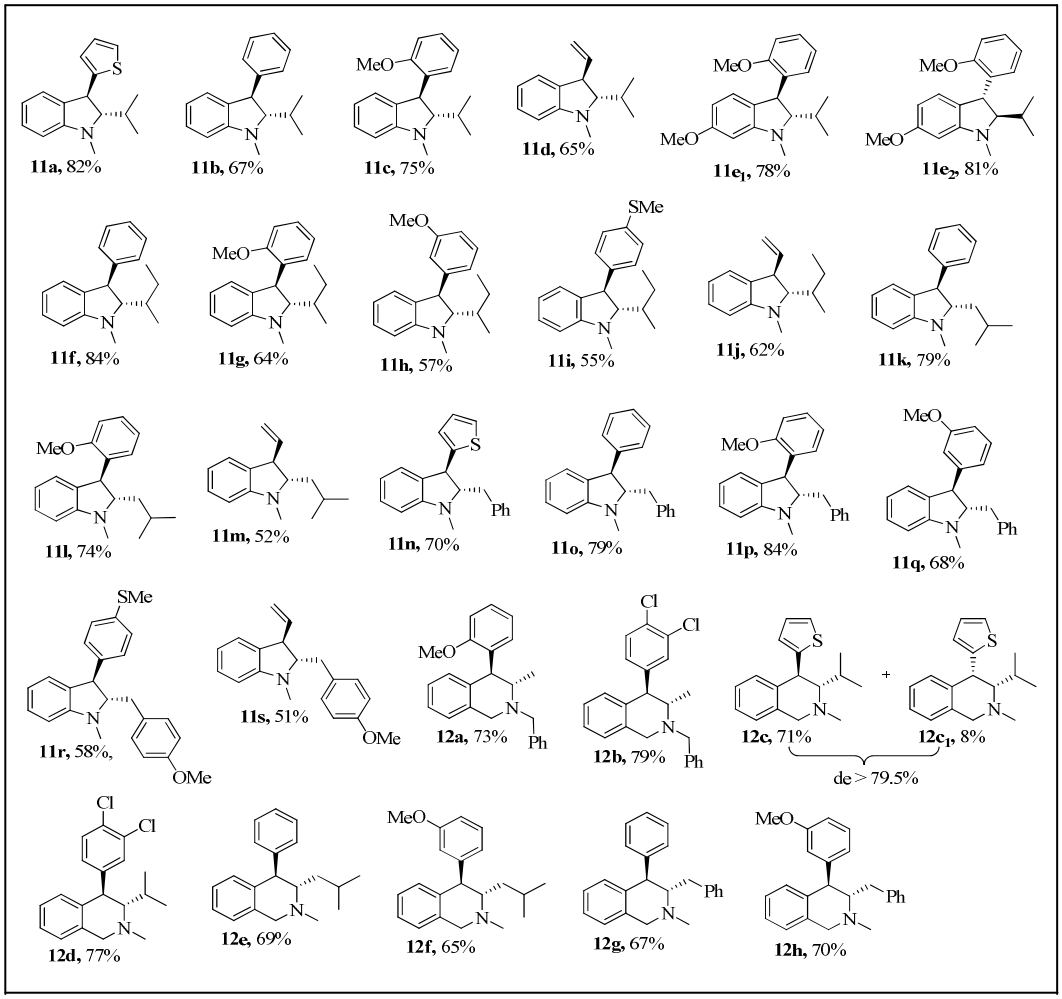


Figure 3: Synthesis of indoline and tetrahydroisoquinoline derivatives (**11a-s**, **12a-h**)[a]



[a]all products were obtained with > 95% de except **12c** and **12c**$_1$ as determined by 300 & 400 MHz NMR spectroscopy

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Interestingly when the methodology was applied for the synthesis of indolines (**11a-s**), one isomer was detected by chiral HPLC analysis of the products. When the reaction was carried out with a mixture of the two carbinols derived from enantiomerically pure (*S*-) and (*R*-) amino acids, analysis of chiral HPLC experiments showed only two peaks for the two enantiomers of the *trans*- indolines, (t_R = 9.134 and 9.236 min in *iso*-propanol:acetonitrile = 05:95 respectively), providing complete diastereoselective Friedel-Crafts cyclization (de > 95). But for tetrahydroisoquinoline (**12c**), unfortunately this diastereoselectivity was low based on isolated products by preparative thin layer column chromatography. The relative stereochemistry of compounds was assigned on the basis of NOESY studies of **11g** (see supporting information). For indolines though the coupling constant value obtained for the coupling of two methine protons were 7-9 Hz, NOESY experiment confirmed the *trans*-selectivity. The *trans*-stereoselectivity of the disubstituted indolines (**11a-s**) and tetrahydroisoquinolines (**12a-h**) can be explained on the basis of the expected conformational preferences in the proposed transition state (*cis*-giving rise to considerably more steric hindrance) of the reaction (Figure 4).

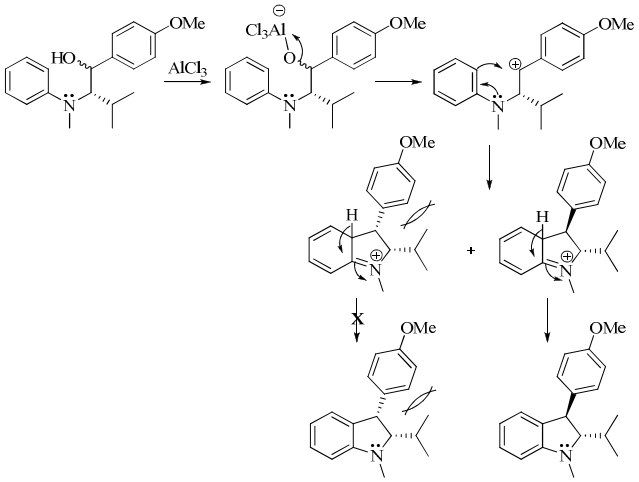

Figure 4: Proposed mechanistic pathway for the synthesis of indoline and tetrahydroisoquinoline derivatives

As a representative example, benzyl group of the *trans*-disubstituted chiral tetrahydroisoquinoline **12a** was selectively debenzylated using H_2/Pd-C affording **13a** with 76% yield, which gives scope for further structural diversification (Figure 5). In order to further establish the efficiency of this process, we applied this methodology for the synthesis of enantiomercally enriched demethoxy-3-*iso*propyl diclofensine (*trans*-isomer). Valine was first converted quantitatively to the aldehyde **9b** using standard protocols (Scheme 1). Grignard reaction of the aldehyde **9b** with 3,4-dichlorophenyl magnesium bromide gave carbinol **10d** in 72% yield. The intra-molecular diastereoselective Friedel-Crafts alkylation of this carbinol through the chiral benzylic carbocation gave (3*S*,4*R*)-demethoxy-3-*iso*propyl diclofensine in 77% yield (**12d**, Figure 3).

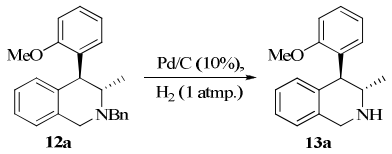

Figure 5: Deprotection of amine (**12a**)

Conclusion:

In summary, we have developed a simple and powerful synthetic route that provides access to enantiomerically enriched disubstituted indolines and tetrahydroisoquinolines from (*S*)-amino acids derived chiral carbocations. This Friedel-Crafts reaction is promoted by Lewis acid ($AlCl_3$) offering *trans*-diastereoselectivity. The rate of the reaction and diastereoselectivity of the product are significantly influenced by steric hindrance of substituents of amino acids and the nature of the aryl groups. Further investigations are underway in our laboratory to expand the applicability of this process.

Experimental Section:

General Remarks

All dry reactions were carried out under argon atmosphere in oven-dried glassware using standard gas-light syringes, cannulas and septa. All reagents and solvents were purchased from commercial sources and used without further purification. Organic solvents were dried by standard methods. Analytical TLC was performed using 2.5 x 5 cm aluminum plates coated with a 0.25 mm thickness of silica gel (60F-254), visualization was accomplished with iodine and under UV lamp. Column chromatography was performed using silica gel (60-120 and 100-200 mesh). Preparative thin layer chromatography was performed on GF254 silica by using requisite distilled solvent system as mentioned below. ^{1}H NMR spectra were recorded on 200, 300 and 400 MHz spectrometer in $CDCl_3$ (all signals are reported in ppm with the internal chloroform signal at 7.26 ppm as standard) at 25 °C. ^{13}C NMR spectra were recorded on 50, 75 and 100 MHz spectrometer in $CDCl_3$ (all signals are reported in ppm with the internal chloroform signal at 77.00 ppm as standard) at 25 °C. In a few cases tetramethylsilane (TMS) at

0.00 ppm was used as the reference standard. ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), double dublet (dd), triplet (t), quartet (q) or multiplet (m). IR spectra were recorded using a FTIR spectrophotometerin cm^{-1}. The high resolution mass spectra (HRMS) were recorded as ESI-HRMS (recorded as ES^+) on a mass spectrometer. Optical rotations were determined on polarimeters using a 1 dm cell at 25 ^oC in chloroform, methanol as the solvents; concentrations mentioned are in g/100 mL. The enantiomeric excess was determined by chiral column (chiralpak 1A) using 5% *iso*-propanol and 95% acetonitrileas the eluentat wavelength 254 nm, flow rate 0.50 mL/min at 25 ^oC. Retention time range is 0 to 30 min. The specific rotation values of the diastereomers and their retention time in chiral HPLC have been defined with respect to the products.

Experimental Section:

General experimental procedure for the synthesis of (6a-j): When a mixture of *S*-amino acid (1 equiv), halobenzene (1 equiv), CuI (10 mol %), and K_2CO_3 (1.5 equiv) was stirred in DMA at 90 °C for 48 h, we could isolate the coupled products **3a-f** in 75-92% yield.[37] The respective amino acids **3a-f** were esterified by using methyliodide (1 equiv) and K_2CO_3 (2 equiv) in DMF at room temperature within 1-2 h. After completion of the reaction (as observed on TLC), DMF was removed *in vacuo*. The mixture was extracted with ethyl acetate (3 x 30 mL), washed with brine and dried over by Na_2SO_4. The concentrated extract (crude product) was subjected to methylation of amine without purification. To a stirred solution of **4a-f** (1.447 mmol) in dry DMF (3 mL for each mmol) was added Ag_2O (4.342 mmol) and methyl iodide (4.342 mmol) in the dark at 0 ^oC and after final addition, reaction mixture was stirred at 0 ^oC to rt for overnight. After completion of reaction, resulting mixture was filtered through celite bed, concentrated *in vacuo* and purified by silica gel column chromatography.

In addition, to a stirred solution of *S*-amino acids (1 equiv) in MeOH (20 mL), $SOCl_2$ (1.5 equiv) was added at 0 ^oC, and then the reaction mixture was stirred for 6 h. After completion (as monitored by TLC), reaction mixture was concentrated *in vacuo* and dissolved in DMF (15 mL) and was heated at 50 ^oC followed by addition of benzyl bromide (1.1 equiv) and K_2CO_3 (2 equiv). After methylation or benzylation (as descrive above) of **4a-f** and **5a-d**, the respective amino esters **6a-j** were reduced with LAH.

General procedure for Parikh-Doering oxidation: An ice cooled solution of the primary alcohols (obtained from the reduction of **6a-j**) (1.034 mmol) in dry DCM and DMSO mixture (1.6 mL DCM and 2 mL DMSO for each mmol) was basified by triethylamine (5.173 mmol) and finally Py·SO_3 salt (5.173 mmol) was added and allowed to stir at room temperature for 30 min. After the completion of the reaction, it was quenched with H_2O and then extracted with DCM for three times (3 x 30 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was used for next step without purification.

Typical experimental procedure for diastereoselective Friedel-Craft's cyclization to access amino acid-derived indoline and tetrahydroisoquinoline scaffolds (11a-s, 12a-h): To a 0.362 molar stirred solution of carbinol (**8a-s**, **10a-h**) in anhydrous DCM (15 mL), 1.5 equiv of anhydrous $AlCl_3$ was added at 0 ^oC and stirred vigorously for 5 min to 2 h. After completion of the reaction (as observed on TLC), water was added under ice-cold condition and the resulting mixture was extracted as descriped above. The crude reaction mixture was purified by silica gel column chromatography as well as preparative thin layer chromatography to generate the desired products.

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