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Organocatalytic [4+1]-Annulation Approach for the Synthesis of Densely Functionalized Pyrazolidine Carboxylates†

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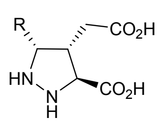
A novel one-pot [4+1]-annulation process for the asymmetric synthesis of densely functionalized pyrazolidine carboxylates is described. The *in situ* generated γ-hydrazino-α,β-unsaturated ester obtained *via* proline catalysis acts as a four-atom component, and Corey's sulfur ylide or ethyl bromoacetate acts a one-atom carbon source to construct pyrazolidine carboxylate units in a highly enantio- and diastereoselective fashion.

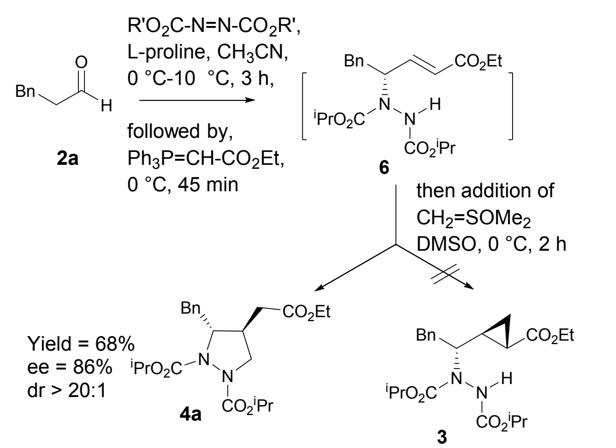
The pyrazolidine and pyrazoline are interesting class of nitrogen-containing heterocyclic structural units found in many complex natural products[1] with significant biological activities (e.g. anticancer,[2] antidepressant,[3] antibacterial,[4] anticonvulsant,[5] antiviral,[6] etc.) and other uses (as arthropodicidal agent[7] in agriculture or optical brightening agent).[8] Furthermore, they can be considered as powerful starting materials for the synthesis of enantiopure azaprolines[9] and densely functionalized 1,3-diamino derivatives[10] after reductive cleavage of the N-N bond. In particular, recent SAR studies have established that aza-kainic acid derivatives (**1**) have proven exhibiting potent neuroexcitatory activity.[11]



1, aza-kainoids

One of the most efficient strategies for the construction of such fused skeletons generally relies on [3+2] cycloadditions of hydrazones to olefins in the presence of Bronsted[12]/Lewis[13] acids or with strong heating.[14] Their asymmetric synthesis are also reported employing chiral Zr/BINOL,[15] Si-based Lewis acids,[16] transition metal (Pd, Ni, Au)-catalyzed intramolecular annulations[17] including sequential organocatalysis.[18] However, these methods are rather limited due to harsh reaction conditions, complex chiral pool resources, expensive chiral ligands and metal catalysts often involving multistep reaction sequences. To the best of our knowledge, no method has been previously reported for the synthesis of densely substituted pyrazolidine carboxylates in "one-pot" fashion using organocatalysis.

In recent years, proline-catalyzed sequential reactions have gained prominence for the asymmetric synthesis of structurally diverse molecular architectures.[19,20] As part of our program directed towards asymmetric synthesis of bioactive molecules employing organocatalytic sequential reactions,[22] we envisaged that *in situ* trapping of γ-hydrazino-α,β-unsaturated ester **4**[20e] with Corey's sulfur ylide (dimethyloxosulfonium methylide)[23] under basic conditions should provide the corresponding highly functionalized cyclopropane carboxylate **3**, potent and selective group II metabotropic glutamate receptor (mGluR) antagonists.[3e]



Scheme 1 In situ Trapping of γ-hydrazino-α,β-unsaturated ester **6** with dimethyloxosulfonium methylide

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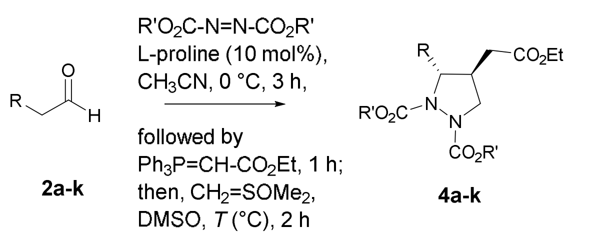
Surprisingly, the reaction took a different course to afford the corresponding 3,4-disubstituted pyrazolidine carboxylate **4a** as a single diastereomer in 68% yield (Scheme 1).

In this communication, we describe a one-pot sequential procedure for a tandem [4+1] annulation reaction of γ-hydrazino-α,β-unsaturated ester **6** generated *in situ* with Corey's sulfur ylide or ethyl bromoacetate that proceeds to give densely functionalized chiral pyrazolidine carboxylates **4** & **5** in a highly enantio- and diastereoselective manner (Table 1 & 2).

Table 1 L-Proline catalyzed sequential α-amination/ Wittig olefination/ Corey-Chaykovsky reaction of aliphatic aldehydes[a]

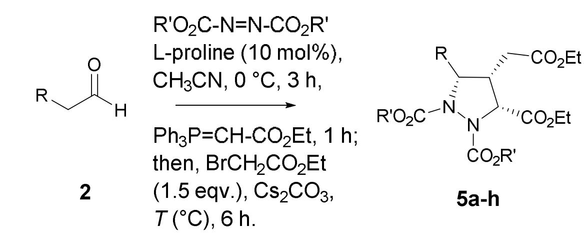


entry	aldehyde (**2a-k**) (R)	amine (R')	*T* (ºC)	products(**4a-k**) Yield (%)[b]	ee (%)[c]
1	benzyl (**2a**)	^{i}Pr	0	68	86
2		^{i}Pr	10	75	86
3		**^{i}Pr**	**25**	**80**	**86**
4		Et	25	79	81
5		^{t}Bu	25	70	86
6	4-methylbenzyl (**2b**)	^{i}Pr	25	71	84
7	4-methoxybenzyl (**2c**)	^{i}Pr	25	67	87
8	4-thiomethylbenzyl (**2d**)	^{i}Pr	25	75	92
9	2-CN-4,5-methylene-dioxybenzyl (**2e**)	^{i}Pr	25	65	81
10	2-NO$_2$-4,5-methylene-dioxybenzyl (**2f**)	^{i}Pr	25	69	92
11	2-NO$_2$-4,5-methylene-dioxybenzyl (**2f**)	^{t}Bu	25	66	94
12	2-bromo-3,4,5-trimethoxy-benzyl (**2g**)	^{i}Pr	25	72	94
13	naphthalene-1-yl-methyl (**2h**)	^{i}Pr	25	68	90
14	3-benzyloxypropyl (**2i**)	^{i}Pr	25	70	92
15	propyl (**2j**)	^{i}Pr	25	79	nd
16	methyl (**2k**)	^{i}Pr	25	80	nd

[a] Aldehyde (2.5 mmol), amine (R'O$_2$C-N=N-CO$_2$R') (2.5 mmol), L-proline (10 mol %), Ph$_3$P=CHCO$_2$Et (3.75 mmol), dimethyloxosulfonium methylide (5.0 mmol); [b] diastereomeric ratio (dr > 20:1) was determined from proton NMR analysis of the crude product; [c] %ee were determined from chiral HPLC analysis; nd = not determined.

In order to optimize the reaction conditions, initially the amination/Wittig olefination of hydrocinnamaldehyde **2a** was carried out following our amination protocol [20e] that produced the corresponding γ-hydrazino-α,β-unsaturated ester **6** *in situ*. This was followed by the addition of a solution of dimethyloxosulfonium methylide in DMSO [sulfur ylide (2.0 equiv), prepared *in situ* from O=SMe$_3$I/NaH in DMSO] at 0 °C that gave **4a** as a single diastereomer in 68% yield with 86% ee (entry 1). A significant improvement in yield (80%) was, however, realized when the reaction was conducted at 25 °C for 2 h. Increase of temperature (50 °C) resulted in complex reaction mixture. Also, use of other solvents such as CH$_2$Cl$_2$ and THF for the tandem protocol resulted in a sluggish reaction with poor yields (< 10%). Furthermore, (*S*) - α, α-diarylprolinol silyl ether as a modified proline catalyst was found to be less effective for the reaction. We then turned our attention to investigate the scope of amine sources, the results of which indicated that diisopropyl was found to be better candidate (Table 1, entry 3). With the optimized reaction condition in hand, we next examined the scope of the reaction. Aldehydes bearing Br, CN, NO$_2$, OMe, SMe and methylenedioxy groups on the aromatic nucleus, and benzyl ether substitutions in aliphatic compounds were found to be well-tolerated under the reaction condition. For all the cases studied, the products **4a–k** were indeed obtained in high yields (65-80%) and excellent enantioselectivities (80 – 94%) with dr > 20:1 (Table 1, entry 6-16).

Table 2 L-Proline catalyzed sequential α-amination/ Wittig olefination/ N-alkylation/ Michael addition reaction of aliphatic aldehydes[a]



entry	aldehyde (**2**) (R)	amine (R')	*T* °C	products (**5a-h**) Yield (%)[b]	ee (%)[c]
1	benzyl	^{t}Bu	25	-	-
2		^{t}Bu	50	-	-
3		^{t}Bu	80	50 (**5a**)[d]	86
4		**Et**	**50**	**72 (5a)**[d]	**96**
5	4-methoxybenzyl	Et	50	77 (**5b**)[d]	96
6	4-F-benzyl	Et	50	64 (**5c**)[d]	95
7	3,4-dimethylbenzyl	Et	50	75 (**5d**)[d]	94
8	2-NO$_2$-4,5-methyl-enedioxybenzyl	Et	50	64 (**5e**)[e]	88
9	naphthalene-1-yl-methyl	Et	50	79 (**5f**)[d]	94
10	pentyl	Et	50	72 (**5g**)[d]	nd
11	methyl	Et	50	62 (**5h**)[f]	nd

[a] Aldehyde (2.5 mmol), amine (R'O$_2$C-N=N-CO$_2$R') (2.5 mmol), L-proline (10 mol %), Ph$_3$P=CHCO$_2$Et (3.75 mmol), ethyl bromoacetate (3.75 mmol), Cs$_2$CO$_3$ (6.25 mmol); [b] isolated yield of products; [c] %ee were determined from chiral HPLC analysis; [d] diastereomeric ratio (dr > 20:1) was determined from proton NMR analysis of the crude product; [e] dr = 7:3; [f] dr = 6:1; nd = not determined

In order to further extend the scope of [4+1]-annulation strategy, the *in situ* generated amino ester **6** (R = Bn & R′ = ^{t}Bu) was treated with ethyl bromoacetate (1.5 equiv) in presence of K_2CO_3 as base at 50 °C and found that the annulation was unsuccessful. However, when Cs_2CO_3 was used as base and heating the mixture at 80 °C, the annulation proceeds smoothly producing the desired pyrazolidine dicarboxylate **5a** in 50% yield and 86% ee with dr > 20:1. The best results were obtained when the amine source was changed to R′ = Et (72% yield, 96% ee, and dr = 20:1 at 50 °C) (entry 4, Table 2). With this optimized reaction conditions, other substrates bearing F, NO_2, Me and OMe substituents on the aromatic nucleus underwent this [4+1] annulations cascade smoothly, affording the corresponding pyrazolidine dicarboxylates **5a-h** in high yields with excellent enantio- and diastereoselectivities (Table 2).

The absolute configuration of the newly generated stereogenic centers was assigned on the basis of the previously established configuration of γ-hydazino-α,β-unsaturated ester.[20e] The relative stereochemistry in pyrazolidines **4** and **5** is proven unambiguously from X-ray Crystallographic analysis[24] (Figure 1, CCDC 1041539) as well as COSY and NOESY NMR studies.[25]

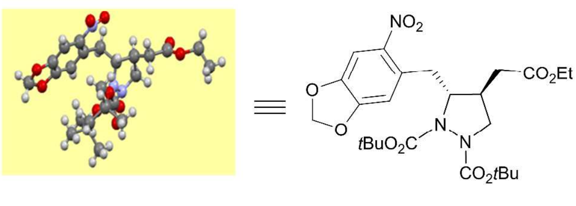
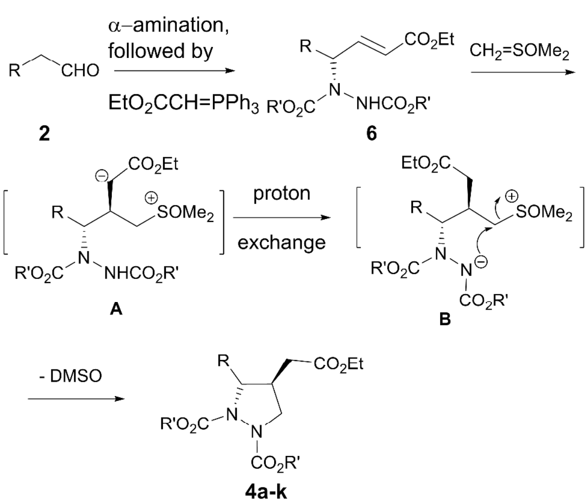


Figure 1 ORTEP diagram of **4f** (R′ = ^{t}Bu).

A probable mechanistic pathway is shown in Scheme 2 in which sulfur ylide adds onto β-carbon of the *in situ* generated γ- amino-α,β-unsaturated ester **6** to form species **A**.



Scheme 2 Probable mechanistic pathway for the formation of **4a-k**

This in turn is followed by a facile proton exchange[24] from the carbamate nitrogen to the basic carbanion **A** to give the stable species **B**, which then subsequently undergoes intramolecular cyclization with the removal of DMSO to afford products **4a-k**, all occurring sequentially under "one-pot" fashion.

To rationalize the observed high '*anti*' diastereoselectivity between the two substituents in the formed pyrazolidines **4a-k**, Felkin Anh model[25] has been proposed (figure 2). In this model, nucleophilic attack of the sulfur ylide takes place exclusively at the '*Si*' face of olefin incorporating Bürgi-Dunitz trajectory[26] leading to highly diastereoselective pyrazolidines **4a-k**, following transition states (TS-I to TS-III).

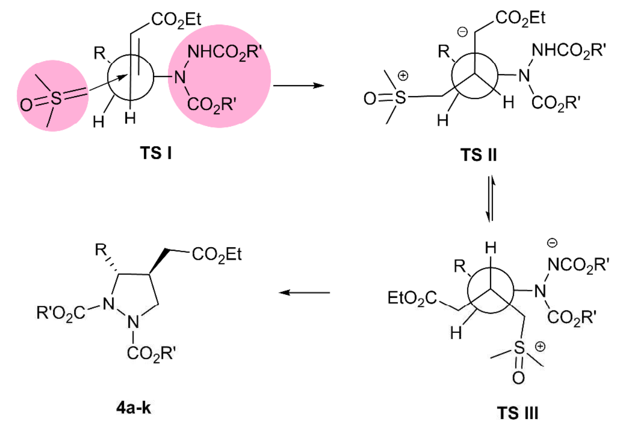
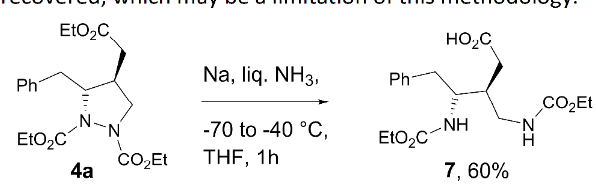


Figure 2 Proposed transition state model (R = alkyl or alkylaryl and R′ = Et, ^{i}Pr, ^{t}Bu).

In the case of **5a-h**, only one diastereomer was obtained predominantly out of four possible diastereomers during Michael addition. This high diastereoselectivity can be explained on the basis of the chelation controlled favorable transition state model.[21]

To demonstrate its potential applicability, **4a** was subjected to reductive cleavage of N-N bond under metal/ NH_3 conditions (Na in liquid NH_3, -70 to -40 °C, THF, 1 h) to afford the corresponding *anti*- 1, 3-diamino acid **7** (60% yield)[29], which are common structural subunits present in many natural products and also useful as chiral ligands (Scheme 3). We have carried out several experiments to deprotect carbamate moieties in **4**, **5** and **7** to demonstrate the further utility of this methodology. Unfortunately, we have ended up with complex reaction mixtures in the case of benzyl (Cbz) and *tert*. butyl carbamates (Boc). The deprotection of ethyl under basic condition was also not successful; starting material was recovered, which may be a limitation of this methodology.[30]



Scheme 3 Reductive cleavage of N-N bond.

Conclusions

In conclusion, we have described, for the first time, a novel [4+1]-annulation strategy involving a sequential α-amination/ Wittig olefination/ Corey- Chaykovsky reaction or intramolecular Michael reaction of aldehydes that leads to the synthesis of densely functionalized pyrazolidine carboxylates **4** & **5** containing two to three stereogenic centers with high yields and excellent enantio- and diastereoselectivities. The reductive cleavage of N-N bond in pyrazolidine afforded optically active 2,3-disubstituted 1,3-diamino acid **7**. The ready availability of starting materials, milder reaction conditions and the formation of two to three stereogenic centers under "one-pot, metal-free conditions" makes this protocol quite useful in organic synthesis.

Notes and references

‡ Both authors contributed equally to this work.

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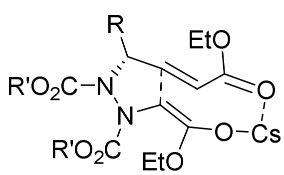
21 *syn*, *syn* diastereoselectivity obtained during Michael addition can be explained using chelation controlled favorable transition state model as shown below:

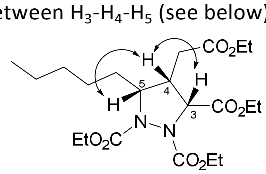


22 a) S. P. Kotkar and A. Sudalai, *Tetrahedron Lett.*, 2006, **47**, 6813; b) V. Rawat, P. V. Chouthaiwale, V. B. Chavan, G. Suryavanshi and A. Sudalai, *Tetrahedron Lett.*, 2010, **51**, 6565; c) V. Venkataramasubramanian, I. N. C. Kiran and A. Sudalai, Synlett, 2015, **26**, 355.

23 E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353.

24 CCDC - 1041539 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccd. Cam.uk/data_request/cif.

25 The relative stereochemistry of **5g** was confirmed by COSY and NOESY studies. A significant NOESY correlation was observed between H_5-H_4 and H_4-H_3 confirming the *syn* relationship between H_3-H_4-H_5 (see below).



5g

26 Attempts to deuterate the NH proton of carbamate **6** under various reaction conditions to ascertain the proton exchange phenomena were unsuccessful.

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29 Hydrolysis of ester to carboxylic acid was observed during reductive N-N bond cleavage; for detailed experimental procedure see supporting information.

30 Carbamate deprotection in **4**, **5** and **7** was unsuccessful with following reaction conditions:
1. R' = ^{t}Bu; a) TFA, CH_2Cl_2, 25 °C to 70 °C, 1 h to 12 h; b) Methanolic HCl, 25 °C, 12 h.
2. R' = Bn; a) 10% Pd,C/H_2 (1 atm), MeOH; b) Raney-Ni, H_2 (60 psi), MeOH.
3. R' = Et; K_2CO_3, EtOH, 25 °C to 70 °C

