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Diastereoselective Synthesis of Functionalized 5-Amino-3,4-Dihydro-2*H*-Pyrrole-2-Carboxylic Acid Esters: One-Pot Approach Using Commercially Available Compounds and Benign Solvents

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Abstract: A novel three-step four-transformation approach to highly functionalized 5-amino-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid esters, starting from commercially available phenylsulfonylacetonitrile, aldehydes, and *N*-(diphenylmethylene)glycine *tert*-butyl ester, was developed. The one-pot strategy delivered this class of amidines bearing, for the first time, three contiguous stereocenters, in good to high yield and diastereoselectivity. The entire sequence was carried out using diethyl carbonate and 2-methyl tetrahydrofuran as benign solvents, operating under metal-free conditions. The process could be conveniently scaled-up, and the synthetic utility of the products was demonstrated.

Compounds bearing the 2-amino-1-pyrroline core are of significant interest in the area of medicinal chemistry, being a class of small cyclic amidines with rigid non-planar scaffold, suitable for the inhibition of the β-secretase 1 (BACE1),[1] an enzyme involved in Alzheimer's disease (Figure 1).[2] Moreover, the 5-amino-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid unit is found integrated in natural pyrroloamide metabolites such as Norformycin and Anthelvencins A and B, exhibiting antivirus, antibacterial, and anthelmintic activities (Figure 1).

Application of 2-amino-1-pyrroline as ligands in metal catalysis has been also reported.[4] The synthesis of amidines has been largely explored over the years,[5] due to their wide application in organic synthesis as strong bases/catalysts[6] and intermediates for the synthesis of heterocyclic compounds. Among the cyclic amidines, the five-membered unit 5-amino-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ester 1 has been exclusively synthesized using pyroglutamic acid as the starting reagent, according to the approach illustrated in Scheme 1 a.[8]

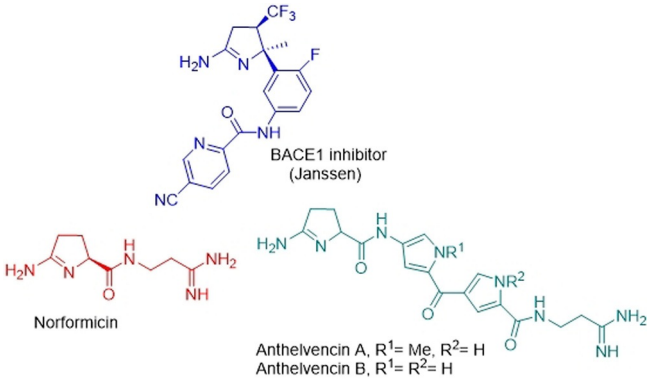
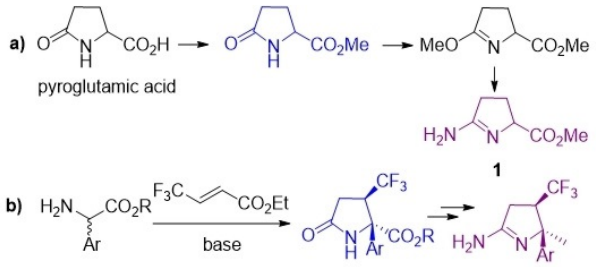


Figure 1. Bioactive and natural products bearing the 5-amino-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid unit.



Scheme 1. Established stepwise approach to 5-amino-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ester **1** and recent modification.

Although the three-step sequence provides key building-block **1** in satisfactory overall yield, it has some limitations, being unsuitable for any functionalization at positions 3 and 4 of the five-membered ring. Moreover, the stepwise approach requires isolation of the intermediates along the sequence, thus showing poor sustainability. Recently, Fustero and co-workers reported an interesting stereoselective modification of route a) adding a preliminary one-pot aza-Michael/lactamization sequence, by reacting α-amino acid esters and trifluoromethyl crotonates (Scheme 1 b).[9a] The procedure enabled the formation of fluorinated derivatives, bearing a quaternary center at position 2 and a tertiary stereocenter at position 3, which proved to be potent BACE1 inhibitors.[9]

Considering the paucity of synthetic strategies, one-pot approaches to new functionalized amidines of type **1**, which pay attention to environmental issues, would be highly desirable in view of the utility of this scaffold in medicinal chemistry and

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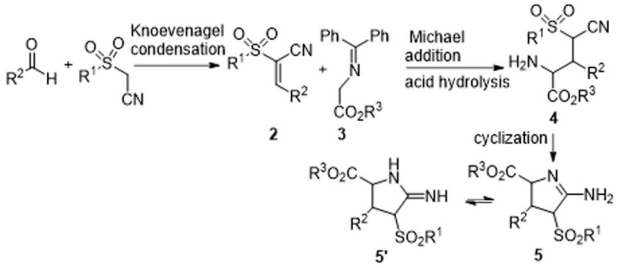
biosynthetic studies.[10] Given our interest in the development of stereoselective organocatalytic methodologies to prepare heterocyclic compounds,[11] we envisaged a one-pot process suitable to access 5-amino-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ester **5**, functionalized at positions 3 and 4 (Scheme 2).



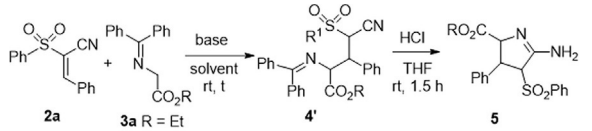
Scheme 2. One-pot approach to functionalized 5-amino-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid esters **5**.

A base-promoted Knoevenagel condensation employing commercially available aldehydes and aryl sulfonyl acetonitrile would stereoselectively afford electron-poor alkene **2**.[12] The same reaction conditions would be suitable for the Michael addition of commercially available glycinate ester of benzophenone Schiff base to alkene **2**. In situ mild acid hydrolysis of the imine would give adduct **4**, which according to previous work[13] would undergo cyclization to 5-amino-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ester **5** by NH_2 attack onto the CN group.

In this work, we report a first approach which enables to functionalize positions 3 and 4 of the 5-amino-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid ester scaffold. A one-pot sequential protocol has been conveniently developed using commercially available reagents and benign solvents, exploiting a Knoevenagel condensation/Michael reaction/hydrolysis/cyclization sequence. The final heterocycles, which are of interest in different areas, were selectively obtained in good to high yield and diastereocontrol. Moreover, the sequence is scalable, and elaboration of the products has been demonstrated.

At the outset of the study, model alkene **2a** and ester glycinate benzophenone Schiff bases **3** were reacted in order to optimize the conjugate addition reaction to adduct **4'** by using different bases (Table 1). The Michael addition was firstly performed using ethyl ester glycinate benzophenone Schiff base **3a** at room temperature in THF, followed by hydrolysis of the crude mixture (entries 1–6). We were pleased to observe that when using 20 mol% of 1,4-diazabicyclo[2.2.2]octane (DABCO), the Michael addition proceeded satisfactorily to give the adduct **4'a**, which after treatment with 2 N HCl underwent selective cyclization to amidine **5a** (entry 1). ^{1}H NMR analysis of the crude reaction mixtures of **4'a** and **5a** showed the presence of only two of out of four diastereomers, in 77:23 ratio, which was maintained over the hydrolysis and cyclization steps. The presence of the 2-imino tautomer **5'a** of compound **5a** was not observed, in agreement with previous data (Scheme 2).[14] Piperidine and *N*,*N*-dimethylamino pyridine (DMAP) provided the product with different efficiency and stereoselectivity, which pleasingly improved up to 89:11 ratio (entries 2 and 3). Inorganic bases, although being effective, proved to be poorly stereoselective (entries 4 and 5). These preliminary results prompted us to check tertiary amines in order to achieve good levels of diastereoselectivity at stoichiometric loading. Pleasingly, sterically hindered *N*,*N*-disopropyl ethyl amine (DIPEA) afforded **5a** in 77% yield and 91:9 diastereomeric ratio (d.r.) (entry 6). The *tert*-butyl ester glycinate benzophenone Schiff base **3b** was then reacted under the same reaction conditions leading to **5b** in 20% yield and 95:5 d.r. (entry 7).

Table 1. Optimization study for the Michael addition and hydrolysis step.[a]



Entry	Base [mol%]	Solvent	*t* [h]	d.r. **4'**[b]	Yield **5**[c] [%] (d.r.)[b]	**5**
1	DABCO (20)	THF	24	77:23	82 (77:23)	**5a**
2	piperidine (20)	THF	5	n.d.	70 (52:48)	**5a**
3	DMAP (20)	THF	120	90:10	52 (89:11)	**5a**
4	Cs_2CO_3 (20)	THF	15	56:44	89 (50:50)	**5a**
5	LiOH (20)	THF	3	52:48	70 (54:46)	**5a**
6	DIPEA (100)	THF	72	92:8	77 (91:9)	**5a**
7	DIPEA (100)	THF	72	95:5	20 (95:5)	**5b**
8	Et_3N (100)	THF	72	90:10	55 (90:10)	**5b**
9[d]	DIPEA (100)	THF	31	95:5	55 (95:5)	**5b**
10[d]	DIPEA (100)	AcOEt	31	95:5	54 (95:5)	**5b**
11[d]	DIPEA (100)	MeTHF	31	95:5	38 (95:5)	**5b**
12[d]	DIPEA (100)	EtOH	23	90:10	72 (90:10)	**5b**
13[d]	DIPEA (100)	DEC	24	95:5	72 (95:5)	**5b**

[a] Reaction conditions: **2a** (0.1 mmol), **3** (0.12 mmol) in 0.2 mL of solvent. In the hydrolysis step the reaction mixture was diluted in THF (0.5 mL) and 60 μL of HCl 2 N were added. [b] Determined by ^{1}H NMR analysis on the crude reaction mixture. [c] Yield of isolated product. [d] The Michael reaction was carried out at 50 °C and at $C = 0.9$ M.

When using less sterically hindered triethyl amine under the same reaction conditions, the conversion to product **5b** increased although a slightly decreased stereocontrol was observed (entry 8). Finally, the first step was carried out at 50 °C under more concentrated conditions using DIPEA (entry 9). Interestingly, the conversion increased after a shorter reaction time and more importantly the stereoselectivity ratio was maintained to 95:5. Under these conditions, the first step was screened using more environmentally friendly solvents, such as ethyl acetate, ethanol, 2-methyl tetrahydrofuran (MeTHF), and diethyl carbonate (DEC) (entries 10–13). The solvents were then removed under reduced pressure and the crude mixture was hydrolyzed in THF under usual conditions. DEC was found to be the most useful medium, providing compound **5b** in 72% yield and 95:5 d.r. (entry 13).

The structure and the relative configuration of the three stereocenters were confirmed by single-crystal X-ray analysis on the major diastereoisomer, which enabled us to assign the compound as (*trans*,*trans*)-**5b** isomer (Figure 2).

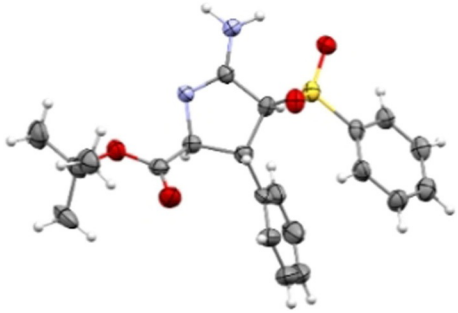
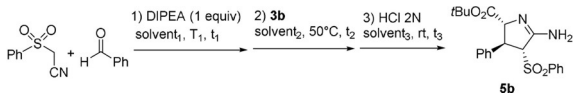


Figure 2. ORTEP-drawing of the molecular structure of the major diastereoisomer (±)-**5b** with ellipsoids shown at 50% probability level. Color code: oxygen (red), nitrogen (blue), sulfur (yellow), carbon (grey), hydrogen (white).

Table 2. Optimization study for the one-pot approach starting from model reagents.[a]



Entry	Solvent$_1$, T_1 [°C], t_1 [h]	Solvent$_2$, t_2 [h]	Solvent$_3$, t_3 [h]	Yield **5b**[b] [%]	d.r. **5b**[c]
1	DEC, RT, 8	DEC, 22	THF, 1.5	75	92:8
2	DMC, RT, 8	DMC, 24	THF, 1	75	88:12
3	DMC, RT, 8	DMC, 29	MeTHF, 1	77	90:10
4	DEC, RT, 9	DEC, 25	DEC, 31	66	94:6
5	DEC, 50, 3.5	DEC, 21	MeTHF, 1	77	92:8

[a] Reaction conditions: benzaldehyde (0.15 mmol), (phenylsulfonyl)acetonitrile (0.15 mmol) DIPEA (0.15 mmol) in 150 µL of solvent. In the second step **3b** (0.18 mmol). After ending of Michael addition, DEC or DMC was removed under reduced pressure. In the hydrolysis step the reaction mixture was dissolved in THF or MeTHF (0.75 mL) and 100 µL of HCl 2 N were added. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis on the crude reaction mixture.

Further optimization was then carried out starting from commercially available benzaldehyde and phenyl sulfonylacetonitrile to include the Knoevenagel condensation step into the one-pot procedure (Table 2). DEC was used as the solvent for the condensation to form the alkene at room temperature in the presence of 1 equivalent of DIPEA (entry 1). After the reagents were converted into alkene **2a**, compound **3b** was added according to the conditions reported in entry 13 of Table 1.

Product **5b** was isolated in 75% yield and 92:8 d.r. The same sequence performed in dimethyl carbonate (DMC) for the first and second step furnished compound **5b** in good yield but slightly reduced diastereoselectivity (entry 2). When THF was replaced by more convenient MeTHF in the hydrolysis and cyclization steps, the product **5b** was recovered in 77% yield and 90:10 d.r. (entry 3). The sequence was then entirely carried out in DEC, which demonstrated to be the most effective solvent for the stereocontrol (entry 4). However, hydrolysis and cyclization proceeded rather slowly and after a prolonged reaction time, product **5b** was isolated in 66% yield. Finally, the reaction conditions reported in entry 1 were modified replacing THF with MeTHF and performing the Knoevenagel condensation at 50 °C (entry 5). In this case, shorter reaction times could be applied for the overall process and amidine **5b** was recovered in 77% overall yield and 92:8 d.r.

Under conditions illustrated in entry 5 of Table 2, the scope of the one-pot process was next investigated (Figure 3). The protocol appeared to be of general application starting from differently substituted aromatic and heteroaromatic aldehydes. Cyclic amidines **5c–f**, bearing electron-withdrawing groups

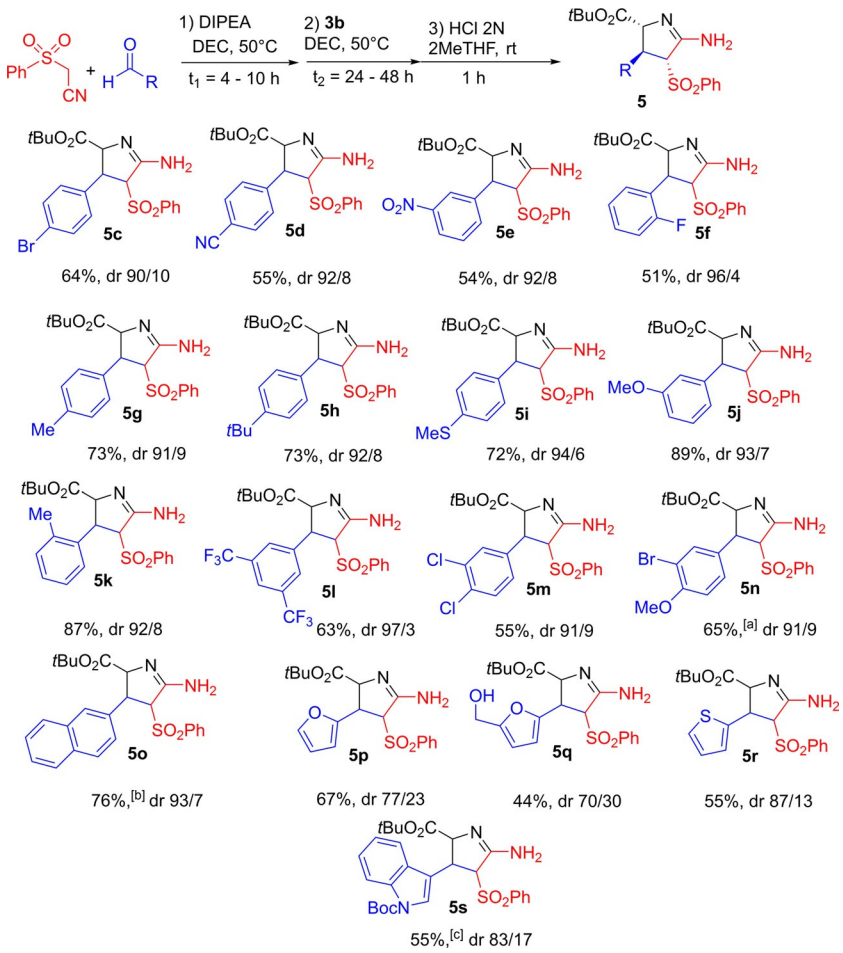
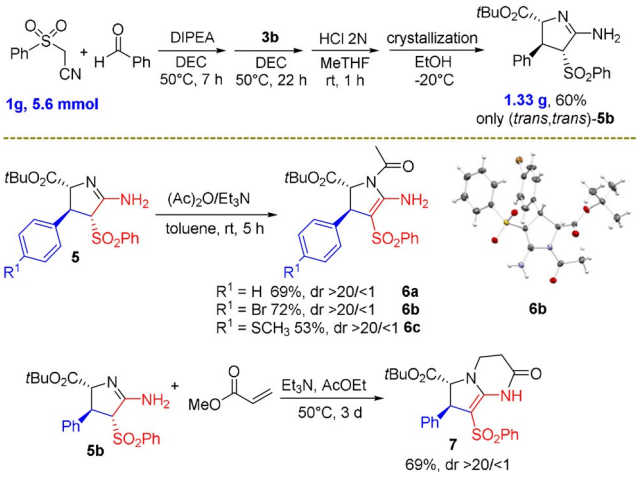


Figure 3. Substrate scope in the synthesis of heterocycles **5**. Reaction conditions: phenyl sulfonylacetonitrile (0.15 mmol), aldehyde (0.15 mmol), DIPEA (0.15 mmol) in 150 µL of DEC at 50 °C until disappearance of reagents. Then **3b** (0.18 mmol) was added. After ending of Michael addition, DEC was removed under reduced pressure. In the hydrolysis step, the reaction mixture was dissolved in MeTHF (0.75 mL) and 100 µL of HCl 2 N were added. Yields refer to isolated product. d.r. was determined by ^{1}H NMR analysis on the crude reaction mixture. [a] t_1 = 16 h. [b] t_1 = 21 h. [c] t_1, t_2 = 2 h, 216 h.

at *para*, *meta*, and *ortho* positions of the aromatic ring, were isolated in good overall yield and high diastereoselectivity. Compounds **5g**–**k**, bearing electron-donating substituents in the aromatic ring, were obtained in excellent overall yields (up to 89%) and high diastereoselectivity. Interestingly, doubly substituted starting aromatic aldehydes were smoothly converted into the corresponding products **5l**–**n** with high to excellent level of diastereocontrol (d.r. up to 97:3). Finally, cyclic amidines **5o**--**s**, bearing 2-naphthyl or oxygen-, sulfur-, and nitrogen-containing heteroaromatic moieties at position 3 of the five-membered ring, were prepared in satisfactory yields and moderate to high diastereoselectivity. It is important to point out that the protocol can be effectively applied to incorporate cheap and renewable platform molecules derived from biomass, such as furfural and hydroxymethylfurfural, into amidines of high added value (**5p**,**q**). The heterocyclic compounds **5p**,**q** were isolated in satisfactory overall yield and d.r., considering the susceptibility of furfural and hydroxymethylfurfural to decomposition. The protocol has some limitations when applied to aliphatic aldehydes, which are known to suffer of competitive pathways in the Knoevenagel condensation, affording the alkenes in very low yields.[12b,15]

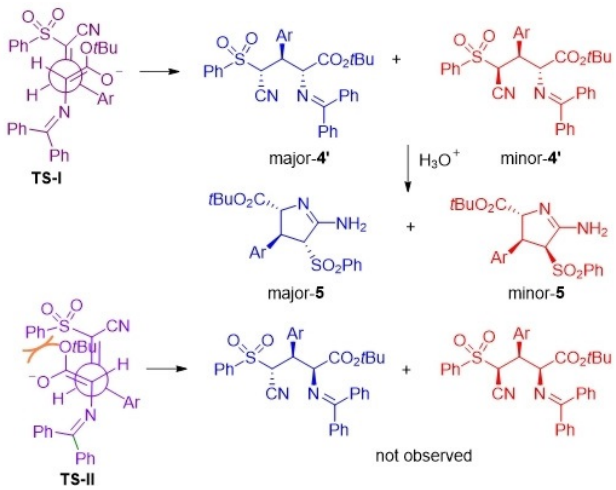
To verify the applicability of the process, model reaction was scaled up at 1 g of phenyl sulfonylacetonitrile (Scheme 3). Pleasingly, at the end of the process after aqueous work-up, the crude mixture was crystallized in EtOH affording pure major *trans*,*trans*-**5b** in 60% yield. Finally, post-functionalizations on the amidine reactive group using diastereomeric mixtures of selected compounds **5b**,**c**,**i** were performed (Scheme 3). Under acetylation conditions compounds **5b**,**c**,**i** were converted into product **6a**,**b**,**c** in 69, 72 and 53% yield as the sole diastereoisomer, respectively. The structure of compounds *trans*-**6** was confirmed by single-crystal X-ray analysis on diastereoisomer **6b**. More interestingly, after treating model amidine **5b** with methyl acrylate, a single diastereoisomer of the bicyclic product **7** was obtained in 69% yield, via an aza-Michael addition/lactamization sequence. In all the elaborations, reagent **5** underwent a stereoablative process leading to the formation of products **6** and **7**, bearing a new endocyclic C=C double bond.[16]



Scheme 3. Scale-up procedure and post-functionalizations of 5-amino-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid esters **5**. Only the major isomer of the epimeric mixture at C-4 of compounds **5** is shown (**5b** d.r. 92:8; **5c** d.r. 90:10; **5i** d.r. 94:6).

Formation of the *trans*,*trans*-**5** diastereoisomer has been rationalized assuming the involvement of an open transition state in the Michael addition step (Scheme 4). The diastereochemical outcome of the process is established in the Michael addition step, since according to results reported in Table 1, the diastereoselectivity is maintained after hydrolysis and cyclization. Given the sterically demanding base used, the diastereoselectivity would be consistent with an open transition state model, where the trisubstituted alkene is attacked by the (*E*)-*N*-protected glycine enolate in a staggered conformation about the forming C–C bond. The unfavorable OR/$PhSO_2$ interaction in **TS-II**, suggests that **TS-I** should be energetically preferred. Protonation of the adduct from the less sterically hindered face would give major adduct-**4'** (blue). Hydrolysis and cyclization would then proceed to give the final *trans*,*trans*-amidine **5** (blue), whose structure was confirmed by X-ray analysis. Post-functionalizations illustrated in Scheme 3 are in agreement with this proposal. After acetylation of compounds **5** as mixture of diastereomers, a single *trans*-isomer of product **6** was obtained via stereoablative removal of the epimeric stereocenter, as confirmed by single-crystal X-ray analysis.

In summary, a novel and straightforward approach to functionalized 5-amino-3,4-dihydro-2*H*-pyrrole-2-carboxylic acid esters has been efficiently developed. The process exploits a Knoevenagel condensation/Michael addition/hydrolysis/cyclization sequence in a single flask to access libraries of cyclic amidines of potential utility in medicinal chemistry. Cyclic amidines are isolated in good to high yield and generally high diastereoselectivity. The feasibility of a convenient scale up procedure, enabling the isolation of pure major diastereomer, has been demonstrated. Of note, this one-pot protocol employs all commercially available materials, green and biodegradable solvents derived from renewable sources. Further investigations to extend the one-pot approach to other suitable cyano-containing reagents are underway in our laboratory.



Scheme 4. Proposed stereochemical outcome of the one-pot sequence.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amidines · diastereoselectivity · green solvents · metal-free · one-pot reaction

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[15] When an aliphatic alkene **2**, obtained under different reaction conditions, was treated under conditions reported in Table 1, entry 5, the final product **5** was isolated after prolonged reaction time in moderate yield and poor diastereoselectivity (see the Supporting Information).

[16] For a recent review, see: V. Bhat, E. R. Welin, X. Guo, B. M. Stoltz, *Chem. Rev.* **2017**, *117*, 4528 – 4561.

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