Diastereoselective Synthesis of Substituted Chromenopyrrolidinones from Amino Acid Derived Nitriles

Heikinheimo, Annakaisa; Nieger, Martin; Koskinen, Ari M. P.

2023-07-25
Georg Thieme Verlag
http://hdl.handle.net/10138/572751
Heikinheimo, A, Nieger, M & Koskinen, A M P 2023, 'Diastereoselective Synthesis of Substituted Chromenopyrrolidinones from Amino Acid Derived Nitriles', Synlett, vol. 34, no. 12, pp. 1512-1518. https://doi.org/10.1055/a-1992-6650

Diastereoselective Synthesis of Substituted Chromenopyrrolidinones from Amino Acid–Derived Nitriles

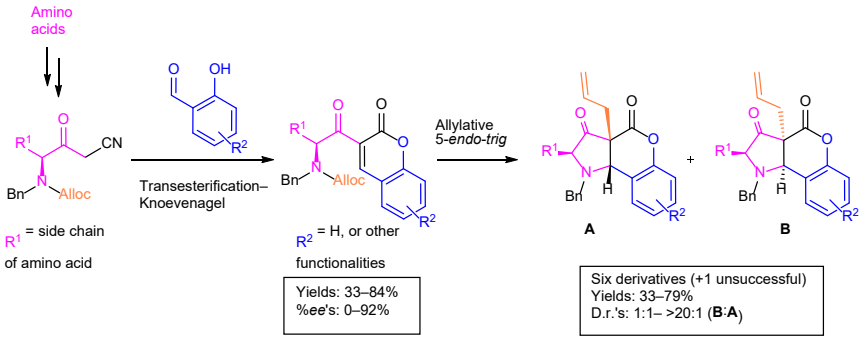
Annakaisa Heikinheimo[a,1]
Martin Nieger[b]
Ari M.P. Koskinen*[a]

[a] Department of Chemistry and Materials Science, Aalto University, School of Chemical Engineering, PO Box 16100, FI-00076 Aalto, Finland.

[b] Department of Chemistry, University of Helsinki, Helsinki (Finland)

ari.koskinen@aalto.fi

Dedicated to Professor Masahiro Murakami



Received:
Accepted:
Published online:
DOI:

Abstract Novel, substituted chromenopyrrolidininones have been synthesized from natural amino acid derivatives through an unprecedented sequence involving a Knoevenagel-transesterification sequence and an allylative palladium-catalyzed cyclization reaction. The products are nature-inspired heterocycles derived from natural amino acids. The targets could be synthesized with varying degrees of stereoselectivity: racemization is a known issue with amino acids and provided a formidable challenge to our method development, as well. Altogether, six derivatives were synthesized with yields from moderate to good.

Key words Pyrrolidinone, coumarin, chromenopyrrolidine, 5-*endo-trig*, amino acid racemization.

Differently substituted chromenopyrrolidines are potential new core structures for interesting pharmaceutical developments. Some syntheses of chromeno[4,3-*b*]pyrrolidines have been reported, as well as syntheses of similar targets with slightly modified core structures, especially of those with nitrogen at position 12 or 13 (chromeno[3,4-*b*]pyrrolidines, *e.g.* by Bakthadoss *et al.*[2]) or without a ketone at position 9 (chromenopyrroles, *e.g.* by Cao *et al.*[3] **Figure 1**). If the different oxidation states of the *N*-pentacycle are also considered, the number of reported syntheses and interesting targets increases further. A recent review by Dalpozzo *et al.* highlights recent advances in the asymmetric synthesis of chromene derivatives.[4]

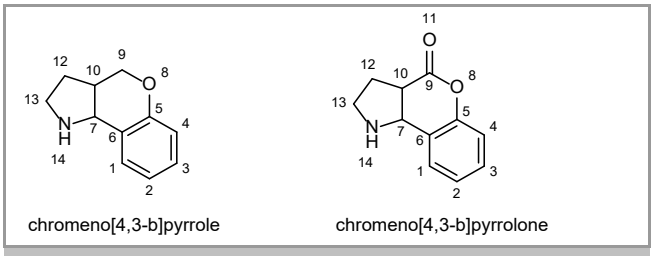
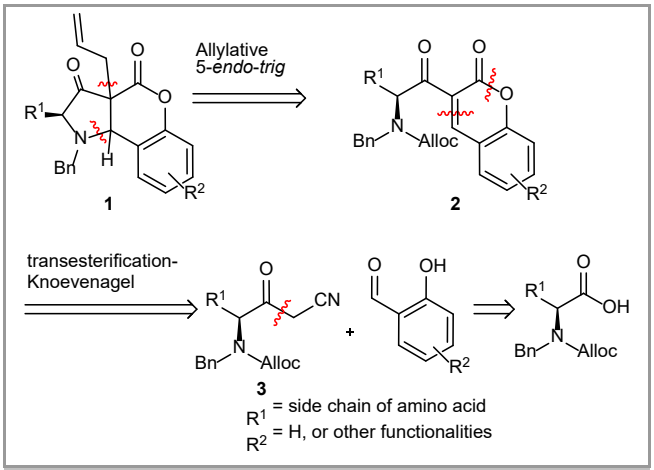


Figure 1. Core structures of some chromenopyrrolidine synthetic targets. The nomenclature is simplified here for easier comparison and distinction between these structures.

To the best of our knowledge, there are only a few synthetic reports on targets containing a chromeno[4,3-*b*]pyrrolone core depicted in **Figure 1**.[5] These strategies employ related starting materials in [3+2] cascade reactions with bifunctional organocatalysts.

Some time ago we reported a unique efficient enantioselective 5-*endo-trig* cyclization leading to novel pyrrolidine structures.[6] We envisioned that proper modification of this route would also give access to a new class of the title compounds. **Scheme 1** shows the general synthesis plan: synthesis of substituted coumarin compounds from relevant amino acids would deliver the active substrates for cyclization to give the target chromenopyrrolidinones in the final step.



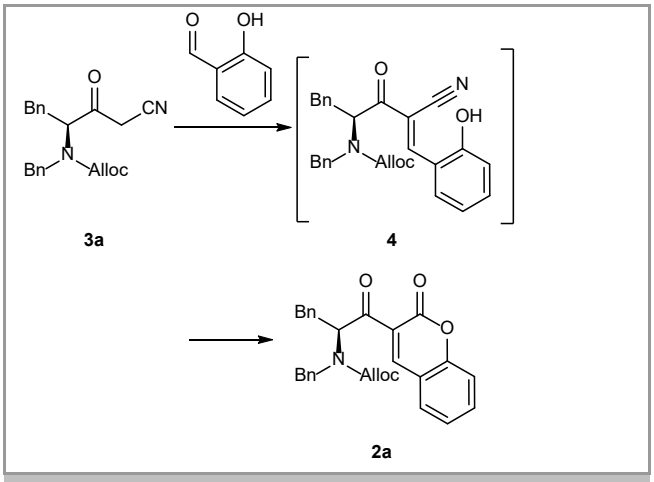
Scheme 1. Retrosynthesis of chromenopyrrolidinones.

Using a β-ketoester corresponding to the β-ketonitrile **3a** as an intermediate initially seemed like a good, simple idea. However, despite several attempts of forming the β-ketoesters from activated amino acid derivatives under either basic or acidic conditions, the products were partly or completely racemic.

We therefore decided to rely on the original pyrrolidinone synthesis and use β-ketonitrile **3a**, derived from L-phenylalanine, in a Knoevenagel condensation with salicylaldehyde, sequenced with intramolecular nitrile hydrolysis (**Scheme 2**). This sequence seemed promising as the Knoevenagel condensation of this and similar substrates had already been studied extensively in our group and proved safe in terms of enantiopreservation. Intramolecular hydrolysis of the nitrile might be achieved with standard Brønstedt acid protocols or even with milder conditions given the favorable aromatization and formation of a six-membered ring associated with the transformation.

This indeed delivered the desired product: the Knoevenagel conditions developed earlier were applied as such, and the products were isolated by silica column chromatography. This already gave the coumarin product in 21% yield (25 mg) on a 0.26 mmol (95 mg) scale. Additionally, 75 mg of another compound was obtained. This was presumed to be Knoevenagel product **4** (corresponding to a yield of 62%): the NMR spectra could not be reliably interpreted but HRMS supported this presumption. It was further dissolved in THF and treated with a drop of aqueous HCl (1 M). In a few minutes, full conversion to **2a** was observed, and the product was isolated, giving a combined yield of 86%. Chiral HPLC suggested nearly complete preservation of *ee* for the product fraction isolated prior to acid treatment. However, HCl was causing lowering of *ee*.

As for the progression of the transformation, we presumed that the intermediate product from the first step is the Knoevenagel product (**4**, **Scheme 2**). The intermediate was isolated and purified using neutralized silica (pre-treated with triethylamine) in a flash column, but the NMR spectra of the isolated solids (bright yellow color as compared to the nearly colorless coumarin product) were still dubious. Thus, it was also not possible to determine the *E*/*Z*-ratio of the intermediate.



Scheme 2. Coumarin formation from phenylalanine-derived β-ketonitrile. Various conditions.

Hydrolysis of the nitrile was first achieved with HCl catalysis, so we decided to seek for milder conditions with alternative reagents. Acetic acid and $NaHCO_3$ were tested, but only trace amounts or no product were detected. We considered the possibility of silica gel catalysis: the coumarin product was originally isolated by running it through silica, and a literature precedent was found to back up this idea.[7] Silica also seemed like a very mild catalyst for the transformation. By adding silica gel straight to the Knoevenagel reaction mixture and stirring at room temperature, the coumarin product was obtained in moderate to good yield (40–75%). However, the enantiomeric excess was still found to be compromised (70–82%), with the yield and *ee* depending on reaction time. Isolating the intermediate and applying silica gel catalysis as a separate step did not change these numbers. Figure 2 illustrates indicatively the dependence of *ee* and yield on reaction time (as calculated from the addition of silica gel) based on a few representative examples. Later results were found to roughly follow these trends up to around 3–4 hours. After this, the yield hits a plateau at around 75% but the *ee* keeps dropping until it reaches 0% (not shown in the figure).

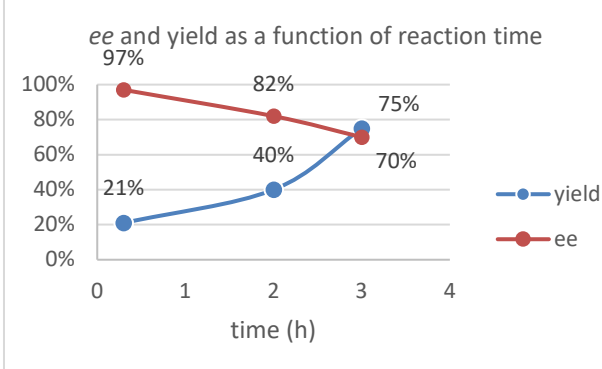


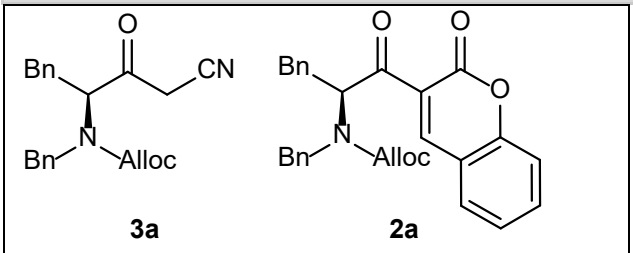
Figure 2 Dependence of *ee* and yield on reaction time (t, calculated from the addition of silica gel). 20 mol-% of morpholine were used for these experiments. Conditions: **3a** (100 mol-%), CH_2Cl_2 (0.5 M), molecular sieves (3 Å, 100 w-%), salicylaldehyde (110 mol-%), morpholine (20 mol-%), 60 min, rt, Ar; then silica gel (300 w-%), CH_2Cl_2 (diluting to 0.1 M), t (h), rt.

Optimization of reaction conditions

Using dichloromethane as the solvent for both steps, the reaction proceeded efficiently. Other solvents – tetrahydrofuran, diethyl ether, acetonitrile, and ethanol – were also tested, but both steps were significantly slower in them. In ethanol, significant amounts of side products were also formed. Thus, we settled for dichloromethane and decided to run more experiments on racemization.

Experiments were conducted to control the individual effects of the reaction variables on racemization of the β-ketonitrile substrate (**3a**) and the coumarin product (**2a**). **Table 1** summarizes the relevant experiments. When the β-ketonitrile was stirred with morpholine in dichloromethane overnight, the substrate was completely racemized (Entry 1). When stirred with silica gel in dichloromethane overnight, the substrate racemized to some degree (from > 98% to 70% *ee*, Entry 2). In two days under the same conditions, the substrate was completely racemized (Entry 3). Similar experiments were run for the coumarin product (Entries 4 and 5): morpholine was found to induce complete racemization of the product overnight, whereas silica gel did so partly, with the *ee* dropping from 75% to 35%.

Table 1. Racemization during the coumarin formation was investigated with control experiments.



Entry	Substrate	Reagent[a]	t	%*ee*	
				before	after
1	**3a**	morpholine	o/n	>98	0
2	**3a**	silica gel	o/n	>98	70
3	**3a**	silica gel	2d	>98	0
4	**2a**	morpholine	o/n	75	0
5	**2a**	silica gel	o/n	75	35

[a] 300 mol-% of silica gel or 23 mol-% of morpholine were used

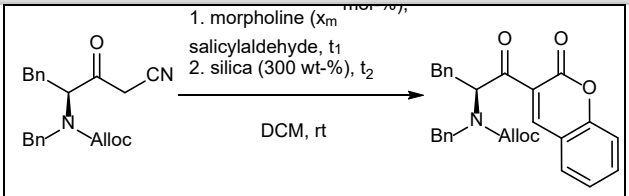
The intermediate product from the Knoevenagel reaction was heated (T = 100 °C) overnight and mostly gave the product by crude NMR (sample filtered through a short pad of silica gel). We tried using different amounts of silica, but this did not have major effects on the progression or outcome of the reaction. If the amount of silica was much less than 300 wt-%, longer reaction times were needed, but adding more did not have any effect.

We then experimented on how varying the amount of morpholine would affect the outcome (Table 2). Entry 1 shows the typical conditions and results of several experiments for the synthesis of phenylalanine-derived coumarin. The yield is typically around 70% with an *ee* of 75%. When the amount of morpholine is reduced from 20% to 10% (Entry 3) and further to 5% (Entry 5), the *ee* gets slightly better but the yield starts diminishing – longer reaction times are needed. To keep the yield around 70%, either the amount of amine needs to be raised or the time of the second step (t_2) needs to be longer. Both alterations in the reaction setup were found to induce reduction in the *ee*. In fact, the whole transformation could be done using only silica gel as the catalyst, in dichloromethane. However, full conversion took a long time (at least o/n) and full racemization was inevitable (Entry 6).

We wanted to test if the use of a bulkier base would help prevent scrambling of the α-hydrogen (Entries 7 and 8): 10 mol-% of tetramethylpiperidine gave the product in 81%*ee* in three hours, whereas overnight the product was fully racemized. This compares to the results obtained with morpholine (Entry 7 vs. Entry 3).

Adding morpholine and silica gel both at the start gave similar results in terms of yield and *ee* in comparison to separate steps (Entry 3 vs. Entry 4).

Table 2. Coumarin synthesis with the β-ketonitrile substrate.

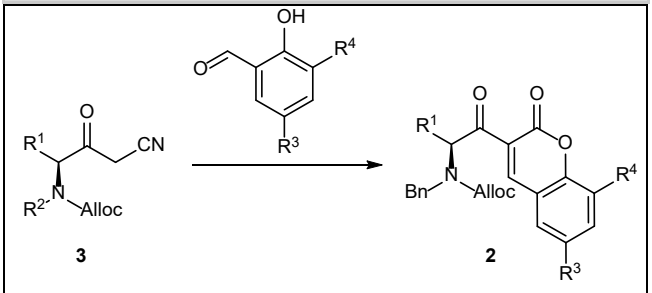


Entry	x_m (mol-%)	t_1 (min)	t_2 (h)	Yield (%)	%*ee*
1	20	45	3	70	75
2[d]	23	60	3	nd	75
3	10	0	3	52	82
4	10	45	3	27[b] (50[c])	81
5	5	45	3	44[b] (57[c])	83
6	-	-	o/n	nd	0
7	10[a]	40	4.5	56	81
8	10[a]	5	o/n	66	0

[a] 2,2,6,6-tetramethylpiperidine was used as base;
[b] impure fractions not collected;
[c] yield calculated from crude NMR;
[d] anhydrous solvent used.

A selection of substituted aminocoumarins (chromenones) was synthesized with this method (**Table 3**). L-Phenylalanine-derived substrates (Entries 1–4) gave products 2a–2d with varying yields (33–84%) with *ee*'s between 60 and 75%.[8] β-Ketonitriles derived from other amino acids (L-alanine, L-valine, L-leucine, and L-proline) gave the products in moderate yields (35–64%). Leucine- and valine-derived substrates (**2f** and **g**, respectively) gave the best *ee*'s (87–92%). Reaction times were adjusted as deemed appropriate for each substrate by following the reactions by TLC.

Table 3. Aminocoumarins were synthesized using β-ketonitriles derived from selected amino acids as starting materials.



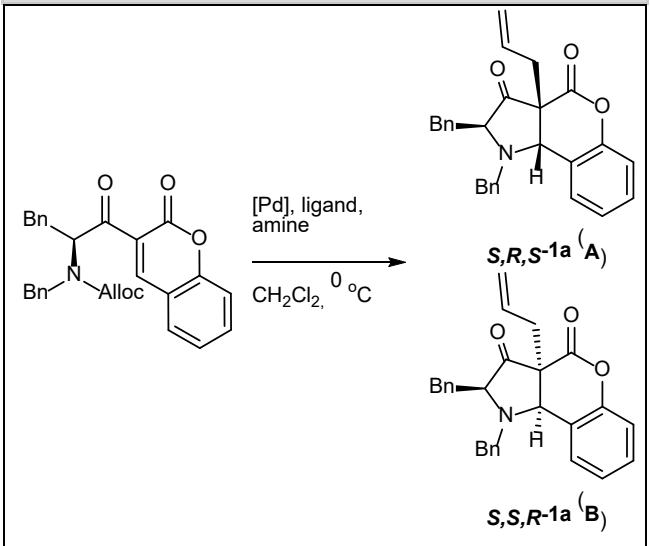
Entry	R^1 (L-aa)	R^2	R^3	R^4	Product	Yield (%)	%*ee*
1	Bn (Phe)	Bn	H	H	**2a**	84/45	74/82

2	Bn (Phe)	Bn	H	Cl	**2b**	38	62
3	Bn (Phe)	Bn	^{t}Bu	H	**2c**	63	72
4	Bn (Phe)	Bn	NO_2	H	**2d**	33	66
5	Me (Ala)	Bn	H	H	**2e**	59	nd
6	^{i}Pr (Val)	Bn	H	H	**2f**	58/35	87/92
7	^{i}Bu (Leu)	Bn	H	H	**2g**	41	92
8	-$CH_2CH_2CH_2$-(Pro)		H	H	**2h**	64	nd

In order to find a solution to the racemization problem, we devised synthesis plans using selected nitrogen protecting groups (Bn = benzyl,[9] Pf = phenylfluorenyl[10]) that have been shown to effectively protect the sensitive amino acid α-position from racemization. Although the desired coumarins could be synthesized without racemization, cleavage of the protecting groups proved problematic and gave only low yields. Therefore, neither strategy was pursued further.

Subjecting the phenylalanine-derived coumarin (**2a**) to the reaction conditions of the original cyclization, the cyclized product was obtained with a diastereoselectivity of about 4:1 (**Table 4**, Entry 1).[11] The relative configurations of the isolated products were concluded by NOESY measurements. A ligand screen revealed that by choosing a proper bidentate chiral ligand for palladium, diastereoselectivity and yield were improved remarkably: with both (+)- and (−)-DIOP, a diastereoselectivity of >20:1 (**B:A**) was observed (Entries 2 and 3), whereas BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthalene) and SEGPHOS ([(4,4′-bi-1,3-benzodioxole)-5,5′-diyl]bis(diphenylphosphine)) did not deliver any product.

Table 4. Ligand screen.

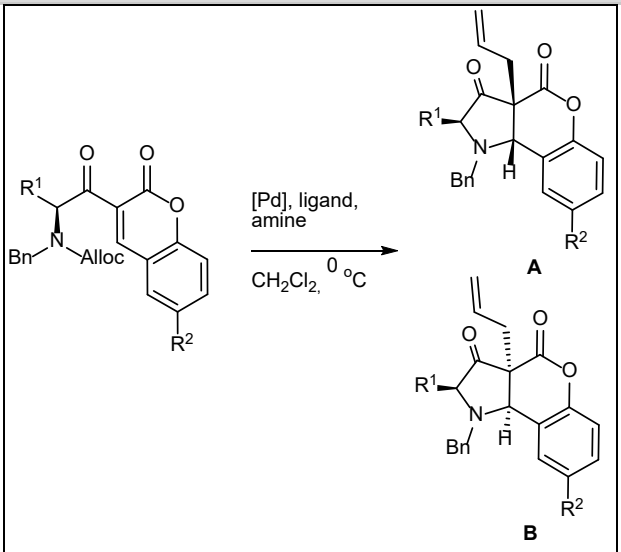


Entry	Ligand	d.r. /A:B)[a]	t (h)	Yield (%)
1	PPh_3	1:3.4	22	37
2	(+)-DIOP	<1:20	22	58
3	(-)-DIOP	<1:20	24	51

[a] d.r. determined from the isolated product mixture
[b] Isolated yield

The selectivity was further studied with a substrate bearing *tert*-butyl substitution in the coumarin skeleton and with a valine-derived substrate, and interesting results emerged (**Table 5**). Most notably, the selectivity was most efficiently reversed with a bulkier R^1 group (iso-propyl from valine vs. benzyl from phenylalanine), with the valine derivative giving now a 4.5:1 selectivity for diastereomer **A** with both PPh_3 and (+)-DIOP (Entries 2 and 5). With (−)-DIOP, no selectivity was seen (Entry 8). *tert*-Butyl substitution had a similar but weaker effect with (+)-DIOP delivering the **A**-isomer in a modest 2:1 selectivity (Entry 6). Triphenylphosphine gave no selectivity (Entry 7).

Table 5. Comparing diastereoselectivity during cyclization with valine- and phenylalanine-derived coumarin substrates.



Entry	R^1	R^2	Ligand	Product	Yield (%)[d]	d.r. (A:B)	Major isomer isolated
1[c]	Bn	H	PPh_3	**1a**	37	1:3.4[a]	**B** (29%)
2	Bn	H	(+)-DIOP	**1a**	58	<1:20[a]	**B**
3	Bn	H	(-)-DIOP	**1a**	51	<1:20[a]	**B**
4	Bn	^{t}Bu	PPh_3	**1c**	62	1:1[a]	**A** (13%, 1:10 d.r.)
5	Bn	^{t}Bu	(+)-DIOP	**1c**	77	2:1[a]	**A** (not separated)
6	^{i}Pr	H	PPh_3	**1f**	73	4.5:1[b]	**A** (51%, 14:1 d.r.)
7	^{i}Pr	H	(+)-DIOP	**1f**	77	4.5:1[b]	**A** (58%, 14:1 d.r.)
8	^{i}Pr	H	(-)-DIOP	**1f**	nd	1:1[b]	-
9	^{i}Bu	H	PPh_3	**1g**	67	1:1[a]	-
10	^{i}Bu	H	(+)-DIOP	**1g**	72	10:1	**A**

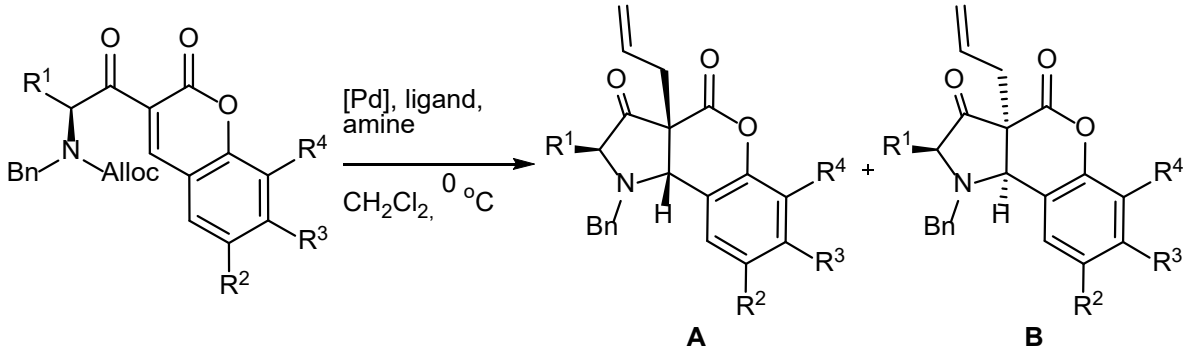
[a] d.r. determined from the isolated product fractions by 1H NMR
[b] d.r. determined from the crude mixture by 1H NMR
[c] Pyrrolidine was used instead of morpholine
[d] Combined isolated yield of diastereomers

Compound **1a** was obtained as practically the only product and could be further purified chromatographically to give a pure diastereomer. The diastereomers of valine-derived chromenopyrrolidinone **1f** (**A** and **B**) could be partially separated by chromatography, and the major isomer **A** was further purified by crystallization (**A** started crystallizing in the test tubes during chromatography). Luckily, we were able to

obtain crystals that could be fully analyzed by X-ray diffraction, and the absolute stereochemistry of *S*,*R*,*S*-**1f** was verified (see SI).

Selected chromenopyrrolidinones were synthesized, the relevant results are collected in **Table 6** (partly same entries as in **Table 5**). Coumarins derived from phenylalanine (Entries 1–4), alanine (Entry 5), leucine (Entry 6), and valine (Entry 7) were used as substrates. Synthesis of proline-derived chromenopyrrolidinone **1h** was also attempted but no product was obtained despite several trials.

Table 6. A small library of chromenopyrrolidinone compounds was synthesized from selected L-amino acids.



Entry	R^1	R^2	R^3	R^4	Ligand	Product	Yield[a]	d.r. (A:B)
1	Bn	H	H	H	(+)-DIOP	**1a**	58%	<1:20[e]
2	Bn	H	H	Cl	PPh_3	**1b**	43%	1:5[g]
3	Bn	*t*Bu	H	H	PPh_3	**1c**	65%	1:1[b]
4	Bn	NO_2	H	H	PPh_3	**1d**	33%	1:8[e]
5	Me	H	H	H	PPh_3	**1e**	79%	3:3:1[e,f]
6	*i*Bu	H	H	H	(+)-DIOP	**1g**	72%	10:1[e]
7	*i*Pr	H	H	H	(+)-DIOP	**1f**	77%	4.5:1[b,c,d]

[a] Isolated, combined yield of diastereomers
[b] d.r. calculated from crude
[c] diastereomers partly separable by column chromatography
[d] major diastereomer obtained pure by crystallization
[e] d.r. calculated from isolated fractions
[f] stereochemistry not assigned
[g] d.r. could not be determined reliably by NMR

Conclusion

Overall, we developed a chiral pool–based and step-economic synthesis of substituted chromenopyrrolidines that comprise a chromeno[4,3-*b*]pyrrolone core and contain three stereocenters. The major drawback of the transformation was found to be its sensitivity in terms of *ee* preservation. Racemization experiments showed that β-ketonitrile **3a** as the substrate and coumarin **2a** as the product are just as sensitive to the racemizing effects of the reaction conditions.

The *ee*'s of the products varied between 75–97% depending on the substrates (variation in amino acid side chain and substitution on the aldehyde), reaction time, and amount of base. As optimization of both *ee* and yield is desirable but contradictory, a compromise must be made between these two. The yields could not be pushed higher than 70–75%, and this was usually reached in three hours for the nitrile hydrolysis step. However, the yields and required reaction times depend on the β-ketonitrile and aldehyde substitution, and optimization should be done for each substrate separately.

The tendency for racemization was dependent on the size of the amino acid alkyl chain: valine and leucine gave better *ee*'s in comparison to phenylalanine.

Amino acids are known for their tendency for racemization. Yet, we were surprised it happens under such mild conditions as in our case.

We thought it likely that silica gel as a Lewis acid or hydrogen bond donor and morpholine as a base cause the racemization at the α-center. However, it is evident from our experiments, that both are able to work alone, as well: morpholine is more detrimental to the enantiomeric purity of both the β-ketonitrile starting material and the amino coumarin product, but silica gel also racemizes both compounds to some degree.

The yields of the coumarin products varied from low to good. At least two reasons explain this: the reactions were not always pushed to completion because of the deteriorating *ee*, and a compromise was sought with each substrate – the β-ketonitrile was always fully consumed, but there was usually some Knoevenagel intermediate left in the crude. Still, when the reactions were allowed to reach completion, the yields remained moderate or good at best (<80%).

Funding Information

Magnus Ehrnrooth Foundation is gratefully acknowledged for funding (2018–2020).

Acknowledgment

The authors wish to thank Dr Oskari Karjalainen for insightful discussions and Samuel Higgs for preliminary experiments.

Supporting Information

YES (this text will be updated with links prior to publication) CCDC 2214257 (1f) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

References and Notes

(1) New address: A. Heikinheimo, CABB Oy, Kemirantie 1, 67900 Kokkola, Finland.

(2) Bakthadoss, M.; Sivakumar, N.; Sivakumar, G.; Murugan, G. *Tetrahedron Lett.* **2008**, *49*, 820–823.

(3) Cao, J.; Liu, J. Y.; Zhang, Y. M.; Wang, Z. Y.; Xu, P. F. *Org. Chem. Front.* **2019**, *6*, 674–678.

(4) Dalpozzo, R.; Mancuso, R.; Liu, Y. K. *Targets Heterocycl. Syst.* **2020**, *24*, 227–274.

(5) (a) Yoshida, Y.; Ishii, S.; Watanabe, M.; Yamashita, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1534–1538; (b) Tian, L.; Xu, G. Q.; Li, Y. H.; Liang, Y. M.; Xu, P. F. *Chem. Commun.* **2014**, *50*, 2428–2430; (c) Kowalczyk, D.; Albrecht, Ł. *J. Org. Chem.* **2016**, *81*, 6800–6807; (d) Cao, J.; Fang, R.; Liu, J.-Y.; Lu, H.; Luo, Y.-C.; Xu, P.-F. *Chem. Eur. J.* **2018**, *24*, 18863–18867; (e) Wang, J.; Li, Y.; Sun, J.; Wang, H.; Jin, Z.; Chi, Y.R. *ACS Catal.* **2018**, *8*, 9859–9864; (f) Kowalczyk-Dworak, D.; Albrecht, Ł. *Org. Biomol. Chem.* **2019**, *17*, 2624–2628; (g) Li, T.; Wang, J.; Xu,J.; Jin, J.; Chi, J.R.; Jin, Z. *Org. Lett.* **2020**, *22*, 326–330; (h) Das, T. K.; Biju, A. T. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Elsevier Ltd., 2020; Vol. 31, pp 1–82.

(6) Karjalainen, O. K.; Nieger, M.; Koskinen, A. M. P. *Angew. Chem. Int. Ed* **2013**, *52*, 2551–2554.

(7) Petrillo, G.; Novi, M.; Dell'Erba, C.; Tavani, C. *Tetrahedron* **1991**, *47*, 9297–9304.

(8) The typical procedure for the preparation of aminocoumarins from *N*-protected aminoketonitriles is described in the supporting information. The preparation of **2a** is given here as a representative example: **3a** (100 mol-%, 3 mmol, 1.08 g) was dissolved in CH_2Cl_2 (0.5 M, 6 mL) under Ar. Molecular sieves (3 Å, 100 w-%, 1 g) were added followed by salicylaldehyde (110 mol-%, 3.3 mmol, 370 mg, 320 µL) and morpholine (20 mol-%, 52 mg, 52 µL). This mixture was stirred at rt for 60 min. Silica gel (300 w-%, 3 g) was added followed by more CH_2Cl_2 (diluting to 0.1 M, 24 mL) to facilitate proper mixing, and the mixture was taken under ambient air. After stirring for 3 h, the mixture was concentrated under reduced pressure, and the resulting dry powder was loaded on a flash column. The crude mixture was purified by flash chromatography eluting with a mixture of EtOAc and heptane (1:5). **2a** (74%, 1.04 g, 2.2 mmol) was obtained as a slightly yellow, sticky oil. **HPLC** (Chiralpak IA; 15% IPA:hex; retention times: 17.59 min (L-derivative), 15.40 min (D-derivative)): 72% *ee*; **^{1}H NMR** (400 MHz, $CDCl_3$+TMS, rotamers in 2:3 ratio) δ 8.13 (s, 0.6H), 7.84 (s, 0.4H), 7.64-7.57 (m, 1 H), 7.53 (d, *J* = 7.4 Hz, 0.6H), 7.43 (d, *J* = 7.4 Hz, 0.4H), 7.35-7.05 (m, 12H), 5.99-5.74 (m, 1H), 5.54-5.00 (m, 3H), 4.70-4.28 (m, 4H), 3.51-3.32 (m, 1H), 3.00-2.90 (m, 0.6H), 2.89-2.81 (m, 0.4H); **^{13}C NMR** (100 MHz, $CDCl_3$+TMS, rotamers) δ 195.6, 155.7, 154.6, 146.5, 146.1, 138.2, 137.3, 134.0, 133.6, 132.5, 129.5, 129.4, 128.8, 128.5, 128.4, 128.3, 127.5, 126.4, 124.9, 118.3, 117.6, 116.7, 67.6, 66.9, 66.3, 65.8, 52.7, 51.7, 35.4, 34.7; **HRMS-ESI** calculated for $C_{29}H_{25}NO_5$ [M + H] 468.1718, found 468.1789; **IR** (film) ν 1689, 1609, 1559, 1449, 4236, 759 cm^{-1}; **$[\alpha]_D^{20}$** = +15.4 (*ee* 72%) / +31.59 (*ee* 84%) (*c* = 1 in CH_2Cl_2); **R_f** = 0.26 (3:7 EtOAc:hept.).

(9) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1997**, *62*, 2292–2297.

(10) (a) Karppanen, E. J.; Koskinen, A. M. P. *Molecules* **2010**, *15*, 6512–6547; (b) Lood, C. S.; Laine, A. E.; Högnäsbacka, A.; Nieger, M.; Koskinen, A. M. P. *European J. Org. Chem.* **2015**, *2015*, 3793–3805.

(11) The typical procedure for the preparation of chromenopyrrolidinones from *N*-protected aminocoumarins is described in the supporting information. The preparation of **1a** is given here as a representative example: The given *N*-bisprotected amino coumarin (100 mol-%, 1 mmol, 468 mg) was dissolved in CH_2Cl_2 (0.11 M, 11 mL) under Ar and cooled in a water-ice bath at 0°C. Molecular sieves (3 Å, 107 w-%, 500 mg) were added followed by morpholine (23 mol-%, 20 mg, 20 µL). Subsequently, $(AllylPdCl)_2$ (3 mol-%, 11 mg) and (+)-DIOP (9 mol-%, 45 mg) were added simultaneously. The resulting mixture was stirred until complete by TLC (16 h, slowly from 0 °C to rt). The mixture was filtered through a small pad of silica gel, concentrated, and purified by flash chromatography eluting with a mixture of EtOAc and heptane (1:5). **1a (B)** (58%, 246 mg, d.r. >20:1) was obtained as a bright-yellow foamy oil. **^{1}H NMR** (400 MHz, $CDCl_3$+TMS) δ 7.46-6.95 (m, 14H), 5.51-5.39 (m, 1H), 5.00-4.83 (m, 2H), 3.98 (d, *J* = 14.8 Hz, 1H), 3.77 (d, *J* = 14.7 Hz, 1H, overlapping), 3.76 (s, 1H, overlapping), 3.21 (dd, *J* = 6.8, 5.5 Hz, 1H), 2.90 (dd, *J* = 14.3, 6.8 Hz, 1H), 2.78 (dd, *J* = 14.3, 5.5 Hz, 1H), 2.60 (ddt, *J* = 14.0, 6.5, 1.1 Hz, 1H), 2.37 (ddt, *J* = 14.0, 8.5, 0.9 Hz, 1H); **^{13}C NMR** (100 MHz, CDCl3+TMS) δ 205.7, 164.0, 151.3, 137.5, 137.1, 130.7, 130.6, 130.5, 129.6, 128.3, 128.3, 127.2, 126.6, 124.5, 120.2, 118.9, 116.9, 70.1, 64.5, 59.3, 55.5, 38.5, 33.5; **HRMS-ESI** calculated for $C_{28}H_{25}NO_3$ [M + H] 424.1913, found 424.1900; **IR** (film) ν 1774, 1141, 732, 695 cm^{-1}; **$[\alpha]_D^{20}$** = −5.0 (c = 1.0, CH_2Cl_2); **R_f** = 0.45 (3:7 EtOAc:hept.).