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Very Important Publication

Diastereospecific Enantiodivergent Allylation of Pyrazolones as an Entry to β-Aminoamides

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Abstract: A diastereospecific enantiodivergent allylation of pyrazolones is reported which is catalyzed by a planar chiral pentaphenylferrocene based palladacycle. With the same catalyst batch both product enantiomers were selectively available. The method is applicable to structurally diverse substrates and gave products with enantiomeric excesses between 85 and 94%. In addition, we could show that pyrazolones are transformable into β-aminoamides.

Keywords: β-aminoamide; asymmetric catalysis; ferrocene; palladacycle; [3,3]-rearrangement

Introduction

Pyrazolones (systematic name: 4,5-dihydro-1H-pyrazol-5-one) represent an extraordinary class of five-membered aza-heterocycles, which are both widespread in natural products and extensively used in the pharmaceutical industry.[1] They are among the oldest synthetic pharmaceuticals[2] and show significant biological properties.[1c,3] Their range of pharmaceutical uses is very diverse. Among other things, they are used as tumor cell inhibitors, show an antimicrobial effect[4] and are evaluated as a tumor necrosis factor (TNF) inhibitor in rheumatism therapy (Figure 1, top left).[5] Other prominent examples include Edaravon (Figure 1, top middle, also marketed as Radicava)[1a,6] for the treatment of amyotrophic lateral sclerosis (ALS, a neurodegenerative disease, approval in 2017) as well as acute ischemic stroke and Antipyrin, the oldest synthetic, non-opioid analgesic (Figure 1, top right).[3a]

Next to the many pharmaceutical applications, pyrazolones are for instance used as building blocks for dyes and markers or as inhibitors against corrosion in steel (Figure 1, bottom left).[7] They also serve as ligands in complexes used as fluorescent dyes.[8] Furthermore, their use as efficient dopant in organic

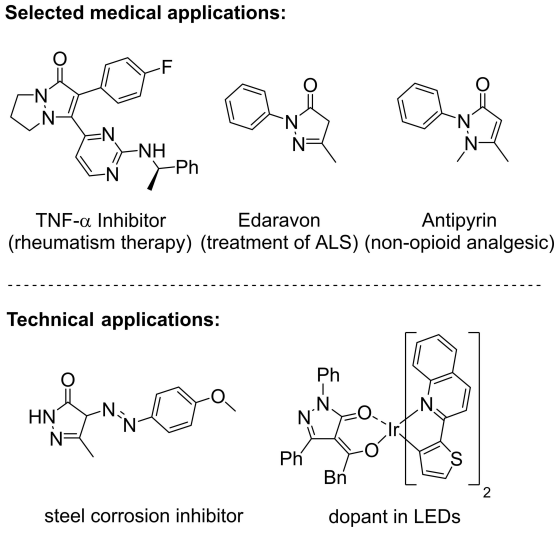


Figure 1. Selected applications of pyrazolones.

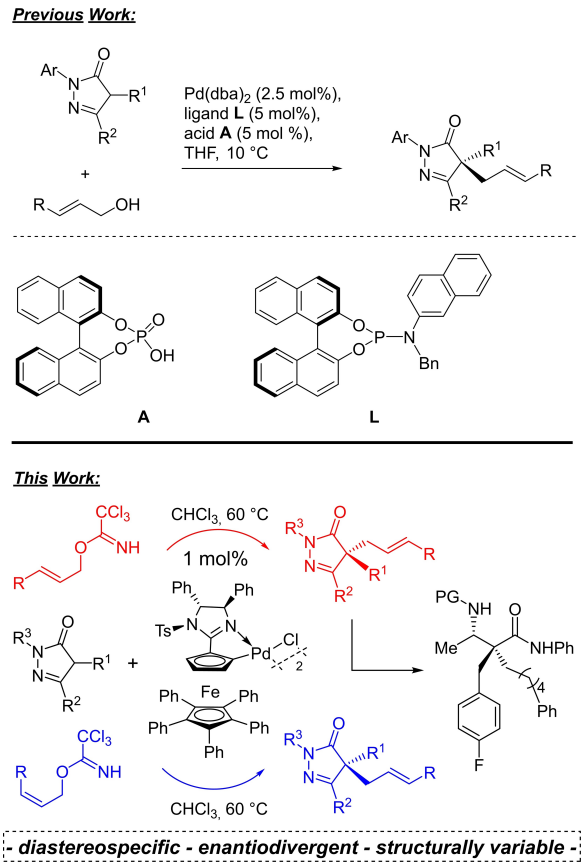
and polymeric light-emitting diodes (OLED & PLED) has been reported (Figure 1, bottom right).[9]

This wide range of applications demonstrates that pyrazolones form a particularly potent class of compounds in many areas. Therefore, their synthesis and functionalization is extensively studied.[10]

Arguably, the most important approach for asymmetric synthesis takes advantage of the nucleophilicity of the C(4) carbon.[10a,11] Edaravone, for example, has a pK_A value of 7.0 and, in its anionic form, reacts quickly with aldehydes in aldol condensations.[10c]

Gong et al. published the first catalytic asymmetric allylation of pyrazolones using allylic alcohols (Scheme 1, top).[12] They made use of the combination of a chiral Pd(0) complex and a chiral phosphoric acid cocatalyst, which provided the products in high yields and enantioselectivity. As a limitation, they found that pyrazolones carrying an aromatic R^2 at the imino C(3) react with moderate enantioselectivity.

Later, the same group also developed an oxidative method with alkenes.[13] Further studies employing Pd(0) catalysts for the synthesis of compounds bearing CF_3 substituted allylic side chains,[14] sequential Mannich additions/allylations[15] and allenylations were reported.[16] In addition, Rh catalysts in combination with methylalkynes were used.[17]



Scheme 1. Comparison to previous work.

Herein, we report the catalytic asymmetric allylation of pyrazolones using a Pd(II) catalyst. The latter, a planar chiral pentaphenylferrocene imidazoline palladacycle (PPFIP) was found to offer a very broad substrate scope that allows for variation of all four residues R & R^1–R^3 and tolerates also aromatic substituents R^2 as well as non-aromatic N(1) substituents.

In addition, we showcase that the catalysis products are suitable building blocks toward chiral highly enantioenriched β-aminoamides, a class of compounds which is also of large pharmaceutical importance.[18] For instance, Sitagliptin is used for the treatment of type II diabetes,[19] Bestatin as tumor therapeutic agent,[20] while Knyostatin (KNI-272) is an HIV protease inhibitor (Figure 2).[21]

Previous catalytic asymmetric syntheses[18a,22] of this structure type mainly used Mannich reactions,[18a,23] enzyme catalyzed resolutions,[24] reductive aminations,[25] enamine reductions,[26] and aza-Michael additions.[27]

Results and Discussion

As model reaction we selected the allylation of pyrazolone **1a** with the (*E*)-configured allylic imidate **2A** (Table 1). Planar chiral ferrocenyl palladacycles, initially developed by our group for [3,3]-rearrangements of allylic imidates,[28,29] were studied as catalysts, because in our previous work we also found that they are capable of activating pronucleophiles with C,N-π-bonds in α-position to a C,H-acidic C atom via enolization.[30]

Trichloroacetimidates **2**, which are prepared in one step from the corresponding allylic alcohol and trichloroacetonitrile, were found to be suitable substrates in the present work, as the corresponding [3,3]-rearrangements were quite slow under the investigated conditions with most of the studied catalysts. Alternative allylic substrates like alcohols, acetates and

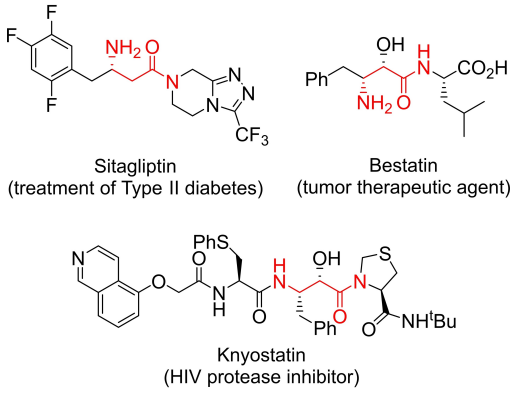
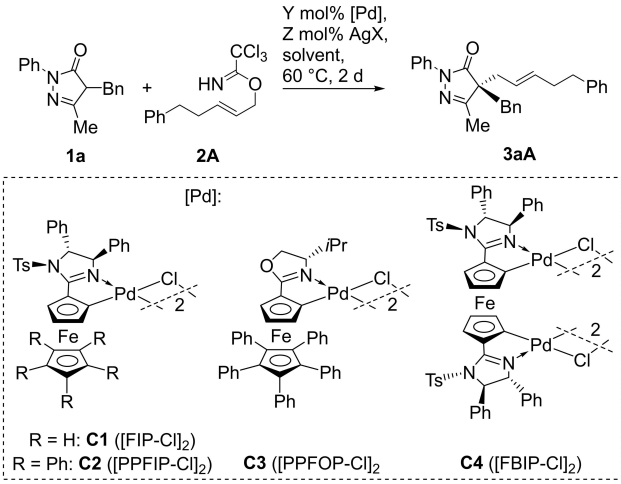


Figure 2. Selected medical applications of β-aminoamides.

Table 1. Development and Optimization of the Asymmetric Allylation of Pyrazolones.



#	[Pd]/X	Y; Z	solvent	conc. **1a** [mol/L]	yield [%][a]	ee [%][b]
1	**C1**/OAc	2.5; 5	$CHCl_3$	0.2	7	19
2	**C2**/OAc	2.5; 5	$CHCl_3$	0.2	65	83
3	**C3**/OAc	2.5; 5	$CHCl_3$	0.2	20	83
4	**C4**/OAc	1.25; 5	$CHCl_3$	0.2	26	61
5	**C2**/OTs	2.5; 5	$CHCl_3$	0.2	63	79
6	**C2**/acac	2.5; 5	$CHCl_3$	0.2	67	91
7	**C2**/–	2.5; 0	$CHCl_3$	0.2	95	93
8	**C2**/–	2.5; 0	THF	0.2	0	–
9	**C2**/–	2.5; 0	toluene	0.2	40	86
10	**C2**/–	1.0; 0	$CHCl_3$	0.2	41	80
11	**C2**/–	1.0; 0	$CHCl_3$	0.5	90	93

[a] Yield determined by ^{1}H-NMR.
[b] Enantiomeric excess determined by HPLC. OAc: acetate; OTs: tosylate; acac: acetylacetonate; THF: tetrahydrofuran.

carbonates were initially also examined, but no sufficient reactivity was found.

The chloride bridged [FIP-Cl]$_2$ **C1** (2.5 mol%, FIP = ferrocenylimidazoline palladacycle)[28] – activated with AgOAc (5 mol%) by a chloride/acetate exchange before use to facilitate substrate binding[31] – provided **3aA** in very small yield and nearly racemic form (Table 1, entry 1). In contrast, the analogous pentaphenyl ferrocenyl imidazoline palladacycle [PPFIP-Cl]$_2$ **C2** activated in the same way provided the product in a useful yield and with promising enantioselectivity (entry 2). The same ee was also attained with the related oxazoline catalyst [PPFOP-Cl]$_2$ **C3**,[28d] which on the other hand gave the product in poor yield (entry 3). This can be partly explained by competing allylic imidate rearrangement, for which **C3** is a very proficient catalyst.[28d] A poor product yield was also obtained with the bisimidazoline bispalladacycle [FBIP-Cl]$_2$ **C4**,[29] but in this case enantioselectivity was only moderate (entry 4).

With **C2** several silver salts such as AgOTs and Ag(acac) were investigated for catalyst activation, but could not significantly improve the product yields (entries 5 and 6). In contrast, the non-activated chloride bridged dimeric complex **C2** delivered the product in considerably increased yield (95%, entry 7) and with high enantioselectivity (ee = 93%). This higher productivity is a result of obviation of a dimerization of the pyrazolone substrate, which was found with the activated catalysts.

Investigation of different solvents gave no improvements (see e.g. entries 8 & 9). Noteworthy is the result of entry 8, where THF was used, as no desired product was formed. As judged from ^{1}H-NMR, **1a** exists in THF in its enamine and enol form (broad signals at 9.51 and 9.62 ppm), while the keto form is missing (no signal with the typical coupling pattern for the benzylic CH_2, see Supporting Information). This might hamper efficient pyrazolone coordination to the catalyst.

Reduction of the catalyst loading to 1 mol% still gave product **3aA** with unchanged enantiomeric excess and in high yield after increasing the concentration from 0.2 to 0.5 M (compare entries 10 & 11).

The conditions of Table 1, entry 11 were then applied to various pyrazolones **1** and allylimidates **2** (Table 2). Interestingly, different product enantiomers equipped with an (*E*)-configured allylic side chain were formed, each with high enantioselectivity, starting from allylic imidates **2** depending on their double bond geometry. (*E*)-**2** thus provided products **3** with the depicted absolute configuration, whereas (*Z*)-**2** provided the optical antipodes (*ent*)-**3**. The reaction is thus diastereospecific and enantiodivergent, because both enantiomers are available with the same catalyst batch. The absolute configurations were determined by comparison of optical rotation data to literature known products.

All three pyrazolone residues R^1-R^3 were varied in **1**. The relevant groups are highlighted by color in Table 2. Next to a Me residue in C(3) position ($R^2 = CH_3$) also branched alkyl groups such as *i*Pr can be used (product **3 bA**). Complementary to Gong's work, aromatic residues R^2 were also well accepted and did not disturb the enantioselectivity (e. g. **3 cA**). A variety of residues R^1 at C(4) was also accommodated, such as benzyl residues carrying different functional groups (donors and acceptors, see products **3 dA**–(***ent***)-**3 hA**). Likewise, alkyl moieties were well tolerated (**3 iA**–**3 kA**; the ee of **3kA** was determined after desilylation, see Supporting Information). As a limitation we found, that with a phenyl residue R^1 no desired product was obtained (not shown).

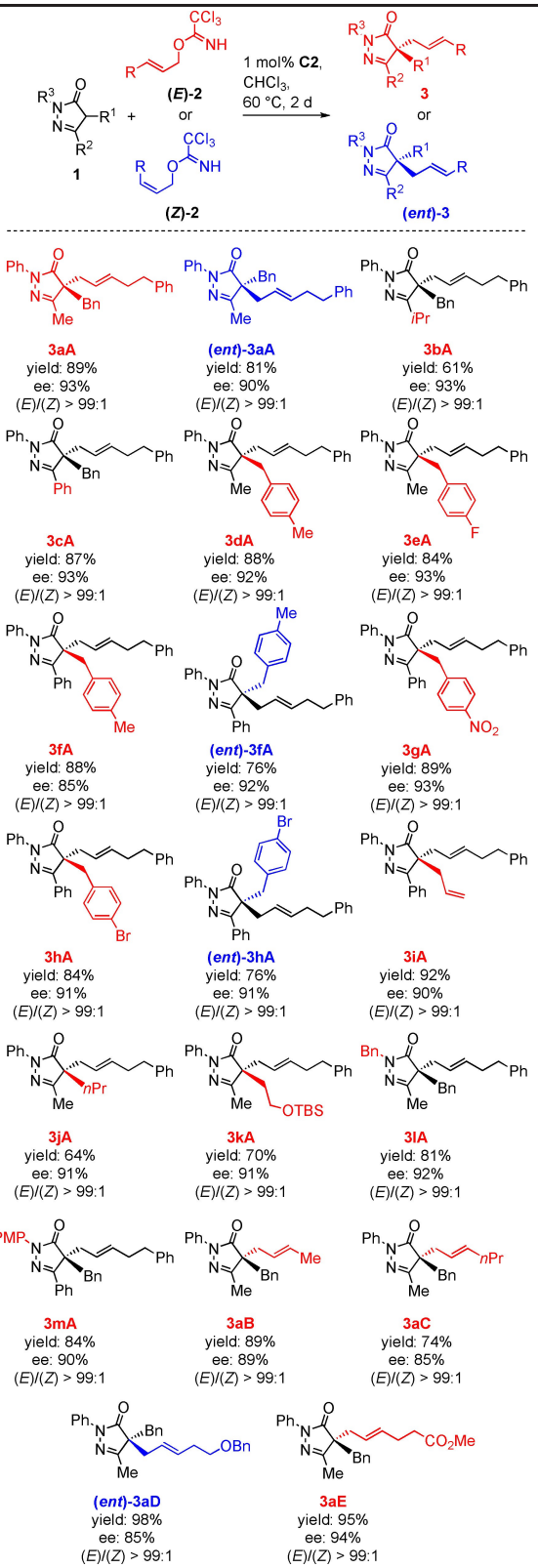
Furthermore, other N-substituents R^3 than Ph can be used. We studied a benzyl (**3lA**) and *para*-methoxyphenyl (PMP) moiety (**3 mA**) as they might be synthetically interesting as N-protective group.

Finally, different allylic imidates bearing different aliphatic residues (**3 aB**–**3 aE**) were tolerated. Also here, versatile functional groups may be present as is showcased for an ether moiety in (***ent***)-**3 aD** and an ester group in **3 aE**.

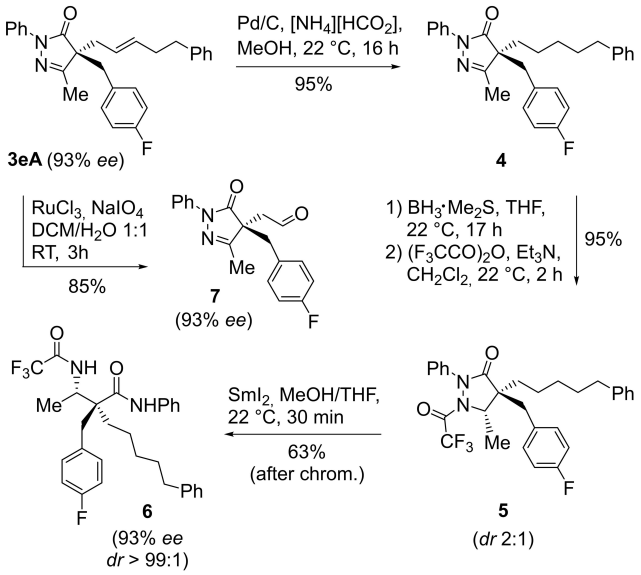
Surprisingly, pyrazolones have never been reported as precursors to enantioenriched β-aminoamides by reduction of the imino moiety and the N,N-bond. To explore this strategy we first reduced the C,C double bond by transfer hydrogenation using catalytic Pd/C and ammonium formate as hydrogen source (Scheme 2). The resulting pyrazolone **4** was then reduced by $H_3B{\cdot}SMe_2$ in THF to the corresponding pyrazolidinone, which was N-protected prior to isolation. This proceeded in 95% overall yield with moderate diastereoselectivity.[32–34] The relative configuration of the major diastereomer of **5** was determined by 2D-NOESY-NMR spectroscopy (see Supporting Information).

N,N-cleavage was eventually accomplished by SmI_2 at room temperature to give the β-aminoamide diastereomers **6** after 30 min in nearly quantitative yield with unchanged ee.[35] Both diastereomers were

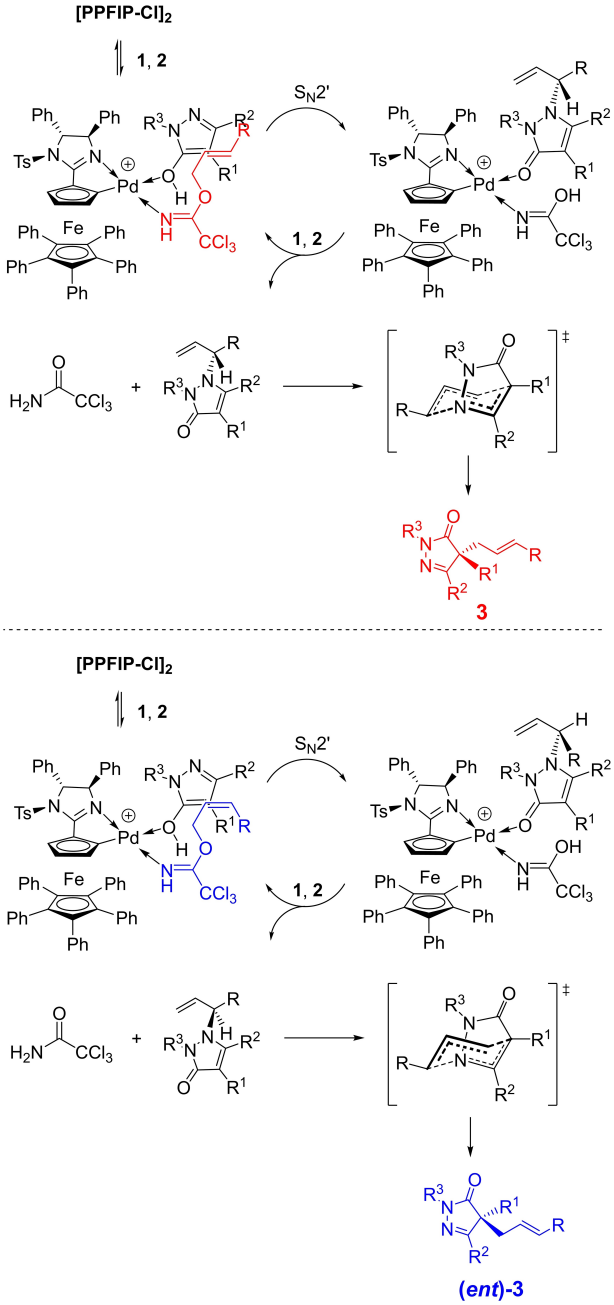
Table 2. Investigation of the Substrate Scope.[a,b]



[a] Yield of isolated product.
[b] ee determined by HPLC/GC.



Scheme 2. Synthesis of β-aminoamide **6** from pyrazolone **3eA**.



Scheme 3. Plausible simplified mechanism and possible explanation of enantiodivergency.

separated by column chromatography providing diastereomerically pure **6** in 63% yield.

Mechanistically, the diastereospecific reaction outcome, i.e. formation of different product enantiomers starting from different double bond isomers, might be explained by an initial enantioselective N-allylation of the pyrazolones creating a stereocenter at the branched allylic moiety, followed by a [3,3]-rearrangement (Scheme 3). We have recently reported a similar sequence for an Ir(I)/Pd(0) catalyzed C-allylation of isoxazolinones, which was shown by control experiments and DFT studies to proceed via an initial N-allylation and a following thermal sigmatropic rearrangement via a chair-like transition state.[36]

In the present study, we suggest an initial S_N2' reaction for the N-allylation step (Scheme 3). The imidate could bind to the Pd(II) center increasing the leaving group properties of the imidate while the pyrazolone could be enolized by coordination. According to our model, both geometric isomers of the starting materials would provide different enantiomers during the N-allylation and the rearrangement would occur via chirality transfer like in the above mentioned study by us,[36] which might either proceed thermally or Pd(II) catalyzed. Unfortunately though, we were not able to detect any N-allyl intermediate during monitoring by NMR, which might indicate that the rearrangement is fast. In addition, we were not able to prepare the anticipated branched N-allylated compounds by alternative methods for control studies.

By ESI-HRMS we could at least detect a pyrazolone complex of the catalyst with the expected isotopic pattern in the reaction mixture. Moreover, we found a species in which either an allylation product (C- or N-allylated) binds to the catalyst or alternatively can be described by a complex in which the pyrazolone substrate plus the corresponding allyl fragment are coordinated to the Pd (for details see Supporting information).

Conclusion

In conclusion, we have reported a diastereospecific enantiodivergent allylation of pyrazolones with allylimidates. Both enantiomers were selectively available

by the choice of the imidate's C,C double bond geometry using the same catalyst batch. This reaction type was controlled by a planar chiral pentaphenylferrocene based palladacycle catalyst that allowed for enantiomeric excesses between 85 and 94% with yields in a range of 61–98%. In analogy to previous work reported by us, the reaction outcome might be explained by a sequence of N-allylation followed by a thermal [3,3]-rearrangement. The method tolerates variations of all three substituents at the pyrazolone and the imidate's olefin substituent. Complementary to previous work, also aromatic residues at the pyrazolone's imino C atom were accepted. Moreover, we demonstrated that scalemic pyrazolones are building blocks for the synthesis of β-aminoamides, a compound class of medicinal relevance. They were accessible by reduction of the imino moiety and a subsequent reductive N,N bond cleavage.

Experimental Section

General Procedure for the Asymmetric Allylic Alkylation of Pyrazolones: $[PPFIP\text{-}Cl]_2$ **C2** (1.0 mol%) and pyrazolone (1.0 equiv., 0.059–0.885 mmol) were placed in a flame dried reaction vial. A solution of imidate (1.5 equiv.) in $CHCl_3$ (0.5 M) was added at 60 °C under nitrogen atmosphere and the reaction mixture was shaken in a synthesizer at 340 rpm for the indicated time. The reaction mixture was loaded directly onto a silica gel column and purified by column chromatography (EE: PE/1:10) to yield the corresponding products.

Reduction of 3eA to 4: A suspension of allylic pyrazolone **3 eA** (1.0 equiv., 0.130 mmol, 56.00 mg), Pd/C (10%, 10.0 mg) and ammonium formiate (7.0 equiv., 0.098 mmol, 35.00 mg) in methanol (3.0 mL) was stirred at room temperature for 17 h and subsequently filtered over Celite. The organic phase was removed under reduced pressure and the crude product was purified by column chromatography (EE:PE/1:20) to isolate the reduced pyrazolone **4 a** (52.93 mg, 0.124 mmol, 95%, 93% ee) as a colorless oil. The enantiomeric excess was determined by HPLC analysis: Chiralpak IA column, n-hexane/i-PrOH (98/2), 1.0 mL/min, detected at 245 nm.

Reduction and Protection of 4 to 5: $BH_3{\cdot}Me_2S$ (10.0 equiv., 0.677 mmol, 51.40 mg) was added to Pyrazolone **4** (1.0 equiv., 0.068 mmol, 29.00 mg) in THF (1.0 mL) at room temperature and the reaction solution was stirred for 17 h. Then water was added particularly carefully to the reaction solution and the aqueous phase was extracted with CH_2Cl_2 (3 × 5.0 mL). The organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Triethylamine (2.0 equiv., 0.136 mmol, 13.70 mg, 18.77 µL) was added to the crude product in CH_2Cl_2 (1.0 mL) at room temperature. Then trifluoroacetic anhydride (1.5 equiv., 0.102 mmol, 21.32 mg, 14.13 µL) was added to the reaction solution at 0 °C and the mixture was stirred for 2 h at room temperature. The reaction was quenched by adding water and the aqueous phase was extracted with CH_2Cl_2 (3 × 5.0 mL). The organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by chromatography with silica gel (PE/EE: 10:1) to yield **5** (34.02 mg, 0.065 mmol, 95%, *dr* 2:1, 93% *ee*) as a colorless liquid. The enantiomeric excess was determined by HPLC analysis: Chiralpak IA column, *n*-hexane/*i*-PrOH (97/3), 1.0 mL/min, detected at 245 nm. For analytical purposes, a diastereomerically pure sample was obtained by column chromatography with silica gel (PE/EE: 10:1).

Ring Opening of 5 to 6: A SmI_2-solution (0.1 M in THF, 2.0 equiv., 0.144 mmol, 1.44 mL) was added to pyrazolidinone **5** (1.0 equiv., 0.072 mmol, 38.00 mg, *dr* 2:1) in MeOH (0.2 mL) at room temperature. After 30 min at room temperature the reaction was quenched by adding saturated aqueous $NaHCO_3$ (5.0 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 5.0 mL). The organic phase was washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by chromatography with silica gel (PE/EE: 8:1) to yield the separated major diastereomer **6** (23.90 mg, 0.045 mmol, 63%, *dr* > 99:1, 93% *ee*) and minor diastereomer **6'** (12.00 mg, 0.023 mmol, 32%, *dr* 1: > 99, 93% *ee*) as colorless liquids. The enantiomeric excess was determined by HPLC analysis: Chiralpak IC column, *n*-hexane/*i*-PrOH (95/5), 1.0 mL/min, detected at 245 nm.

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