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A Short Enantioselective Synthesis of (*S*)-Levetiracetam through Direct Palladium-Catalyzed Asymmetric *N*-Allylation of Methyl 4-Aminobutyrate

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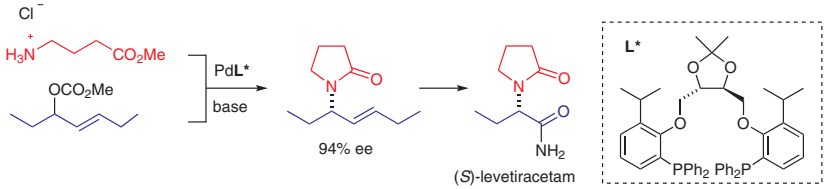

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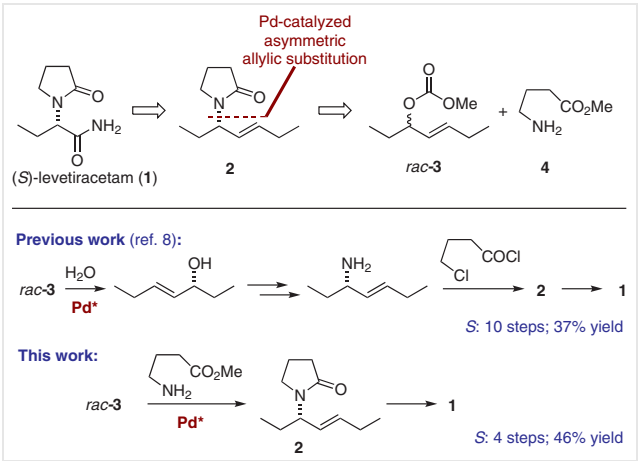
Abstract An exceedingly short and enantioselective synthesis of the antiepileptic drug (*S*)-levetiracetam was elaborated. As the chirogenic key step, a Pd-catalyzed asymmetric *N*-allylation of methyl 4-aminobutyrate was achieved in the presence of only 1 mol% of a catalyst prepared in situ from $[Pd(allyl)Cl]_2$ and a tartaric acid-derived C_2-symmetric diphosphine ligand.

Key words asymmetric catalysis, palladium catalysis, chiral ligands, amino acid derivatives, ozonolysis, levetiracetam

Epilepsy is the most common neurological disorder, affecting about 50 million people all over the world.[1] Treatment consists primarily of the use of antiepileptic agents such as levetiracetam (**1**), which shows no significant drug–drug interactions and has favorable pharmacokinetic properties, making it one of the most commonly prescribed anticonvulsants.[2]

Despite its structural simplicity, the synthesis of **1** in nonracemic form is not trivial, as reflected by the various protocols that have been developed. Classical approaches are based on the late construction of the pyrrolidone unit from (*S*)-2-aminobutanamide (or the corresponding esters) obtained by desulfurization of methionine, resolution, or biocatalysis.[3] Notably, the direct nucleophilic introduction of the pyrrolidone ring in an S_N2 fashion has been achieved only with less readily available substrates.[4] Asymmetric approaches toward **1** involve the use of Evans's auxiliary in the diastereoselective ethylation of a pyrrolidone-1-yl-acetic acid derivative[5] and the highly enantioselective hydrogenation of the dehydroamino acid (enamide) derivative corresponding to **1**.[6]

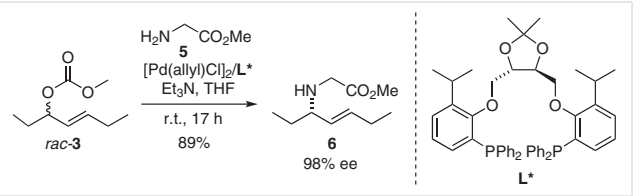
In the course of our research into asymmetric Pd-catalyzed *N*-allylation of amino acid derivatives,[7] we envisioned challenging (benchmarking) the developed methodology for the synthesis of **1** according to the retrosynthetic analysis shown in Scheme 1. Our main goal was to achieve the direct *N*-allylation of methyl 4-aminobutanoate (**4**), as a synthetic equivalent of pyrrolidone, with high enantioselectivity by employing the racemic carbonate *rac*-**3**. Efficient conversion of the cyclized product **2** into (*S*)-levetiracetam (**1**) should then be achieved through oxidative cleavage of the double bond and amide formation. A conceptually related approach had recently been described by Stecko and co-workers, who initially employed an enantioselective Pd-catalyzed hydrolysis of *rac*-**3** to prepare the (*R*)-allylic alcohol; this was further transformed into the corresponding (*S*)-amine through a stereospecific [3,3]-rearrangement before the pyrrolidone unit was established



Scheme 1 Retrosynthetic analysis of levetiracetam (**1**) based on an asymmetric Pd-catalyzed allylic substitution

by reaction of the amine with 4-chlorobutanoyl chloride.[8] Although the Stecko synthesis provides the target **1** with a respectable overall yield, its low step economy[9] reflects the difficulties associated with the direct introduction of suitably functionalized amines in asymmetric allylic substitution reactions.[10,11]

Addressing this particular challenge, we recently succeeded in developing a powerful protocol for the Pd-catalyzed asymmetric *N*-allylation of α-amino acid esters by employing a new class of tartaric acid-derived C_2-symmetric chiral diphosphine ligands, such as (*S*,*S*)-*i*Pr-MediPhos (**L***),[12] which not only gave rise to high enantioselectivities, but also formed particularly active catalysts (Scheme 2).[7] Here, we describe an adaptation of this methodology in an exceedingly short and efficient synthesis of levetiracetam (**1**), according to the strategy outlined in Scheme 1.

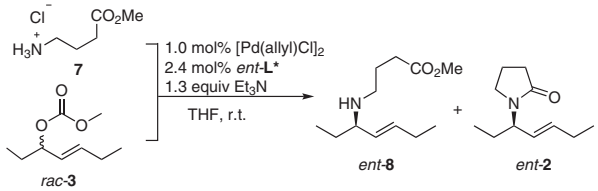


Scheme 2 Highly enantioselective Pd-catalyzed *N*-allylation of methyl glycinate (**5**) by using the chiral diphosphine (*S*,*S*)-*i*Pr-MediPhos (**L***)

Although our initial attempts to employ pyrrolidin-2-one directly as a nucleophile in a Pd-catalyzed reaction with *rac*-**3** failed due to a lack of conversion, the use of methyl 4-aminobutyrate (**4**) (generated in situ from the commercially available stable crystalline hydrochloride **7** and triethylamine) in the presence of dppe as an achiral ligand resulted in the clean formation of a mixture of the allylic amine *rac*-**8** and the corresponding cyclized pyrrolidone derivative *rac*-**2** (Table 1; entry 1). On using the diphosphine ligand (*R*,*R*)-*i*Pr-MediPhos (*ent*-**L***) in the *N*-allylation of **4**, full conversion of *rac*-**3** was observed after just 2.5 hours, giving a 9:1 mixture of *ent*-**8** and *ent*-**2**. Upon prolongation of the reaction time, the amount of the pyrrolidone product *ent*-**2** steadily increased, indicating that the cyclization of *ent*-**8** occurs as a secondary process under the reaction conditions. After 58 hours at room temperature, the content of the desired product *ent*-**2** was 93%. Determination of the enantiomeric excess proved to be difficult, as the enantiomers of neither the amine *rac*-**8** nor the lactam *rac*-**2** could be separated on the available GC columns. However, after conversion of lactam **2** into ester **9** (see below), the enantiomeric excess could be determined by means of chiral GC. In this way, the resulting sample of *ent*-**2** (Table 1, entry 4) was found to have an enantiomeric purity of 93% ee. The expected (*R*)-configuration was confirmed by correlation of the molecular rotation of *ent*-**9** ($[\alpha]_D$ = 41° in $CHCl_3$) with the reported value.[3b]

In contrast to our original reaction system (Scheme 2),[7] the *N*-allylation of **7** showed only a small increase in enantioselectivity upon lowering the concentration (Table 1, entries 4–7). Although the reaction proceeded with ≤94% ee at a concentration of 0.50 M, the content of the desired pyrrolidone derivative *ent*-**2** in the mixture was only about 45% after 17 hours.

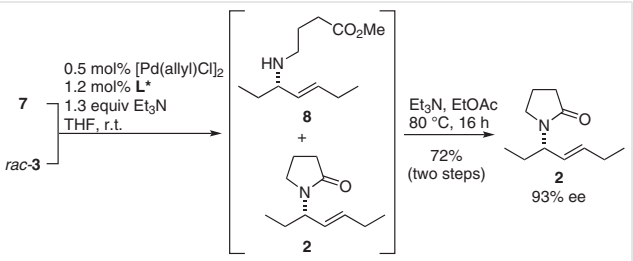
Table 1 Optimization of the Asymmetric *N*-Allylation of Methyl 4-Aminobutyrate (**4**)[a]



Entry	Ligand	Conc.[b] (mol/L)	Time (h)	Conv.[c] (%)	Product ratio[c] (%)		ee[d] (%)
					ent-**8**	*ent*-**2**	
1	dppe	2.00	13	100	54	46	(*rac*)
2	*ent*-**L***	2.00	2.5	100	89	11	n.d.[e]
3	*ent*-**L***	2.00	17	100	59	41	n.d.
4	*ent*-**L***	2.00	58	100	7	93	93
5	*ent*-**L***	1.00	17	100	52	48	93
6	*ent*-**L***	0.50	17	100	55	45	94
7	*ent*-**L***	0.25	19	≤5	–	–	–

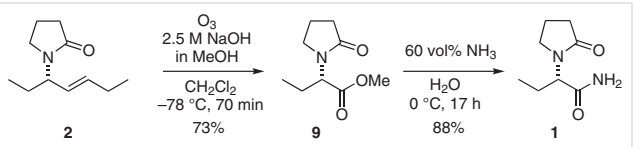
[a] Reactions were performed on a 0.5 mmol scale using 1.3 equivalents of **7**.
[b] Concentration of *rac*-**3**.
[c] Product ratio as determined by GC-MS.
[d] Determined at the stage of **9** (after ozonolysis of *ent*-**2**) by GC on a chiral stationary phase.
[e] n.d. = not determined.

To synthesize the (*S*)-form of the key intermediate **2**, the *N*-allylation of **7** was performed under the optimized conditions by employing just 1 mol% of the Pd catalyst prepared from the (*S*,*S*)-biphosphine ligand **L***. After removal of the metal catalyst by filtering the solution through a pad of Celite and evaporating all the volatiles, the crude 1:1 mixture of **8** and **2** was treated with Et_3N in ethyl acetate for 16 hours at 80 °C to ensure complete cyclization of **8** to **2**. In this way, the desired γ-lactam **2** was obtained in a total yield of 72% over the two steps (Scheme 3) in an operationally straightforward manner.



Scheme 3 Procedure for the synthesis of desired pyrrolidine derivative **2**

To complete the synthesis of levetiracetam (**1**), we used the ozonolysis conditions of Marshall et al.[13] to induce oxidative degradation of the allylic amine **2** to form the methyl ester **9** directly (Scheme 4). The final conversion of **9** into the corresponding amide **1** was then efficiently achieved by treatment with aqueous ammonia (Scheme 4).[14]



Scheme 4 Completion of the synthesis of (*S*)-levetiracetam (**1**)

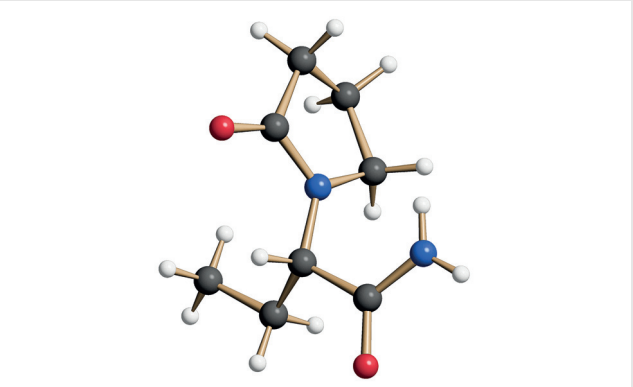


Figure 1 Structure of synthetic (*S*)-levetiracetam in the crystalline state

Because the synthesized sample of (*S*)-levetiracetam (**1**) was obtained in pure crystalline form, we were able to confirm its absolute configuration additionally by means of X-ray crystallography (Figure 1),[15] thereby confirming all previous configurational assignments.

In conclusion, we have elaborated a short and efficient synthesis of the antiepileptic drug (*S*)-levetiracetam (**1**) by adapting our recently developed protocol for the enantioselective Pd-catalyzed *N*-allylation of amino acid esters as the key step.[16] We also demonstrated that methyl 4-aminobutyrate (**4**), liberated in situ from the corresponding hydrochloride **7**, is a useful synthetic equivalent for pyrrolidone in such reactions. In addition, we identified an improved two-step protocol for the oxidative conversion of the allylamine derivative **2** into the amide **1**. The resulting overall synthesis of **1** proceeds in only four steps with 46% overall yield.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1493-9078.

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(15) CCDC 2074847 contains the supplementary crystallographic data for (*S*)-levetiracetam (**1**). The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures. For earlier X-ray crystal structures of **1** determined at room temperature, see: (a) Song, J.; Lou, K.-X.; Li, X.-J.; Wua, X.-P.; Feng, R.-X. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2003**, *59*, o1772. (b) Bebiano, S. S.; ter Horst, J. H.; Oswald, I. D. H. *Cryst. Growth Des.* **2020**, *20*, 6731; (Structure determined at high pressure to investigate pressure-dependent polymorphism).
(16) Detailed experimental procedures and characterization data are given in the Supporting Information.

1-[(2*E*)-1-Ethylpent-2-en-1-yl]pyrrolidin-2-one (2)

Under an atmosphere of argon, a Schlenk flask was charged with $[Pd(allyl)Cl]_2$ (1.10 mg, 3.01 μmol, 0.50 mol%) and ligand **L*** (5.40 mg, 7.04 μmol, 1.17 mol%). Anhyd THF (0.6 mL) was then added and the solution was stirred for 20 min at r.t. before carbonate *rac*-**3** (103 mg, 0.60 mmol) was added neat from a syringe. After 20 min, methyl 4-aminobutyrate hydrochloride (**7**; 116 mg, 0.76 mmol) and Et_3N (0.11 mL, 0.79 mmol) were added, and stirring was continued for 16 h. QuadraSil AP (~50 mg) was then added to capture Pd, and the mixture was stirred for 1 h then filtered through a short pad of Celite with EtOAc. After removal of the solvent under reduced pressure, the crude product mixture of **2** and **8** was dissolved in EtOAc (1 mL) and Et_3N (0.11 mL, 0.79 mmol), then heated at 80 °C for 20 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography [silica gel, cyclohexane–EtOAc (1:1)] to give a yellowish oil; yield: 78 mg (0.43 mmol; 72%); $[\alpha]_\lambda^{20}$ (*c* = 0.24, $CHCl_3$): $[\alpha]_{365}$ –364.6, $[\alpha]_{436}$ –206.7 °, $[\alpha]_{546}$ –111.1, $[\alpha]_{579}$ –96.0, $[\alpha]_{589}$ –92.5°.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.64 (dtd, ^3J = 15.5 Hz, ^3J = 6.3 Hz, ^4J = 1.3 Hz, 1 H), 5.34 (ddt, ^3J = 15.5 Hz, ^3J = 6.6 Hz, ^4J = 1.6 Hz, 1 H), 4.48 (Ψq, ^3J = 7.0 Hz, 1 H), 3.27 (Ψqt, ^3J = 9.6 Hz, ^3J = 7.0 Hz, 2 H), 2.45–2.35 (m, 2 H), 2.10–1.92 (m, 4 H), 1.68–1.46 (m, 2 H), 0.98 (t, ^3J = 7.5 Hz, 3 H), 0.86 (t, ^3J = 7.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7, 135.0, 126.6, 54.1, 42.5, 31.6, 25.5, 24.9, 18.3, 13.7, 10.8. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{20}NO$: 182.1539; found: 182.1540.

Methyl 2-(2-Oxopyrrolidin-1-yl)butanoate (9)

A round-bottomed flask was charged with a solution of **2** (105 mg, 0.58 mmol) in CH_2Cl_2 (40 mL) and a 2.50 M solution of NaOH in MeOH (3.0 mL, 7.5 mmol). The clear solution was cooled to –78 °C and a weak stream of ozone was introduced until the solution turned blue (70 min). Excess ozone was removed by introducing a weak stream of oxygen for 10 min before the solution was allowed to warm to r.t. H_2O (50 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel, cyclohexane–EtOAc (1:1)] to give a yellow oil; yield: 78 mg (0.42 mmol; 73%); $[\alpha]_\lambda^{20}$ (*c* = 0.26, $CHCl_3$): $[\alpha]_{365}$ –152.9, $[\alpha]_{436}$ –87.1, $[\alpha]_{546}$ –46.1, $[\alpha]_{579}$ –40.0, $[\alpha]_{589}$ –38.6.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.69 (Ψdd, ^3J = 10.7 Hz, ^4J = 5.2 Hz, 1 H), 3.71 (s, 3 H), 3.52 (td, ^3J = 8.7, ^4J = 6.1 Hz, 1 H), 3.35 (td, ^3J = 8.8 Hz, ^4J = 5.5 Hz, 1 H), 2.44 (t, ^3J = 8.1 Hz, 2 H), 2.15–1.96 (m, 3 H), 1.69 (ddq, ^3J = 14.6 Hz, ^3J = 10.7 Hz, ^3J = 7.3 Hz, 1 H), 0.92 (t, ^3J = 7.4 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.0, 171.7, 55.2, 52.2, 43.6, 31.0, 22.3, 18.4, 10.9. HRMS (ESI): *m/z* = $[M + H]^+$ calcd for $C_9H_{16}NO_3$: 186.1124; found: 186.1127.