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Organocatalytic Enantioselective Synthesis of Metabotropic Glutamate Receptor Ligands

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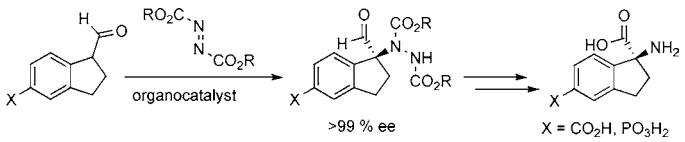
ABSTRACT



(*R*)-Proline catalyzes the amination reaction of functionalized indane carboxaldehydes and allows for the efficient enantioselective synthesis (>99% ee) of the metabotropic glutamate receptor ligands (*S*)-AIDA and (*S*)-APICA.

The catalytic asymmetric synthesis of chiral-nonracemic drugs has become an important focus for chemists in academia and industry.[1] New methodologies that limit the use of toxic substances and that are recognized as atom efficient are highly desirable. In this context, organocatalysis continues to attract attention.[2] Asymmetric organocatalysis utilizes organic molecules to induce chirality in various C−C, C−N, and C−O bond-forming reactions.[3] Many important chiral synthons have been obtained via organocatalysis. For example, efficient and stereoselective preparations of α- and *β*-amino acids,[4] amino alcohols,[5] diols,[6] and carbohydrates[7] have been reported. In continuation of our work in this area[8] we sought to demonstrate that organocatalysis can be useful in the preparation of various medicinally important compounds. In many cases, the syntheses of chiral ligands that show therapeutic potential need to be reevaluated in light of modern asymmetric techniques, especially when the molecules are prepared via chiral pool approaches.[9] Thus, with organocatalysis in mind, a more efficient route to the amino acids listed in Figure 1 was realized. AIDA and APICA

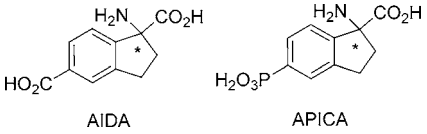


Figure 1. Metabotropic glutamate receptor ligands.

(Figure 1) are known antagonists of metabotropic glutamate receptors (mGluRs), G-protein-coupled receptors associated

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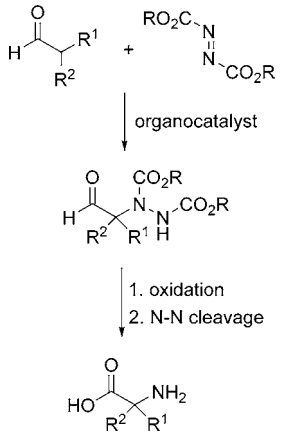
with various neurodegenerative diseases.[10] Their bioactivities have recently rendered them potential drugs of the future.[11] Both (*S*)-AIDA and (*S*)-APICA were found to be the active isomers in various biological assays.[12,13] Although the asymmetric synthesis of these compounds has been reported using chiral pool[12] and chiral ligand-exchange chromatography[13] approaches, there is still a need for a more direct asymmetric route that allows for the multigram preparation of these compounds and their analogues.

The (*S*)-proline-catalyzed amination of aldehydes has recently been reported as an efficient way to prepare chiral amino aldehydes.[14] As outlined in Scheme 1, the corresponding amino acids can be prepared by simple oxidation and N−N bond cleavage of the amino aldehyde adducts. Thus, utilizing this amination sequence, (*S*)-AIDA and (*S*)-APICA could be prepared via organocatalysis. Herein we report a practical and efficient organocatalytic enantioselective synthesis of (*S*)-AIDA and (*S*)-APICA where the amination of branched aldehyde donors is used as a key step.

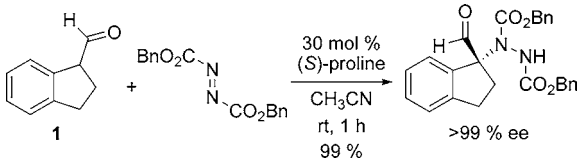
Scheme 1. Organocatalysis in the Preparation of Amino Acids



Brase and co-workers demonstrated that (*S*)-proline can catalyze the reaction of 2-phenylpropionaldehyde with diethylazodicarboxylate to give the corresponding amino aldehyde in 86% ee after 60 h in CH_2Cl_2.[14c] Although this substrate gave good ee, the reaction was fairly substrate dependent, and ees varied from 32 to 86% ee. One substrate that was not tested that was of particular interest to us was indane carboxyaldehyde **1**. Previously, we had found **1** to be a very reactive donor in the quaternary Mannich reaction, where it gave excellent enantio- and diastereoselectivity.[4] Because **1** contains the core structure of AIDA and APICA, the amination of **1** would provide the precursor amino aldehyde, which upon further elaboration would yield the corresponding amino acid.

As indicated in Scheme 2, the coupling of **1** to dibenzylazodicarboxylate (DBAD) is efficiently and selectively catalyzed by (*S*)-proline giving only one enantiomer in quantitative yield. Having demonstrated that high ees could be obtained using indane **1** as the donor, we devised syntheses of (*S*)-AIDA and (*S*)-APICA according to Schemes 3 and 4.

Scheme 2. (*S*)-Proline Catalyzed Amination of Indane Carboxaldehyde **1**



The synthesis of (*S*)-AIDA began with cyanation of commercially available 5-bromoindanone giving **3** in 78%.[15] Wittig olefination afforded **4** as a mixture of *E* and *Z* isomers, and upon hydrolysis of the cyano group and subsequent esterification, **5** was obtained in excellent yield. Various attempts to hydrolyze the enol ether **5** using mineral acids or PTSA resulted in low yields. However, when boron tribromide was used, the demethylation of **5** ensued without affecting the ester functionality,[16] thus providing indane aldehyde **6** in good yield. The functionalized indane **6** proved to be a good substrate for the amination reaction. When a slight excess of aldehyde was reacted with DBAD with 20 mol % (*R*)-proline at ambient temperature, the amination product was obtained in >99% ee and 96% yield in less than 4 h. Subsequent oxidation and esterification gave precursor **7**.

Initially, high-pressure hydrogenation over Ra−Ni was attempted in order to cleave the N−N bond.[14] Because yields were low (less than 10%), an alternative route was carried out utilizing SmI_2. We first applied a one-pot trifluoroacetylation−selective benzyloxycarbonyl deprotection protocol[17]

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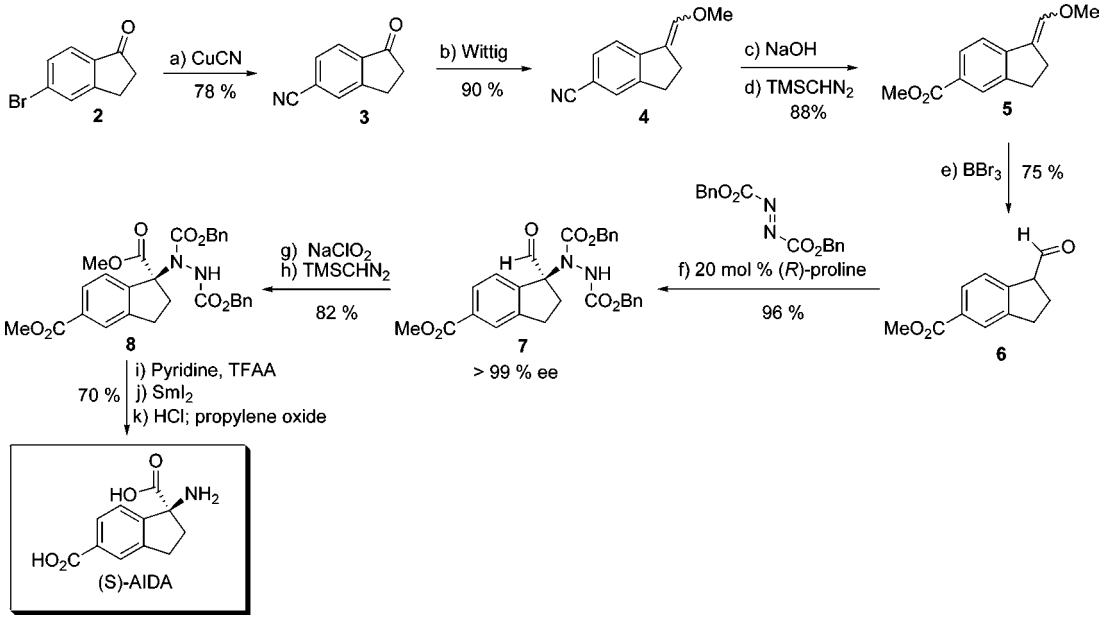
Scheme 3[a]

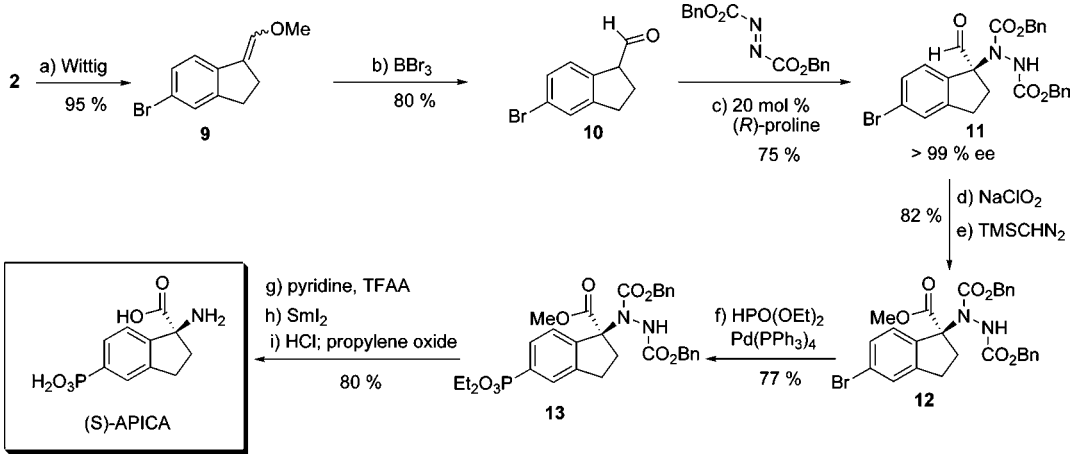


[a] Conditions: (a) CuCN, DMF, reflux, 12 h, 78%; (b) Ph_3PCH_2OMeCl, ^tKOBu, THF, −20 °C, 1 h, 90%; (c) NaOH, EtOH/H_2O, reflux, 4 h; (d) $TMSCHN_2$, MeOH/toluene, 10 min, 88%; (e) 2 equiv of BBr_3, CH_2Cl_2, −78 °C, 4 h, 75%; (f) DBAD, 20 mol % (*R*)-proline, CH_3CN, 4 h, 96%, >99% ee; (g) $NaClO_2$, 2-methyl-2-butene, $^tBuOH/H_2O$; (h) $TMSCHN_2$, MeOH/toluene, 10 min, 82%; (i) pyridine, 40 °C, 15 h, then trifluoroacetic anhydride, 48 h; (j) SmI_2, THF/MeOH, 30 min; (k) 6 M HCl, reflux, 48 h, then propylene oxide, 70%.

to provide the trifluoromethyl hydrazine. Cleavage of the N−N bond was then carried out with SmI_2 using a procedure slightly modified from that originally reported by Friestad.[18] Subsequent deprotection afforded (*S*)-AIDA.

The reaction sequence presented here was found to be very flexible and allowed for the preparation of the phosphonate analogue (*S*)-APICA from **2** (Scheme 4). After Wittig olefination and subsequent generation of aldehyde **10**, the (*R*)-proline-catalyzed amination furnished **11** in optically pure form. Oxidation to the acid followed by esterification afforded bromo-indane **12**, which underwent Pd(0)-catalyzed phosphonate coupling[12c] to give intermediate **13**. Transformation into the trifluoromethylacetyl-protected hydrazine allowed for the samarium-induced cleavage of the N−N bond.[19] Subsequent hydrolysis of the ester functionalities afforded (*S*)-APICA.

Scheme 4[a]



[a] Conditions: (a) Ph_3PCH_2OMeCl, ^tKOBu, THF, −20 °C, 1 h, 95%; (b) 2 equiv of BBr_3, CH_2Cl_2, −78 °C, 4 h, 80%; (c) DBAD, 20 mol % (*R*)-proline, CH_3CN, 4 h, 75%, >99% ee; (d) $NaOCl_2$, 2-methyl-2-butene, $^tBuOH/H_2O$; (e) $TMSCHN_2$, MeOH/toluene, 10 min, 82%; (f) diethyl phosphite, 10 mol % $Pd(PPh_3)_4$, toluene, reflux, 72 h, 77%; (g) pyridine, 40 °C, 15 h, then trifluoroacetic anhydride, 48 h; (h) SmI_2, THF/MeOH, 30 min; (i) 6 M HCl, reflux, 48 h, then propylene oxide, 80%.

In summary, organocatalysis was found to be an effective strategy that allowed for the enantioselective preparation of metabotropic glutamate receptor ligands (*S*)-AIDA and (*S*)-APICA in >99% ee. The synthetic route is general and should allow for the preparation of other analogues in optically pure form.[20] Importantly, the organocatalytic route can be readily scaled up, and either (*R*)- or (*S*)-products can be obtained using (*S*)- or (*R*)-proline, respectively, thus demonstrating the potential for organocatalysis in the preparation of other quaternary amino acids. With organocatalysis still in its infancy, its utility in the preparation of drugs and drug candidates has only recently become apparent;[3] further work in this area from our lab will be reported in due course.

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Supporting Information Available: Full experimental details and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Hydrogenation of **13** over Ra−Ni gave the desired product in 65% yield.

(20) Preliminary results in our lab indicate that the tetrazole analogue can also be prepared via a similar synthetic route.