

Chiral α -Amino Phosphonates via Rhodium-Catalyzed Asymmetric 1,4-Addition Reactions

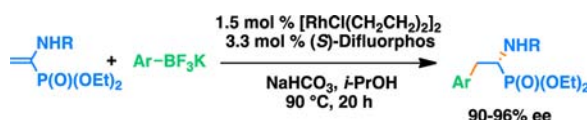
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Received July 22, 2013

ABSTRACT



A new approach for the preparation of enantioenriched α -amino phosphonates and derivatives is described. Indeed, the rhodium-catalyzed asymmetric 1,4-addition of potassium organotrifluoroborates to dehydroaminophosphonates afforded α -amino phosphonates in good yields and high enantioselectivities (up to 96%) using Difluorphos as a chiral ligand.

Optically active α -amino phosphonic acids and derivatives are important synthetic intermediates used in the pharmaceutical and agrochemical industries to prepare target molecules such as peptides, proteins, or even many natural products.¹ These are analogues of α -amino acids² in which the carboxylic acid group has been substituted with a phosphonic acid group. Among the chiral phosphonic acids described, some have been isolated from natural products and possess various biological activities: antiviral, antifungal, herbicides, or anti-HIV.^{1,3} In the synthesis of such compounds, it is important to control the absolute configuration of the α -stereogenic center because the biological properties of the products are correlated: for example (*R*)-1-phospholeucine is a better inhibitor of leucine peptidase than the (*S*)-isomer.¹

Several methods have been described for the preparation of enantiomerically enriched α -amino phosphonic acids

derivatives.¹ Most of the strategies employed involve the formation of a new carbon–hydrogen, carbon–phosphorus, carbon–carbon, or carbon–nitrogen bond. While many reactions using stoichiometric chiral auxiliaries have been described,⁴ catalytic approaches are scarcer. Asymmetric hydrogenation of unsaturated substrates is a first

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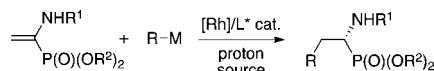
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approach for the formation of enantiomerically enriched α -amino phosphonates.^{5–8} Enantioselectivities up to 96% have been achieved, but the preparation of substrates is not obvious. Another approach has been described by Jørgensen and co-workers via the asymmetric catalytic electrophilic amination (C–N bond formation) of a β -ketophosphonate with dibenzyl azodicarboxylate in the presence of a zinc(II) complex and a chiral bisoxazoline.⁹ The addition of nucleophiles to α -imino phosphonates, in the presence of chiral catalysts, also provides access to enantiomerically enriched α -amino phosphonates via C–C bond formation.¹⁰ However, the most effective approach is currently the catalytic hydrophosphonylation of imines.¹¹ This reaction has been first described by Shibasaki and co-workers in 1995 and is catalyzed by chiral lanthanide complexes.¹² Other chiral catalysts have since been developed, mainly Brønsted acids¹³ or aluminum and others complexes.¹⁴

We report here for the first time a straightforward and alternative approach for the preparation of enantioenriched α -amino phosphonates via the asymmetric rhodium-catalyzed addition of organoboron derivatives to dehydroaminophosphonates (Scheme 1).

Scheme 1. Chiral α -Amino Phosphonates from Rhodium-Catalyzed Asymmetric 1,4-Addition Reactions



We previously reported that the conjugate addition of potassium trifluoro(organo)borates¹⁵ to dehydroalnine derivatives, catalyzed by a chiral rhodium catalyst,

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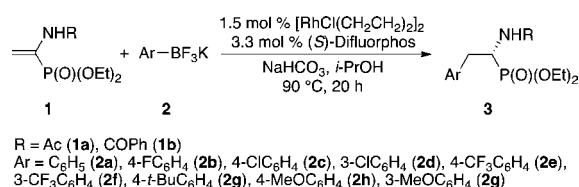
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afforded an access to a variety of protected α -amino esters with high yields and enantiomeric excesses up to 95%.¹⁶ Under these conditions, that is in the presence of a rhodium catalyst associated with Difluorophos ligand and using guaiacol as proton source, moderate conversion (66%) and enantioselectivity (76%) were observed. The use of other chiral ligands did not result in any improvement.

After several optimizations, we were pleased to find that by using $[\text{RhCl}(\text{CH}_2\text{CH}_2)_2]_2$ as a rhodium catalyst precursor and Difluorophos as a chiral ligand, but with isopropanol as solvent and NaHCO_3 as base, α -amino phosphonates were obtained cleanly with improved yields and high levels of enantioselectivity (Scheme 2).

Scheme 2. Enantioenriched α -Amino Phosphonates via Rhodium-Catalyzed Addition/Protonation



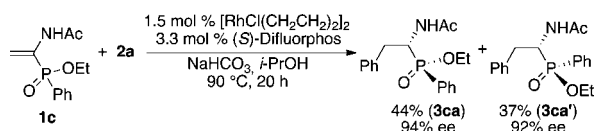
Indeed, the addition of potassium phenyltrifluoroborate (2a) to dehydroaminophosphonate 1a occurred smoothly at 90 °C, providing the enantioenriched α -amino phosphonate 3aa with an enantiomeric excess of 94% (Table 1, entry 1). The other enantiomer was easily obtained, with the same level of enantioselectivity, using (*R*)-Difluorophos as the ligand (entry 2). In order to determine the absolute configuration, the known α -amino phosphonate 3ba was prepared via the addition of potassium phenyltrifluoroborate to dehydroaminophosphonate 1b. The 1,4-addition product

Table 1. Rhodium-Catalyzed Addition of Potassium Aryltrifluoroborates to Dehydroaminophosphonates^a

entry	1	ArBF ₃ K	yield ^b (%)	ee ^c (%)
1	1a	2a	91 (3aa)	94 (–)
2 ^d	1a	2a	65 (3aa)	96 (+)
3	1b	2a	69 (3ba)	92 (<i>R</i>)
4	1a	2b	65 (3ab)	92 (–)
5	1a	2c	72 (3ac)	93 (–)
6	1a	2d	80 (3ad)	94 (–)
7	1a	2e	86 (3ae)	94 (–)
8	1a	2f	84 (3af)	94 (–)
9	1a	2g	76 (3ag)	91 (–)
10	1a	2h	51 (3ah)	94 (–)
11	1a	2i	77 (3ai)	90 (–)

^a Reactions conducted on 0.34 mmol of 1, 2 equiv of 2, 1 equiv of NaHCO_3 , 1.5 mol % of $[\text{RhCl}(\text{CH}_2\text{CH}_2)_2]_2$, and 3.3 mol % of (*S*)-Difluorophos, in isopropanol at 90 °C for 20 h. ^b Isolated yields. ^c Determined by chiral HPLC analysis (see Supporting Information). The sign of the optical rotation or absolute configuration for known compounds is shown in parentheses. ^d Using (*R*)-Difluorophos as a chiral ligand.

Scheme 3. Preparation of Enantioenriched α -Amino Phosphinates



was obtained in 69% yield and with an enantiomeric excess of 92% and proved to be in the (*R*) configuration.⁵

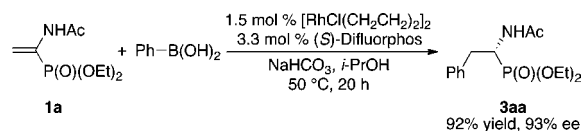
Diversely substituted enantioenriched α -amino phosphonates were readily obtained using this tandem carbometallation/enantioselective protonation process (entries 4–11) with high levels of enantioselectivities (above 90%) whatever the substitution pattern on the aryltrifluoroborate moiety.

These reaction conditions are not limited to the preparation of enantioenriched α -amino phosphonates. Indeed, under identical conditions, the addition of potassium phenyltrifluoroborate (**1a**) to **1c** afforded good yields of diastereoisomeric α -amino phosphinates **3ca** and **3ca'** (Scheme 3) with nearly identical enantiomeric excesses (94% and 92% respectively). This result suggests that the chiral center on the phosphorus atom did not influence the chirality of the newly created chiral carbon center. Single-crystal X-ray diffraction of **3ca** confirmed the (*R,R*) configuration of this isomer (see Supporting Information).

These conditions were also suitable for the addition of arylboronic acids, but with a somewhat lower enantioselectivity. For example, the rhodium-catalyzed asymmetric

addition of phenylboronic acid to **1a** afforded α -amino phosphonate **3aa** in 92% yield and 93% ee (Scheme 4).

Scheme 4. Enantioenriched α -Amino Phosphonates from Boronic Acids



We have developed a new and straightforward method to access enantioenriched, useful α -amino phosphonate and phosphinate derivatives using rhodium-catalyzed asymmetric 1,4-addition of potassium organotrifluoroborates to dehydroaminophosphorous compounds. This simple procedure would allow the fast generation of libraries of such compounds with useful levels of enantioselectivity.

Acknowledgment. N.L. thanks Diverchim for a grant. The authors thanks Lise-Marie Chamoreau (IPCM, Université Pierre et Marie Curie) for X-ray diffraction analysis.

Supporting Information Available. Experimental procedures, description of the compounds, and X-ray diffraction of **3ca**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.