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Substrate-Directed Diastereoselective Hydroaminomethylation of Methallylic Alcohols

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Abstract: Substrate directed diastereoselective hydroaminomethylation of methallylic alcohols has been achieved with the aid of the substrate bound catalyst directing *o*-DPPB-group (*o*-DPPB = *ortho*-diphenylphosphanyl benzoate). The amines **3-7**, **10**, **11** have been obtained in fair to good yields in diastereomer ratios ≥ 94:6 (*syn* : *anti*). © 1998 Elsevier Science Ltd. All rights reserved.

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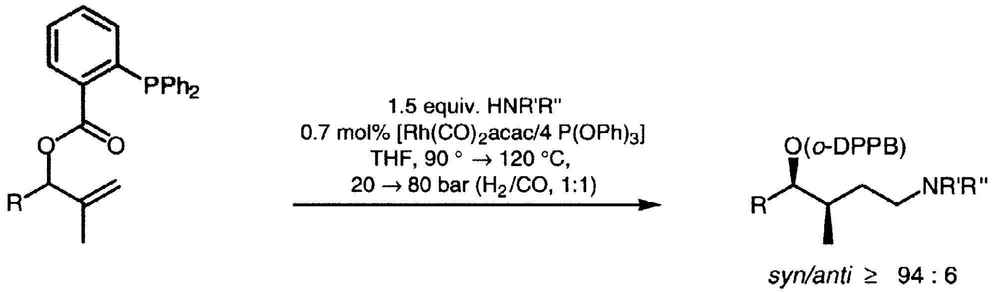
Efficient synthetic methods in organic synthesis are stereoselective framework constructing reactions employing sequential transformations.[1] Hydroaminomethylation of olefins - originally discovered by Reppe in 1949[2] - could in principle become such a process. However, no efficient variants to control stereoselectivity in the course of this reaction are known.[3-5]

We recently found that *o*-diphenylphosphinobenzoic acid (*o*-DPPBA) may be used as an effective substrate bound catalyst directing group in stereoselective hydroformylation of methallylic[6,7] and homomethallylic alcohols.[8] In these processes high 1,2- and 1,3-asymmetric induction is realized by means of the catalyst directing group. We report now that employing the same concept and catalyst directing group (*o*-DPPB = *ortho*-diphenylphosphanyl benzoate) enables the development of a diastereoselective hydroaminomethylation of acyclic methallylic alcohols.



1, 2

3-7, 10, 11

When methallylic *o*-DPPB esters **1**, **2** were subjected to hydroformylation conditions in the presence of a secondary amine (see Table 1) the tertiary amines **3-7** were formed in diastereoselectivities of 95% (see table 1, entries 1-4).[9, 10] Thus, this process allows in one step, the formation of a C-C bond, a C-heteroatom bond, the

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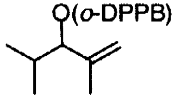
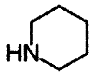
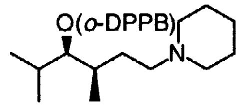
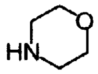
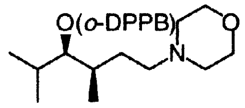
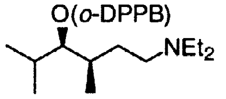
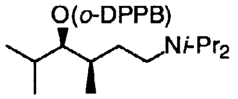
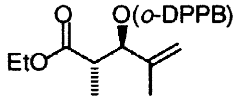
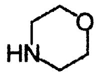
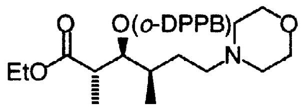
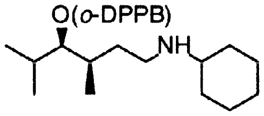
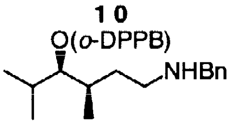
introduction of the ubiquitous amine functionality, and additionally generates a new stereogenic center stereoselectively.

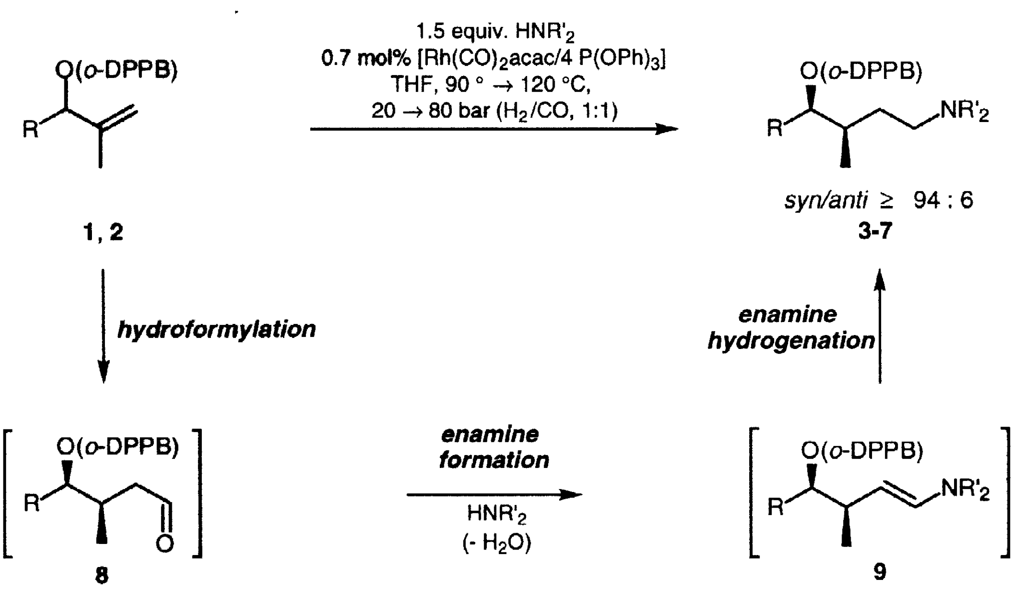
The use of cyclic secondary amines gave the best yields (→ **3**, **4**, Table 1, entries 1 and 2). Conversely, employing acyclic secondary amines such as diethylamine and diisopropylamine provided only moderate yields of *syn*-amines **5** and **6** (entries 1 and 2). Formation of the *syn*-amine as the major diastereomer (95:5) was observed in all cases.[10] Furthermore, the reaction could be used efficiently for the construction of a stereotriad (**2** → **7**, entry 5) - one of the central, structural bulding blocks of the polyketide class of natural products.[11]

Table 1 Results of the diastereoselective hydroaminomethylation of methallylic-*o*-DPPB esters **1**, **2** with secondary and primary amines.

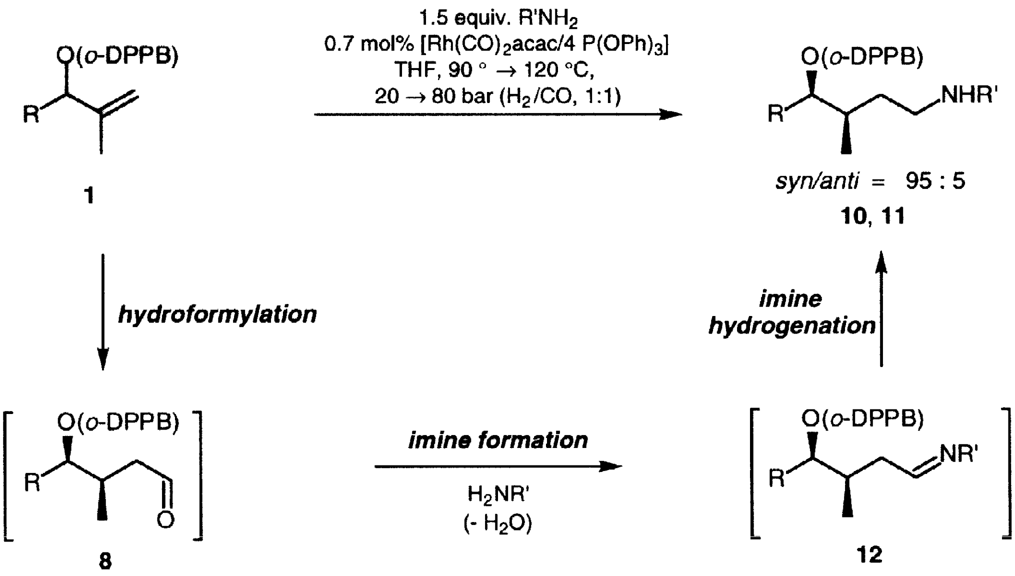
entry[a]	methallylic *o*-DPPB ester	amine	major diastereomer	yield (%)[b]	dr (*syn*:*anti*)[c]
1	 **1**		 **3**	65	95:5
2	**1**		 **4**	64	95:5
3	**1**	$HNEt_2$	 **5**	45	95:5
4	**1**	$HNi\text{-}Pr_2$	 **6**	40	95:5
5	 **2**		 **7**	63	94:6
6	**1**	$c\text{-}HexNH_2$	 **10**	46	95:5
7	**1**	NH_2Bn	 **11**	40	95:5

[a] For a general procedure see ref. 9. [b] Isolated yield after column chromatography. [c] Determined by NMR analysis of the crude reaction mixture.

The mechanism of this sequential transformation involves presumably three steps. First *o*-DPPB directed stereoselective hydroformylation provides the aldehyde **8**,[6, 7] which should react immediately with the secondary amine present, giving rise to the formation of the corresponding enamine **9**. Rhodium catalyzed hydrogenation of this enamine finishes the sequence of reactions, and affords the saturated amines **3**-**7**.



When primary amines such as cyclohexyl- and benzylamine were used the corresponding secondary amines **10** and **11** were obtained (entries 6 and 7) in a diastereomer ratio of 95:5 (*syn*:*anti*). In these cases the reaction sequence must involve imine instead of enamine formation (→ **12**) followed by a Rhodium catalyzed imine reduction (→ **10, 11**).



This result is surprising because known hydroaminomethylation attempts starting from primary amines and alkenes, employing similar rhodium-catalysts, under similar reaction conditions were found to stop generally at the stage of the imine.[5] A plausible explanation for the increased reactivity on reacting methallylic *o*-DPBB ester **1**, takes into account the presence of the catalyst directing *o*-DPPB group. Thus, it is plausible, that after imine formation, a second catalyst precoordination occurs and an intramolecular imine hydrogenation process takes place. Such an intramolecular process should be kinetically favored compared to a corresponding intermolecular reaction pathway. Thus, the *o*-DPPB group may be acting here in two different ways within one sequential transformation. Firstly, this functionality controls diastereoselectivity in the hydroformylation step and secondly controls chemoselectivity in the course of the imine reduction.

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9 General procedure: To a solution of 1.8 mg $Rh(CO)_2acac$ ($7\cdot10^{-3}$ mmol) in THF (5 ml) at 20 °C (exclusion of air and moisture), was added 9 mg $P(OPh)_3$ ($2.8\cdot10^{-2}$ mmol) and the reaction stirred for 15 min at 20 °C. Subsequently methallylic alcohol *o*-DPPB ester (1 mmol) and the corresponding amine (1.5 mmol) were added and the resulting solution transferred by cannula with rinsing (THF, 5 ml) into a carefully evacuated and argon filled stainless-steel autoclave. The autoclave was heated to 90 °C and subsequently pressurized with 20 bar (H_2/CO, 1:1). After stirring for 8 h at 90 °C, the reaction temperature was raised to 120 °C and the reaction pressure was increased to 80 bar (H_2/CO, 1:1). After stirring for a further 24 h at 120 °C the autoclave was cooled rapidly to 20 °C. The reaction solution was filtered through a small plug of silica with *tert*-butyl methyl ether (50 ml). After evaporation of the solvent *in vacuo* the crude product was analyzed by NMR to determine diastereomer ratio (95 : 5). Subsequent column chromatography on silica (solvent: 3/7 ethyl acetate/petrolether) provided the amines **3-7**, **10**, and **11** as highly viscous oils.

10 All compounds were characterized by ^{1}H, ^{13}C, ^{31}P NMR-spectroscopy and elemental analysis. The relative configuration of the amine products was assigned by analogy of their ^{13}C-NMR spectroscopical data with the known *syn*-aldehydes **8**.[7] Spectrosopic data of **3**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.7$ (d, $J = 6.7$ Hz, 3 H, CH_3), 0.75 (d, $J = 6.8$ Hz, 3 H, CH_3), 0.78 (d, $J = 6.8$ Hz, 3 H, CH_3), 1.1-1.9 (m, 10 H), 2.2 (m, 6 H, NCH_2), 4.72 (dd, $J = 7.5$, 4.6 Hz, 1 H, OCH), 6.83 (m, 1 H, ArH), 7.1-7.62 (m, 12 H, ArH), 8.02 (m, 1 H, ArH). ^{13}C NMR (75.469 MHz, $CDCl_3$): $\delta = 13.86$, 18.06, 18.11, 24.28, 25.75 (2C), 29.36, 30.52, 32.71, 54.39 (2 C), 56.89, 82.03, 127.86, 128.16 (d, $J_{C,P} = 6.6$ Hz, 4 C), 128.25 (2 C), 130 29, 131.55, 133.62 (d, $J_{C,P} = 20.8$ Hz, 2 C), 133.75 (d, $J_{C,P} = 20.8$ Hz), 133.83 (d, $J_{C,P} = 21.0$ Hz, 2 C), 134.04, 138.11 (d, $J_{C,P} = 12.3$ Hz, 2 C), 140.94 (d, $J_{C,P} = 28.1$ Hz), 166.08 (d, $J_{C,P} = 2.9$ Hz). ^{31}P NMR (161.978 MHz, $CDCl_3$): $\delta = -3.1$. $C_{32}H_{40}NO_2P$ (501.6): calcd. C 76.62 H 8.04 N 2.79 found C 76.84 H 7.96 N 2.79.

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