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SUBSTRATE-CONTROLLED DIASTEREOSELECTIVITY IN CATALYZED AND UNCATALYZED HYDROBORATIONS OF ALLYLIC AMINE DERIVATIVES

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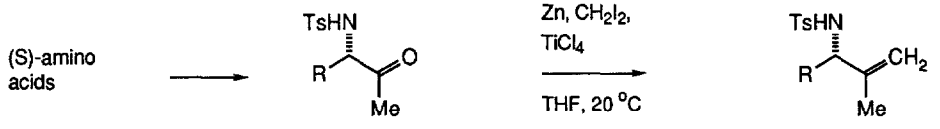
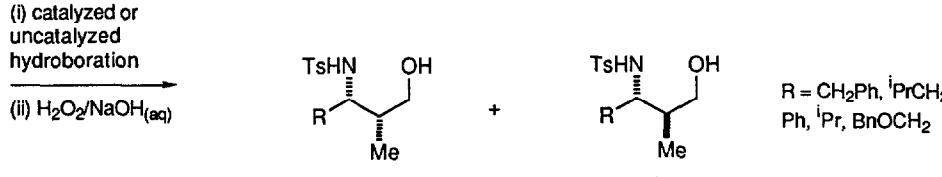
Abstract: Hydroboration of the protected, homochiral allylic amines **(6)** - **(10)** with 9-BBN, and with catecholborane/rhodium catalyst, give different stereoselectivities; the catalyzed reactions provide access to *syn*-3-amino-2-methyl alcohols **(11)** - **(15)**.

1,3-Amino alcohols are frequently sought by organic chemists so it is surprising that little is known about diastereoselective hydroborations of allylic amine derivatives.[1] Recently we[2] and others[3] described how rhodium-catalyzed hydroborations of protected allylic *alcohols* can complement conventional (uncatalyzed) hydroborations of these substrates. In view of the importance of 1,3-amino alcohols and of the potential of rhodium-catalyzed hydroborations,[2-4] we decided to study catalyzed and uncatalyzed hydroborations of the 2-methallylamines **(6)** - **(10)**.



(1) - **(5)** **(6)** - **(10)**



syn anti

(11) - **(15)**

We found that these amines **(6)** - **(10)** could be prepared via Takai methylenation[6] of the N-tosylaminoketones **(1)** - **(5)**; the products derived from homochiral amino acids were optically pure except for compound **(8)** (R = Ph, from

phenyl glycine, 48 % e.e.). Substrates **(6)** - **(10)** were hydroborated in THF using 9-BBN (4 eq. added at -78 °C then allowed to warm slowly to 25 °C and maintained at this temp for 24 h) and using catecholborane (3 eq. at 25 °C for 36 h) in the presence of a rhodium catalyst (2 mol % of $[Rh(COD)Cl]_2$, 8 mol % of PPh_3). In both cases the boron containing products were oxidized and isolated via an aqueous work-up (in the catalyzed reactions this removes catechol). The crude materials from the catalyzed hydroborations contain approximately 8 mol % of triphenylphosphine oxide as the only impurity whereas the 9-BBN hydroborations are contaminated with large amounts of unwanted compounds. Triphenylphosphine oxide is easily removed by filtration through silica thus near quantitative yields can be obtained in the catalyzed processes; isolated yields in the catalyzed processes shown in Table 1 ranged from 87 % (entry 9) to 99 % (entry 3). Fortunately, pure *syn* and pure *anti* diastereomers were available from the catalyzed hydroborations after careful chromatographic separation and/or crystallization; this was helpful in assigning *syn:anti* ratios for the *conventional* hydroborations via ^1H NMR spectra of crude materials. The results of this investigation are given in Table 1.

Table 1. Catalyzed and Uncatalyzed Hydroborations of Substrates (6) - (10)

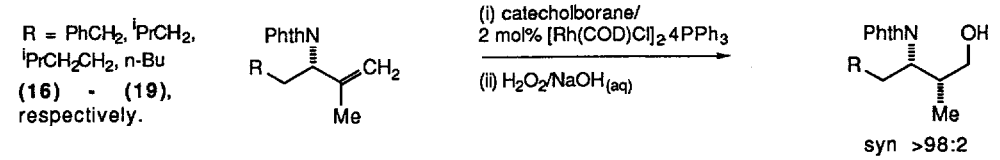
(6) - (10) **(11) - (15)**

Entry	R	Substrate	Product	Method	syn:anti
1	$PhCH_2$	(6)	(11)	catalyzed	7.0:1.0
2	$PhCH_2$	(6)	(11)	uncatalyzed	1.0:1.0
3	$^iPrCH_2$	(7)	(12)	catalyzed	4.0:1.0
4	$^iPrCH_2$	(7)	(12)	uncatalyzed	2.0:1.0
5	Ph	(8)	(13)	catalyzed	1.0:1.0
6	Ph	(8)	(13)	uncatalyzed	1.0:1.0
7	^iPr	(9)	(14)	catalyzed	6.7:1.0
8	^iPr	(9)	(14)	uncatalyzed	1.0:7.4
9	$BnOCH_2$	(10)	(15)	catalyzed	4.0:1.0
10	$BnOCH_2$	(10)	(15)	uncatalyzed	1.0:1.0

Purified isomers of product **(11)** from the catalyzed reaction (entry 1) were converted into tetrahydro-1,3-oxazines (sodium hydride/bromochloromethane) and analyzed via single crystal X-ray diffraction to elucidate the stereochemistry of these materials. Carbon and proton chemical shift differences for the *syn* and *anti* isomers of product **(11)** are also observed for the isomers of compounds **(12)** - **(14)** hence we were able to correlate their stereochemistries.[7] The catalyzed hydroborations give predominantly *syn* products except for substrate **(8)** (entry 5) which reacted without selectivity. Uncatalyzed reactions of these compounds give gross stereochemical mixtures except for the *anti* selective addition to substrate **(9)**. These findings parallel our observations with allylic trifluoroacetates:[2] *catalyzed hydroborations tend to be syn selective and uncatalyzed hydroborations are usually anti selective*. Rhodium-mediated hydroborations of allylic amines may be useful in synthesis because single recrystallizations of the products **(11)**, **(12)**, **(14)**, and **(15)** in entries 1,3,7, and 9 furnish pure *syn* isomers. Recrystallization of the 1:1 *syn:anti* mixture formed from the phenylglycine derivative **(8)** in entry 5 results in considerable enrichment of the *syn* form.

The observations summarized in Table 1 indicate that steric factors influence the outcome of the catalyzed reactions. For instance, the presence of an isopropyl group slightly removed from the chiral center (substrate **(7)**, entry 3) or directly attached (substrate **(9)**, entry 7) enhances *syn* selectivity relative to cases where the "R" substituent is effectively smaller (substrate **(10)**, entry 9). However, steric effects do not account for poor *syn* selectivity observed when a phenyl is directly bonded to the chiral center (substrate **(8)**, entry 5).

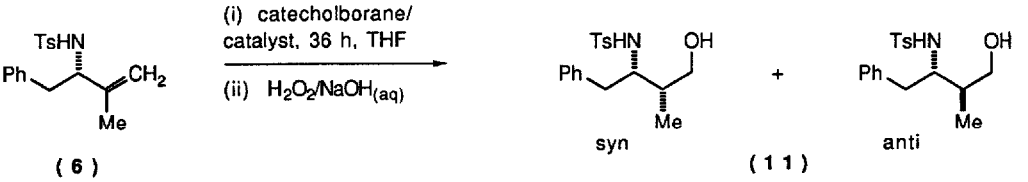
Hydroboration of the phthalyl-protected allylic amines **(16) - (19)** (racemic samples obtained via Mitsunobu reactions of the corresponding secondary alcohols) are intriguing. Catalyzed hydroborations of these substrates are entirely *syn* selective (to within the limits of analysis by 300 MHz ^{1}H NMR of the crude reaction mixtures) indicating the electron withdrawing properties of the phthalyl group have a profound effect. Competing reductions of the phthalyl groups diminish yields of the desired products (less than 44 % in all four cases studied) but compare favorably with conventional hydroborations of these substrates (**(16) - (19)**, 9-BBN), reactions which afford only complex mixtures of compounds with reduced phthalyl units.[8]



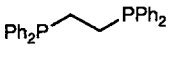
Chemoselective hydroborations of alkenes in the presence of phthalyl groups are potentially valuable in organic synthesis; we are presently investigating the scope of this reaction.

Table 2 below summarizes data obtained for catalyzed hydroborations of a given substrate in the presence of eight different catalyst systems.

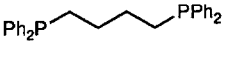
Table 2. The Effects of Catalyst on the Hydroboration of Substrate (6)



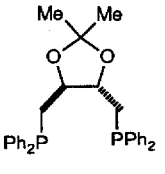
Entry	Catalyst	*syn*-(11):*anti*-(11)	% Yield
1	$[Rh(COD)(PPh_3)_2][PF_6]$	1.0:1.0	50 % (reaction incomplete)
2	$RhCl(PPh_3)_3$	3.0:1.0	78
3	$[Rh(COD)Cl]_2$.4 $P(OEt)_3$	5.7:1.0	92
4	$[Rh(COD)Cl]_2$.4 PPh_3	7.0:1.0	97
5	$[Rh(COD)Cl]_2$.2 DPPE	2.8:1.0	74
6	$[Rh(COD)Cl]_2$.2 DPPB	2.0:1.0	86
7	$[Rh(COD)Cl]_2$.2 (-)-DIOP	3.0:1.0	99
8	$[Rh(COD)Cl]_2$.2 (+)-DIOP	1.5:1.0	91



DPPE



DPPB



(+)-DIOP

The cationic complex cited in entry 1 gives a slow reaction (incomplete in 36 h) and no selectivity. Wilkinson's catalyst is less stereoselective than $[Rh(COD)Cl]_2$/phosphine or $[Rh(COD)Cl]_2$/phosphite (entries 2 - 4). Chelating ligands are generally less suitable for *syn* selective reactions than monodentate ones (entries 5 - 8) and 1,4-bisphosphines (e.g. 1,4-bis(diphenylphosphino)butane, DPPB) are inferior to 1,2-bisphosphines (e.g. 1,2-bis(diphenylphosphino)ethane, DPPE). Entries 7 and 8 illustrate constructive and destructive stereochemical pairing[9] between substrate and ligand chirality. We have already shown that homochiral complexes can be used for *enantioselective* hydroboration of prochiral 1,1-disubstituted alkenes[4] consequently the latter observation is not surprising. However, 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP) is generally not the most effective ligand for transition-metal catalyzed asymmetric induction, doubtless others will emerge that are more suitable for the applications described here and for enantioselective hydroboration.

A model for predicting the stereochemical outcome of catalyzed hydroborations of allylic alcohol and allylic amine derivatives is discussed in the following Letter.

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References and Notes

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7 The structure of these heterocycles are represented below. Coupling constants in these and related ring systems do not give a reliable indication of the relative stereochemistry of the two chiral centers: K. Burgess and M. J. Ohlmeyer, submitted for publication.

8 The rhodium-catalyzed hydroborations therefore are more chemoselective than the uncatalyzed reactions but we were unable to find conditions that completely suppress reduction of the imide functionality.

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