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Asymmetric Synthesis of ?-Borylated Amines via Rhodium-Catalyzed Hydroboration of Allylamine Derivatives

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Asymmetric Synthesis of γ-Borylated Amines via Rh-Catalyzed Hydroboration of Allylamine Derivatives

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Abstract

The Takacs group has explored different areas of Catalytic Asymmetric Hydroboration (CAHB) reaction mainly focusing on variety of amide, oxime ether and phosphonate directing groups. Inspired by the results obtained with BINOL- and TADDOL- derived chiral catalysts along with pinacolborane, we explored the potential of acyclic N-acyl allylamines as substrates for directhydroboration to prepare chiral amine derivatives bearing ?-boronic ester functionality, yields up to 90% with 98:2 enantioselectivity. The major enantiomer obtained is independent of starting alkene geometry, revealing that rhodium-catalyzed cis/trans-alkene isomerization occurs prior to hydroboration. In this poster, we discuss the generation of active catalysts starting from different pre-catalysts. We find that the counterion (e.g., BF4 - , BArF-) plays an important role in the reaction. Furthermore, we find that addition of an external fluoride source (e.g., tetrabutylammonium difluorotriphenylsilicate (TBAT)) significantly impacts the reaction rate. These and other observations lead us to consider a novel catalytic cycle initiated by a rhodium(I)-hydride complex. Finally, the stereospecific transformations of the newly generated C–B bond to access drug candidates will be highlighted to demonstrate the utility of these chiral synthons.

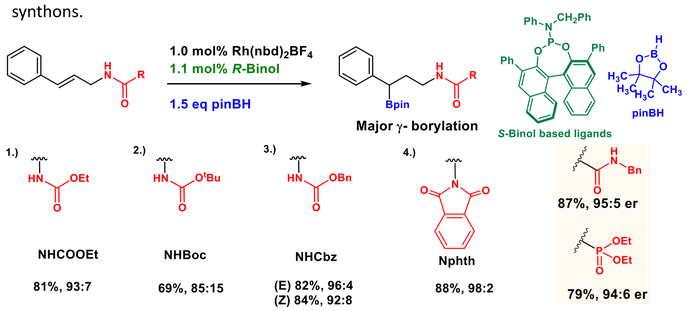


Figure 1: General CAHB reaction conditions with different directing groups (ex: amide, phosphonate and protected *N*-acyl allylamines)

Synthetic utility

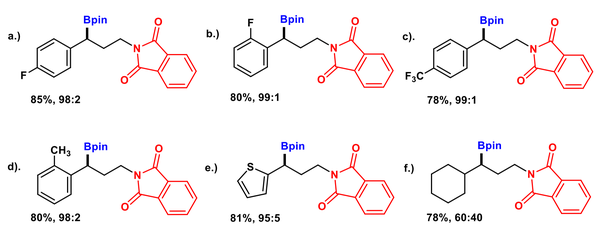


Figure 2: CAHB conditions; 2 mol% $Rh(nbd)_2BF_4$, 2.2 mol% *(R)* 3,3′(Ph)BinolPnBnPh, 1.5 eq. PinBH, room temperature, N_2 Atmosphere, 1-6 hrs reaction time
Note: Yields (isolated) and enantioselectivities (hplc analysis) for corresponding enantiomers were determined after the oxidation of corresponding boronic esters.

Synthetic utility

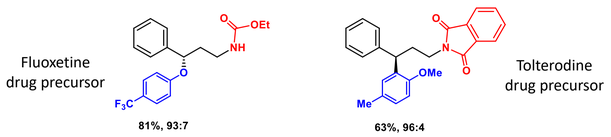


Figure 3: Stereospecific transformations of the newly generated C–B bond to access drug precursors

Probing the CAHB mechanism

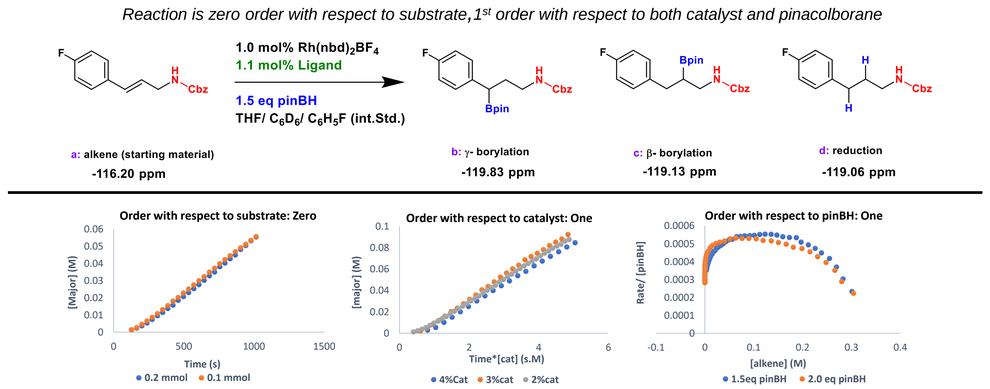
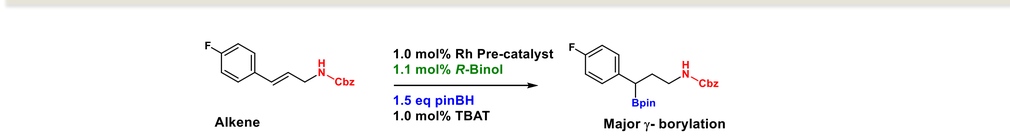


Figure 4: Reaction profile kinetic analysis (RPKA) was used to obtain order with respect to substrate, pinacolborane and the catalyst.

Rh(I)-H plays a role in CAHB



Pre-catalyst	Ligand	Reaction Time/ hr	Yield(%)	er
1mol% $Rh(nbd)_2BF_4$	1.1 mol % L	0.5	93	98:2
1mol% $Rh(cod)_2BF_4$	1.1 mol% L	0.5	89	98:2
1mol% $Rh(cod)_2BArF$	1.1 mol% L	6	90	98:2
1mol% $Rh(cod)_2BArF$ + 1mol%TBAT	1.1 mol% L	0.5	90	98:2
1mol% $[Rh(cod)Cl]_2$	2.2 mol% L	16	25	86:14
1mol% $[Rh(cod)Cl]_2$ +2mol% TBAT	2.2 mol% L	2	88	98:2

Figure 5: Generation of active catalyst, starting from different pre-catalysts resulted similar yields and enantioselectivities. Counter ion (labile fluoride) assisted Rh-H active catalyst formation plays an important role in the CAHB reaction mechanism.

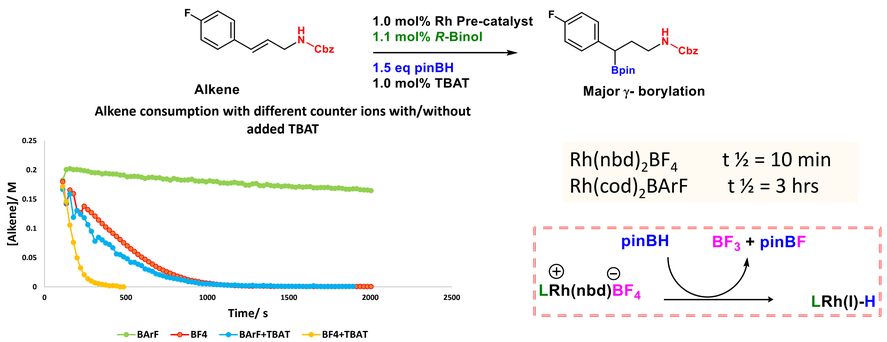
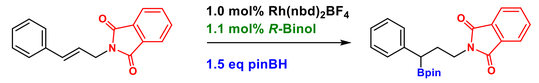


Figure 6: Addition of external fluoride source (e.g., tetrabutylammonium difluorotriphenylsilicate (TBAT)) facilitates faster Rh-H generation in the CAHB reaction.

Rh(I)-H generation



Pre-catalyst	Rh-H generating reagents	Yield(%)	er
1.0 mol% $Rh(nbd)_2BF_4$	1.0 mol% $ZnEt_2$	89	96:4
1.0 mol% $Rh(nbd)_2BF_4$	1.0 mol% n-BuLi	92	97:3
1.0 mol% $Rh(cod)_2BArF$	1.0 mol% $ZnEt_2$	63	97:3
1.0 mol% $Rh(cod)_2BArF$	1.0 mol% n-BuLi	90	95:5
1.0 mol% $Rh(cod)_2BArF$	1.0 mol% TBAT	89	97:3

Figure 7: Other Rh-H generation methods resulted similar stereospecific outcomes for CAHB reaction.

Possible Rh(I)-H mechanism

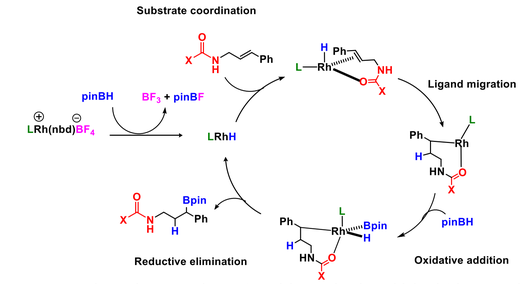


Figure 8: Proposed catalytic cycle initiated by a rhodium(I)-hydride complex. Counter ion (labile fluoride) assisted Rh-H active catalyst formation plays an important role in the CAHB reaction mechanism. Addition of an external fluoride source facilitates faster Rh-H generation in the CAHB reaction.

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Acknowledgements

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