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Application of *P*-chirogenic bisphospholane ligands to rhodium catalyzed asymmetric hydrogenation of α- and β-acetamido dehydroamino acid derivatives

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Abstract—Two previously reported *P*-chirogenic bisphospholane rhodium catalysts have been applied to the asymmetric hydrogenation of α- and β-acetamido dehydroamino acid derivatives. For α-acetamido dehydroamino acid derivatives, catalyst **4** produced very high enantiomeric excesses. These are contrasted with the previously reported enantiomeric excesses using catalyst **2**. Both catalysts provide excellent enantioselectivity (96%) for the β-acetamido dehydroamino acid derivative, (*E*)-methyl 3-acetamido-2-butenoate. However, catalyst **2** produces higher enantioselectivity (89%) for the (*Z*)-isomer when compared to catalyst **4** (83%).
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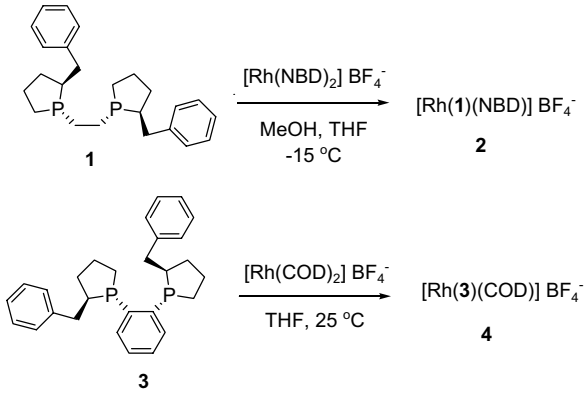
1. Introduction

The synthesis of useful chiral bisphosphine ligands for transition metal-mediated asymmetric catalysis is limited only by known synthetic methodologies.[1] The underdeveloped ligand class of *P*-chirogenic bisphosphines is an example of a synthetically difficult motif which, if easily accessible, could increase the number of useful ligands for asymmetric catalysis. We recently reported synthetic solutions to both enantiomers of *P*-chirogenic bisphospholanes **1** and **3** and their corresponding rhodium complexes **2** and **4** (Scheme 1).[2,3] Herein we report a comparison of the enantioselectivities of these two catalysts in the rhodium catalyzed asymmetric hydrogenation of both α- and β-acetamido dehydroamino acid derivatives.



Scheme 1. Phospholane ligands and their rhodium catalysts.

2. Results and Discussion

The previously reported synthetic routes to ligands **1** and **3** are summarized in Scheme 2. A solution to the ethane-bridged ligand, **1** is shown in Scheme 2a.[3] Methylphosphineborane, **5**, is reacted with two equivalents of *n*-BuLi and then the corresponding anion reacted with **6** to provide a 1:1 mixture of methylphospholanes **7** and **8**. After chromatographic separation, **7** is oxidatively coupled to form the bisphospholane borane, which is subsequently deboronated to provide ligand **1**. Scheme 2b depicts the stereoselective cyclization and epimerization strategy for the synthesis of benzene-bridged ligand **3**.[2] Primary bisphosphine **9** is reacted with 4 equiv of *n*-BuLi and 2 equiv of cyclic sulfate **10** to form bisphospholane **11** stereoselectively. Application of heat to compound **11** epimerizes the phosphine stereocenters to provide ligand **3**.

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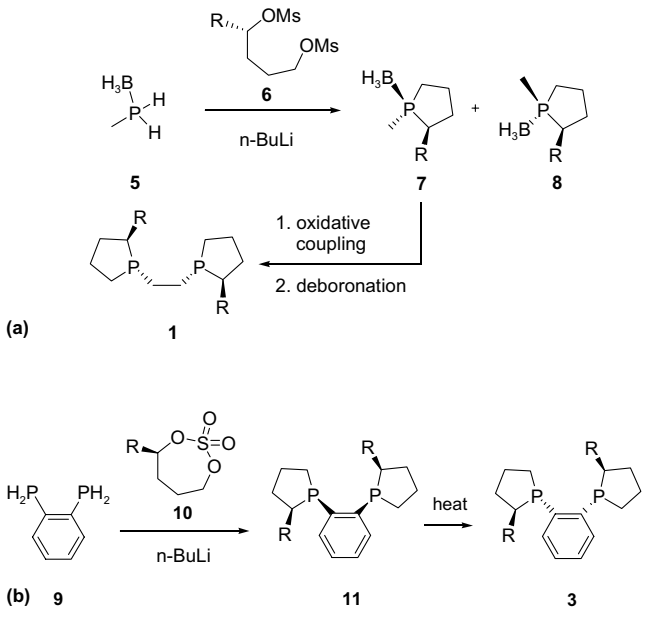
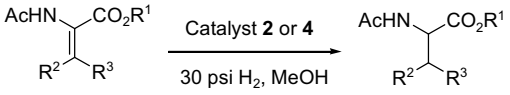


Scheme 2. Synthesis of *P*-chirogenic bisphospholane ligands. (a) Ethane backbone synthesis (R = benzyl); (b) benzene backbone synthesis (R = benzyl).

Table 1 depicts the results of the asymmetric hydrogenation of α-acetamido dehydroamino acid derivatives using both catalyst **2** and **4**. Although enantiomeric excesses using catalyst **2** ranged 77–95% (entries 1–4) (methyl and phenyl substituted substrates), catalyst **4** displayed more consistency and better selectivity for each entry (⩾95% ee). The enantiomeric excesses of catalyst **4** are similar to those reported for Rh–Me–DuPhos.[4] In the case of entry 5, however, catalyst **2** provided better enantioselectivity (96%) than catalyst **4** (86%). β,β-Disubstituted α-acetamido dehydroamino acid substrates are known to be among the most difficult to hydrogenate with high enantioselectivity.[5]

Table 1. Asymmetric hydrogenation of α-acetamido dehydroamino acids

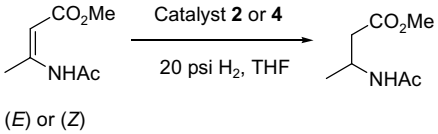


Entry[a]	R^1	R^2	R^3	Ee[b] (%) catalyst **2**	Ee[b] (%) catalyst **4**
1	Me	H	H	95 (*R*)	98 (*S*)
2	H	H	H	86 (*R*)	97 (*S*)
3	Me	Ph	H	84 (*R*)	95 (*S*)
4	H	Ph	H	77 (*R*)	96 (*S*)
5	Me	R_2, R_3 = $-C_5H_{10}-$		96 (*R*)	86 (*S*)

[a] All reactions were performed at room temperature using 1 mol% catalyst loading and 0.2 M substrate concentration. All reactions were complete within 15 min.
[b] Ee of product was analyzed on a Chiral-L-Val column.

Table 2 shows the results of the asymmetric hydrogenation of methyl 3-acetamido-2-butenoate, a β-acetamido dehydroamino acid derivative, using catalysts **2** and **4**. Recent reports have focused on catalysts that can hydrogenate both (*E*)- and (*Z*)-isomers of this substrate class with high enantioselectivity.[6] Both catalysts **2** and **4** provided high ees (96%) for the hydrogenation of the (*E*)-form of the substrate (entries 1 and 3). However, while **4** produced 83% ee for the (*Z*)-form of the substrate (entry 4), catalyst **2** produced an encouraging 89% (entry 3). In both cases, the (*Z*)-isomer was hydrogenated several times more slowly than the (*E*)-isomer.

Table 2. Asymmetric hydrogenation of methyl-3-acetamido-2-butenoate



Entry[a]	Catalyst	Substrate isomer	Time (min)	Ee[b] (%)
1	**2**	*E*	5	96 (*R*)
2	**2**	*Z*	45	89 (*R*)
3	**4**	*E*	15	96 (*S*)
4	**4**	*Z*	75	83 (*S*)

[a] All reactions were performed at room temperature using 1 mol% catalyst loading and 0.2 M substrate concentration.
[b] Ee of product was analyzed on a Chiral-DEX-CB GC column.

3. Conclusion

Both catalysts **2** and **4** provide good enantioselectivity for the catalyzed asymmetric hydrogenation of both the α- and β-acetamido dehydroamino acid derivatives. Although many other chiral phosphine ligand-metal catalysts have a list of similar accomplishments, these *P*-chirogenic ligands and their corresponding rhodium catalysts are exemplary of a phosphine ligand class that shows promise for diversifying the useful chiral ligand and catalyst pool. Work is currently underway in our laboratory in the exploration of novel *P*-chirogenic bisphosphine ligands.

Acknowledgements

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References and notes

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