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Enantioselective hydrogenation of cyclic tetrasubstituted-olefinic dehydroamino acid derivatives†

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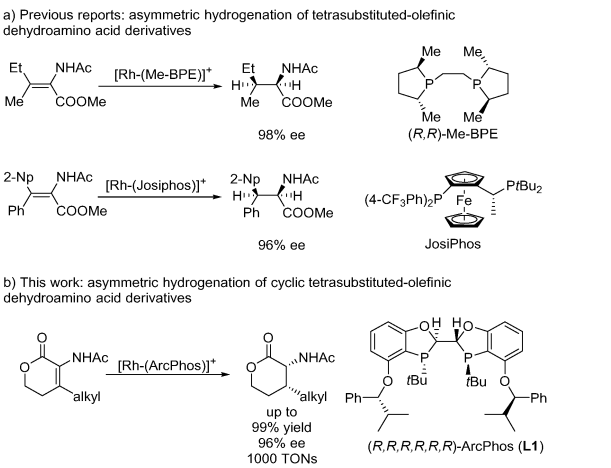
An efficient asymmetric hydrogenation of cyclic tetrasubstituted-olefinic dehydroamino acid derivatives has been achieved with a Rh-ArcPhos catalyst, affording a series of α-acylamino-β-alkyl tetrahydropyranones with two contiguous chiral centers in up to 96% ee and 1000 TON.

Despite the tremendous progress achieved in the field of asymmetric hydrogenation during the last five decades, the asymmetric hydrogenation[1,2,4] of tetrasubstituted olefins to form enantiomerically enriched products with two contiguous chiral centers remains one of the most difficult problems.[5] The asymmetric hydrogenation of dehydroamino acid derivatives, widely applied in both academic research and industrial settings, has become one of the most indepensible methods for the preparation of chiral α-amino acid derivatives. However, only a few methods are available for the preparation of β-branched α-amino acids with two contiguous chiral centers. Burk[3a] and coworkers developed Me-DuPhos and Me-BPE ligands and reported the asymmetric hydrogenation of acyclic β,β-disubstituted dehydroamino acid derivatives with excellent reactivities and enantioselectivities (Scheme 1a). A Merck team[3b] developed an efficient preparation of chiral β,β-diaryl-α-amino acid derivatives by asymmetric hydrogenation using Rh-JosiPhos as the catalyst. Because of the high demand for chiral α-amino acids with multi-stereogenic centers in the field of peptidomimetics and drug discovery, it remains imperative to develop an efficient asymmetric hydrogenation of various tetrasubstituted-olefinic dehydroamino acid derivatives. The asymmetric hydrogenation of cyclic tetrasubstituted-olefinic dehydroamino acid derivatives has not been explored to our knowledge. Herein we report an efficient asymmetric hydrogenation of cyclic tetrasubstituted-olefinic dehydroamino acid derivatives and a series of α-acylamino-β-alkyl tetrahydropyranones have been obtained in excellent reactivities (1000 TONs) and enantioselectivities (up to 96% ee) with a Rh-ArcPhos[5o] catalyst (Scheme 1b).

We embarked on a program to explore efficient asymmetric hydrogenation methods for the synthesis of chiral building blocks by developing structurally novel and unique chiral phosphorus ligands. The BIBOP-type ligands[6] have shown high effectiveness in asymmetric hydrogenation for producing chiral amines, alcohols, α-amino acids, *etc.* Taking advantage of the stereoelectronic effects in ligand design, we developed an electron-rich and conformationally defined ligand ArcPhos



Scheme 1 Asymmetric hydrogenation of tetrasubstituted-olefinic dehydroamino acid derivatives.

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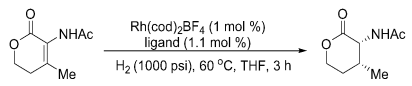
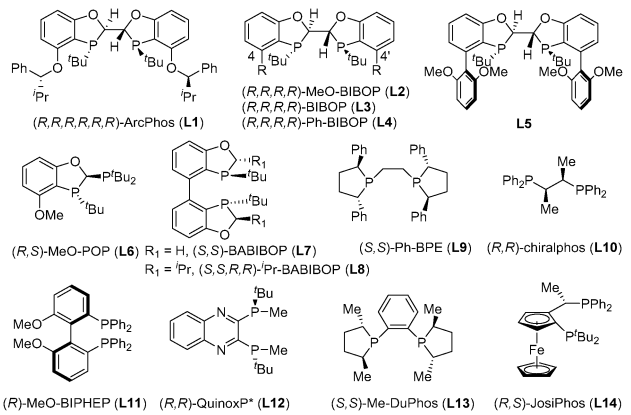
Table 1 Asymmetric hydrogenation of *N*-(4-methyl-2-oxo-5,6-dihydro-2*H*-pyran-3-yl)acetamide (**1a**)



1a 2a

Entries[a]	Ligand	Solvent	Yields (%)	Ee[b] (%)
1	ArcPhos (**L1**)	THF	99	90
2	MeO-BIBOP (**L2**)	THF	99	61
3	BIBOP (**L3**)	THF	<20	63
4	Ph-BIBOP (**L4**)	THF	<20	10
5	BI-BIDIME (**L5**)	THF	<20	31
6	MeOPOP (**L6**)	THF	99	31
7	BABIBOP (**L7**)	THF	99	20
8	^{i}Pr-BABIBOP (**L8**)	THF	99	75
9	Ph-BPE (**L9**)	THF	99	67
10	ChiralPhos (**L10**)	THF	0	ND
11	MeO-BIPHEP (**L11**)	THF	99	0
12	QuinoxP* (**L12**)	THF	0	ND
13	Me-DuPhos (**L13**)	THF	0	ND
14	JosiPhos (**L14**)	THF	99	50
15	ArcPhos (**L1**)	DCM	99	70
16	ArcPhos (**L1**)	EtOAc	0	ND
17	ArcPhos (**L1**)	CH_3CN	0	ND
18[c]	ArcPhos (**L1**)	THF	99	89
19[d]	ArcPhos (**L1**)	THF	99	90
20[e]	ArcPhos (**L1**)	THF	99	84
21[f]	ArcPhos (**L1**)	THF	99	80
22[g]	ArcPhos (**L1**)	THF	99	81

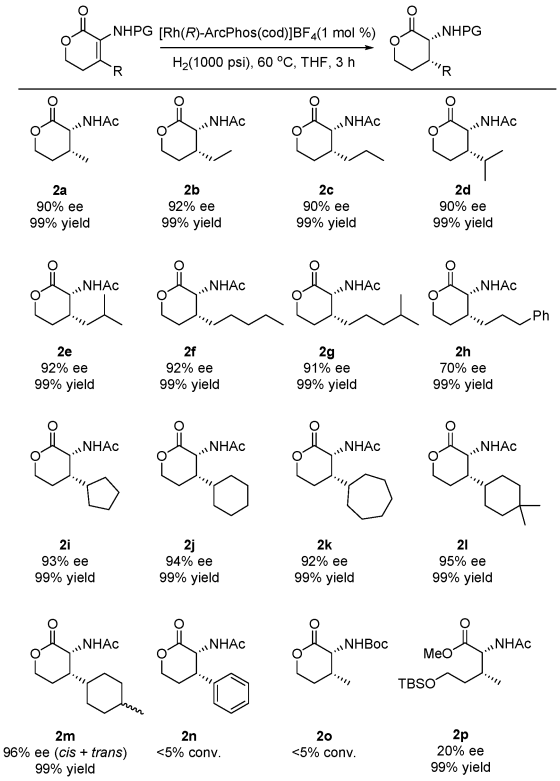


[a] Unless otherwise specified, the reactions were carried out at 60 °C under H_2 (1000 psi) in THF (0.5 mL) for 3 h with **1a** (0.1 mmol) in the presence of the rhodium precursor (1 μmol, 1 mol%) and the ligand (1.1 μmol, 1.1 mol%). [b] Determined by chiral HPLC using a Chiralpak OJ-3 column. [c] 10% 4 Å MS was added. [d] The reaction was carried out with 2 mol% catalyst. [e] The reaction was carried out at 30 °C under 1000 psi H_2. [f] The reaction was carried out at 60 °C under 300 psi H_2. [g] The reaction was carried out at 60 °C under 1200 psi H_2.

containing deep chiral pockets. Its rhodium complex showed excellent reactivities and enantioselectivities in the asymmetric hydrogenation of cyclic tetrasubstituted enamides, forming a series of chiral *cis*-2-alkyl substituted carbocyclic and heterocyclic amine derivatives in excellent ees. We envisioned that the BIBOP-type ligands could also be suitable for the asymmetric hydrogenation of cyclic tetrasubstituted-olefinic dehydroamino acid derivatives. Herein we report our study on the asymmetric hydrogenation of α-acetylamino-β-alkyl-dihydropyranones.

The Rh-catalyzed asymmetric hydrogenation of *N*-(4-methyl-2-oxo-5,6-dihydro-2*H*-pyran-3-yl)acetamide (**1a**) was studied with a series of chiral BIBOP-type ligands as well as some well-known chiral bisphosphorus ligands (Table 1). Hydrogenation was performed in THF under 1000 psi of H_2 at 60 °C for 3 h in the presence of 1 mol% $Rh(cod)_2BF_4$ and 1.1 mol% chiral ligand (Table 1). To our delight, ArcPhos(**L1**) provided complete conversion and an excellent ee in the asymmetric hydrogenation of **1a** (90% ee, entry 1). We further screened a few BIBOP-type ligands (**L2–L5**) in this reaction. As anticipated, the degree of enantioselectivity was highly dependent on the substituents at the 4,4′-positions in the ligand structure. Meanwhile MeO-BIBOP (**L2**) provided a full conversion and a modest ee (61%) (entry 2), while ligands **L3–L5** with H or aryl groups at the 4, 4′-positions (**L3–L5**) provided low reactivities and enantioselectivities, indicating the importance of electron-richness of the phosphorus ligands in promoting the reaction (entries 3–5). Interestingly, the phosphorus ligands MeO-POP (**L6**) and BABIBOP (**L7**) showed sufficient reactivity, albeit with low ees (entries 6 and 7). The use of a sterically more hindered chiral biaryl bisphosphorus ligand iPr-BABIBOP led to a 75% ee (entry 8). For comparison, some commerciallized chiral bisphosphorus ligands such as Ph-BPE (**L9**), Chiralphos (**L10**), MeO-BIPHEP (**L11**), QuinoxP* (**L12**), Me-DuPhos (**L13**), and Josiphos (**L14**) were also evaluated on this transformation and found to be either unreactive or poorly enantioselective (entries 9–14). The ligand Ph-BPE showed a relatively high ee (67% ee, entry 9). It was noteworthy that the ligands Me-DuPhos, Ph-BPE, and MeO-POP, which showed excellent enantioselectivities and activities in the asymmetric hydrogenation of acyclic tetrasubstituted-olefinic dehydroamino acid derivatives, did not work well on this cyclic substrate. Further optimizations of the reaction parameters with the Rh-AcrPhos catalyst were conducted. The solvent appeared to be important for enantioselectivity. While the use of dichloromethane as the solvent provided a 70% ee, no reactivity was oberved when ethyl acetate or acetonitrile was employed (entries 15–17). The addition of 4 Å molecular sieves or the use of a higher catalyst loading (2 mol%) did not affect the enantioselectivities or yields (entries 18 and 19). The use of a low reaction temperature did not enhance enantioselectivity (entry 20). The use of a low or high pressure of H_2 also did not improve ees (entries 21 and 22). The other detailed optimized conditions are given in the ESI† (Table S1). We therefore chose the following optimal reaction conditions for further studies: Rh-ArcPhos, 1000 psi H_2, THF, 60 °C, and 3 h.

Under the optimized reaction conditions with [Rh(**L1**)(cod)]BF_4 (1 mol%) as the catalyst, a series of α-acetylamino-β-alkyl-dihydropyranones (**1a–o**) were hydrogenated, forming α-acylamino-β-alkyl tetrahydropyranones in excellent ees and yields (Scheme 2). More than 90% ees were achieved regardless of the linear or branched alkyl substituent at the β position (**2b–2g**). A long-chain alkyl subsitituent with up to five carbons was also tolerated (**2f** and **2g**). A modest enantioselectivity (70% ee) was obtained on the hydrogenation product **2h** containing phenyl functionality, which might be due to the undesired π-stacking interaction between the phenyl group of **1h** and ArcPhos. When cyclic alkyl moieties were installed at the β-position, excellent enantioselectivities

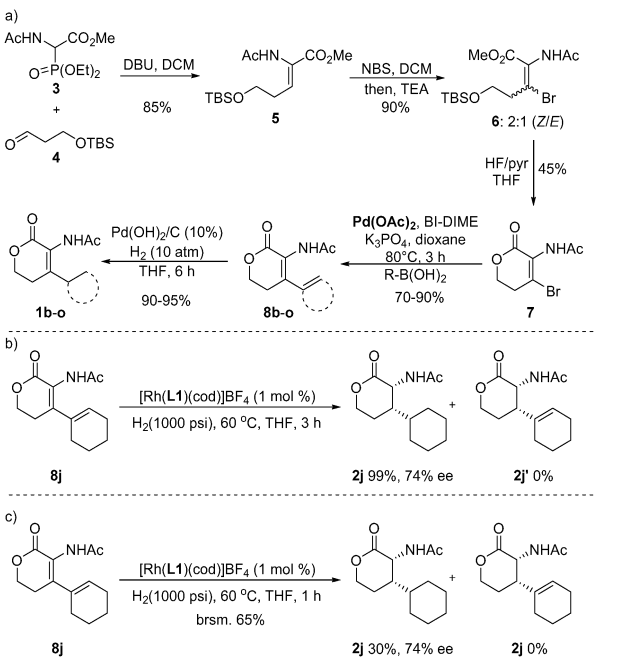


Scheme 2 Preparation of optically enriched α-acylamino-β-alkyl tetrahydropyranones by asymmetric hydrogenation. [a]Unless otherwise specified, the reactions were carried out at 60 °C under H_2 (1000 psi) in THF (0.5 mL) for 3 h with **1a–p** (0.1 mmol) in the presence of [Rh(cod)(**L1**)]BF_4 (1 μmol, 1 mol%); [b]determined by chiral HPLC using a Chiralpak OJ-3 column; [c]the absolute configuration was assigned by analogy on the basis of the established stereochemistry of **2a** by transforming to (*D*)-isoleucine **10** in Scheme 4.

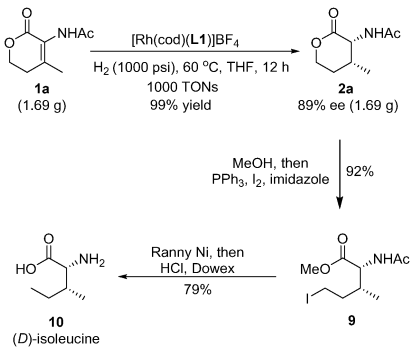
were obtained. The cyclopentyl-(**2i**) and cyclohexyl-substituted (**2j**) products were obtained in full conversions and in 93% and 94% ee, respectively. The cycloheptyl-substituted product **2k** was also obtained in 92% ee. We further investigated the influence of the substituents on the cyclohexyl ring on enantioselectivity. The product **2l** with geminal-dimethyl substituents on the cyclohexyl ring was obtained in 95% ee. The *cis*/*trans* (~3/2) mixture of the methyl cyclohexyl-substituted product **2m** was formed in 96% yield and both isomers provided 96% ees. Nevertheless, both the β-phenyl-substituted substrate **1n** and the *N*-Boc-protected substrate **1o** were unreactive under similar reaction conditions. These results further demonstrated the sensitivity of the electronic properties and the acyl-protected group on the reactivity of hydrogenation. An acyclic tetrasubstituted-olefinic dehydroamino acid **1p** was also employed for asymmetric hydrogenation and a 20% ee was obtained albeit with a complete conversion. The absolute configuration was assigned by analogy on the basis of the established stereochemistry of **2a** by transforming to (*D*)-isoleucine **10** in Scheme 4.

The substrates were prepared as illustrated in Scheme 3a.[7] Horner–Wadsworth–Emmons reaction between phosphonate **3** and aldehyde **4** provided olefin **5**. The bromination of **5** with NBS provided vinyl bromide **6** in 90% yield as a *Z*/*E* isomeric mixture. This was followed by treatment with HF/Pyr to give lactone **7** in 45% yield. Next, various alkenyl boronic acids were employed for the cross-coupling with **7** with a Pd-BI-DIME catalyst, affording dienes **8b–o** in 70–90% yields. The selective hydrogenation of the olefin derived from the alkenyl boronic acids over $Pd(OH)_2$/C afforded substrates **1a–o** in 90–95% yields. Of course, the dienes **8b–o** could also be employed for asymmetric hydrogenation. With Rh-ArcPhos as the catalyst, the hydrogenation of **8j** was conducted under similar hydrogenation conditions and the fully hydrogenation product **2j** was obtained in 74% ee, significantly lower than that observed from the hydrogenation of **1j** (Scheme 3b). The result indicated that the hydrogenation of tetrasubstituted olefins proceeded prior to that of the olefins in the cyclohexene moiety. In order to obtain the partial hydrogenation intermediate, the hydrogenation of **8j** was stopped after 1 h under similar reaction conditions. No partial hydrogenation product **2j′** was obtained and only **2j** was isolated along with unreacted **8j** (Scheme 3c). This experiment demonstrated that the hydrogenation of the cyclohexene moiety proceeded quite fast once the tetrasubstituted olefin was reduced.

To demonstrate the practicality of this method, the hydrogenation of **1a** was conducted in a gram scale with the Rh-ArcPhos catalyst (0.1 mol%) under 1000 psi hydrogen at 60 °C in THF for 12 h, and the desired product **2a** was obtained in 89% ee. Next, the transformation of **2a** to (*D*)-isoleucine was performed.[8] The methanolysis of **2a** followed by iodination under Appel conditions (PPh_3/I_2) afforded iodide **9** in 92% yield.[9] Dehalogenation with RANEY® Ni followed by treatment with conc. HCl afforded smoothly (*D*)-isoleucine (**10**) in 79% yield (Scheme 4).



Scheme 3 Preparation of hydrogenation substrates **1b–o** and the asymmetric hydrogenation of the conjugated diene **8j**.



Scheme 4 Gram-scale hydrogenation and transformation to (*D*)-isoleucine.

In summary, we have demonstrated an efficient asymmetric hydrogenation of cyclic tetrasubstituted-olefinic dehydroamino acid derivatives powered by the Rh-ArcPhos catalyst, affording a series of α-acylamino-β-alkyl tetrahydropyranones with two contiguous chiral centers in up to 96% ee and 1000 TON. The convenient access to a series of optically enriched isoleucine derivatives with this method should facilitate the research in peptidomimetics and drug discovery.

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Conflicts of interest

There are no conflicts to declare.

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