Asymmetric Hydrogenation of Heteroaromatic Ketones and Cyclic and Acyclic Enones Mediated by Cu(I)–Chiral Diphosphine Catalysts

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Abstract: Copper(I)-catalyzed asymmetric hydrogenation of heteroaromatic ketones, cyclic and acyclic enones is reported. The choice of the chiral diphosphine ligand highly influenced enantioselectivity as well as chemoselectivity. Highly enantioselective hydrogenation of *ortho*-substituted heteroaromatic ketones was achieved using BDPP as the ligand. In the 1,2-selective hydrogenation of acylic enone, SEGPHOS gave higher enantioselectivity than BDPP. On the other hand, the bulky ligand DTBM-SEGPHOS had a 1,4-selective nature, leading to the first highly 1,4-selective and enantioselective hydrogenation of cyclic enones.

Key words: asymmetric catalysis, hydrogenations, copper, heteroaromatic ketones, enones

Asymmetric hydrogenations catalyzed by chiral metal complexes are among the most powerful and environmentally benign processes used to produce optically active natural and artificial compounds. Since the initial development of asymmetric reactions, platinum-group metals (e.g., Rh, Ru, Ir, and Pt) have been used as the catalytically active center of various chiral catalysts[1] and show prominent compatibility and wide applicability in many industrial processes.[2] Despite their high performance, recent research has focused on minimizing the use of platinum-group metals and replacing them with an abundant and inexpensive transition metal.[3] A pioneering study by Stryker demonstrating the feasibility of homogeneous copper-catalyzed hydrogenation[4] prompted us to focus our attention on copper-based catalyst systems, and we recently found that a Cu(I) complex, $\{Cu(NO_3)[P(3,5\text{-xylyl})_3]_2\}$, together with (*S*,*S*)-2,4-bis(diphenylphosphino)pentane (BDPP)[5] and NaO*t*-Bu catalyzed asymmetric hydrogenation of aryl ketones. Notably, *ortho*-substituted acetophenone derivatives were hydrogenated to give the corresponding alcohols in a highly enantioselective manner (up to 91% ee).[6] As a part of our continuing efforts aimed at developing an efficient asymmetric Cu(I) catalysis, we report on the asymmetric hydrogenation of heteroaromatic ketones and acyclic and cyclic enones catalyzed by a Cu(I) complex, which was prepared from $[Cu(NO_3)(PAr_3)_2]$ (Ar = Ph or 3,5-xylyl), chiral diphosphine, and NaO-*t*-Bu. *ortho*-Substitution of heteroaromatic ketones positively affected enantioselectivity to afford the desired alcohols in up to 92% ee. In the reaction of enones, the choice of the chiral diphosphine ligand influenced both enantioselectivity and 1,2- and 1,4-selectivity, leading to the highly 1,4-selective and enantioselective hydrogenation of cyclic enones (up to >99% ee).

We first examined the asymmetric hydrogenation of heteroaromatic ketones under the optimized conditions for aromatic ketones ($\{Cu(NO_3)[P(3,5\text{-xylyl})_3]_2\}$/(*S*,*S*)-BDPP/$P(3,5\text{-xylyl})_3$, molar ratio of substrate to catalyst (S/C) = 200, initial H_2 pressure of 5.0 MPa, 30 °C, Table 1).[6] Hydrogenation of 5-methyl-2-acetylfuran (**1a**) and 2-acetylthiophene (**1b**) proceeded smoothly, though enantioselectivities of the corresponding alcohols **2a** and **2b** were moderate, 40% and 36% ee, respectively (entries 1 and 2). On the other hand, the introduction of a methyl group at the *ortho*-position of **1b** greatly enhanced enantioselectivity to 90% ee (entry 3), consistent with a previous observation that the hydrogenation of *ortho*-methyl-substituted acetophenone derivatives affords the corresponding alcohols with higher enantioselectivty.[6]

Regardless of the position of the acetyl group in five-membered heterocycles, the presence of a methyl group at the *ortho*-position to the acetyl group resulted in almost complete formation of the corresponding alcohols **2** with much higher enantioselectivity (89–92% ee, entries 4–6). The present catalysis was also effective for the reaction of six-membered heteroaromatic ketone **1g** with *ortho*-methoxy substitution to the acetyl group, affording the product **2g** in 89% ee (entry 7).

We then examined the asymmetric hydrogenation of cyclic and acyclic enones for chemoselective asymmetric hydrogenation, which potentially provides three kinds of products, that is, ketones, allylic alcohols, and saturated alcohols. Only a few previous chemoselective hydrogenations by Cu catalyst systems have been reported: Stryker reported that the $[CuH(PPh_3)]_6$/$PhPMe_2$ system selectively hydrogenated the carbonyl group of enals and enones to give the corresponding allylic alcohols,[4d] and we reported the same carbonyl selective hydrogenation of enals using a $[Cu(NO_3)(PPh_3)_2]$/1,4-bis(diphenylphosphino)butane (DPPB) system.[7] Accordingly, we applied the present Cu(I) catalyst system, $\{Cu(NO_3)[P(3,5\text{-xylyl})_3]_2\}$/(*S*,*S*)-BDPP/NaO-*t*-Bu,[8] to asymmetric hydrogenation of an acyclic ketone, benzalacetone (**3**), to give the allylic alco-

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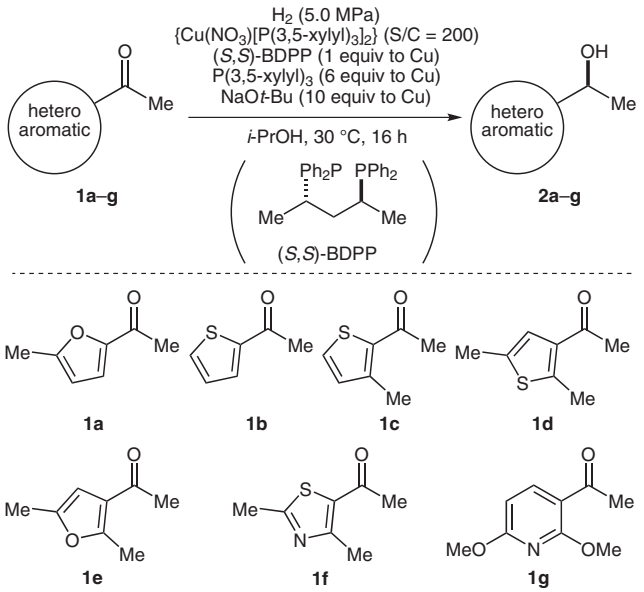
Table 1 Asymmetric Hydrogenation of Heteroaromatic Ketones **1**[a]



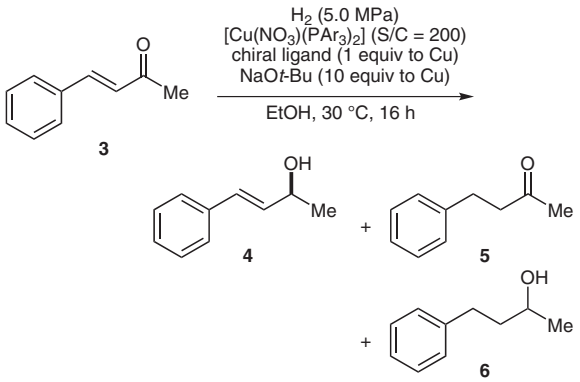
Entry	Substrate	Conv. (%)[b]	Isolated yield (%)[c]	ee (%)[b]	Config[d]
1	**1a**	>99	79	40	(–), (*S*)
2	**1b**	>99	82	36	(–), (*S*)
3	**1c**	97	89	90	(–), (*S*)
4	**1d**	>99	93	92	(–), (*S*)
5	**1e**	99	80	89	(–)
6	**1f**	>99	91	90	(–)
7	**1g**	77	71[e]	89	(–)

[a] The reaction was performed at 3.6 mmol scale.
[b] Determined by GC analysis.
[c] Isolated yield by bulb-to-bulb distillation.
[d] Sign of $[\alpha]_D^{27}$ of each product and absolute configuration of **2a–d**.
[e] Isolated yield by silica gel chromatography.

hol (*S*)-**4** with excellent chemoselectivity (97%) and moderate enantioselectivity (62% ee, Table 2, entry 1). The use of the biaryl ligand (*R*)-SEGPHOS[9] instead of (*S*,*S*)-BDPP improved enantioselectivity to 72% ee while maintaining high 1,2-selectivity (98%, entry 2). Changing the Cu source from $\{Cu(NO_3)[P(3,5\text{-xylyl})_3]_2\}$ to $[Cu(NO_3)(PPh_3)_2]$ resulted in slight decrease of 1,2-selectivity (89%) and significant decrease of enantioselectivity (19% ee, entry 3). On the other hand, the use of DTBM-SEGPHOS, a bulkier variant of SEGPHOS, yielded 1,4-reduction product **5** as a major product (entry 4). These data clearly indicate that Cu(I)–DTBM-SEGPHOS complex preferentially promoted a 1,4-reduction of enone **3** to the saturated ketone **5**, in sharp contrast to the high 1,2-selectivity promoted by the Cu(I)–SEGPHOS complex. We thus anticipated that the Cu catalyst system of (*R*)-DTBM-SEGPHOS could be applied to an asymmetric 1,4-reduction of cyclic enones.

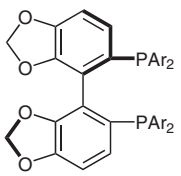
Compared to 1,2-selective reduction of cyclic enones where a diamine-modified Ru catalyst achieved high enantioselectivity and excellent catalytic productivity,[10] 1,4-selective counterparts are quite limited[11] because of the unfavorable *s-trans* coordination of the cyclic enone to transition metals. Thus, although excellent asymmetric 1,4-selective reduction of cyclic enones using Cu-catalyzed hydrosilylation[12] and hydroboration[13] were reported, asymmetric 1,4-selective reduction of cyclic enones using Cu-catalyzed hydrogenation has not been reported. Based on the results shown in Table 2, we examined asymmetric 1,4-selective hydrogenation of isophorone (**7**) using the $\{Cu(NO_3)[P(3,5\text{-xylyl})_3]_2\}$/(*R*)-DTBM-SEGPHOS/NaO*t*-Bu system (Table 3).

Table 2 Asymmetric Hydrogenation of Benzalacetone (**3**)



Entry	Ar	Chiral Ligand	Conv. **4/5/6**[a] (%)[a]		ee of **4** (%)[b]
1	3,5-xylyl	(*S*,*S*)-BDPP	93	97:2:<1	62 (*S*)
2	3,5-xylyl	(*R*)-SEGPHOS	98[c]	98:2:<1	72 (*S*)
3	Ph	(*R*)-SEGPHOS	99	89:9:2	19 (*S*)
4[d]	Ph	(*R*)-DTBM-SEGPHOS	70	38:61:1	–

[a] Determined by GC analysis.
[b] Determined by HPLC analysis.
[c] Isolated yield by bulb-to-bulb distillation was 81%.
[d] Reaction time was 41 h. Isolated yields of **4** and **5** were 5% and 7%, respectively, due to the formation of unidentified oligomeric compounds.



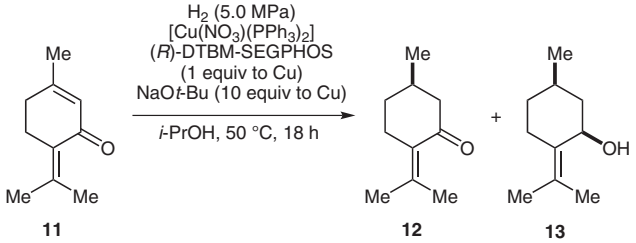
(*R*)-SEGPHOS: Ar = Ph
(*R*)-DTBM-SEGPHOS: Ar = C_6H_2-3,5-*t*-Bu_2-4-OMe

As expected, the desired saturated ketone (*R*)-**9** was obtained in a highly 1,4-selective manner (97%) with quite high enantioselectivity (98% ee), though conversion was unsatisfactory (entry 1). To compensate for this low conversion, we switched the catalyst precursor to less bulky $[Cu(NO_3)(PPh_3)_2]$ and the conversion was improved to 51% while maintaining high 1,4-selectivity (91%) and high enantioselectivity (99% ee, entry 2).[14] The conver-

sion was further improved by increasing the reaction temperature (50 °C, entry 3) or by increasing catalyst loading (S/C = 100, entry 4). Under the conditions shown in entry 3, ketone **9** was reduced to saturated alcohol **10** with 69% conversion whereas the allylic alcohol **8** was not reduced at all. These results indicated that over-reduction proceeded through a 1,4-selective reduction of enone and subsequent C=O bond reduction, and thus the 1,4-selectivity of the Cu(I)–DTBM-SEGPHOS system would be quite high (96:4 to >99:1). In the previous $[CuH(PPh_3)]_6$-catalyzed hydrogenation, the use of excess Ph_3P to Cu was essential to achieve high conversion.[4] In contrast, the present Cu(I)–DTBM-SEGPHOS system proceeded even under Ph_3P-free conditions with comparable selectivity and only slightly less conversion (entry 5), indicating that monodentate phosphine Ph_3P does not participate in the catalytic cycle. To the best of our knowledge, this is the first example of a Cu-catalyzed asymmetric 1,4-selective hydrogenation of enone.[15]

Finally, we applied the Cu(I)–DTBM-SEGPHOS catalyst system to a 1,4-reduction of another attractive substrate, piperitenone (**11**), which is a starting compound for the synthesis of optically active (–)-menthol.[16] Hydrogenation of **11** potentially affords 26 products via the saturation of C=C and/or C=O double bonds. Thus, a highly enantioselective as well as highly chemoselective catalyst is required to obtain the desired (*R*)-pulegone (**12**). The asymmetric hydrogenation of **11** was conducted with 0.5 mol% loading of the Cu(I) catalyst under the same reaction conditions as entry 3 in Table 3 to give (*R*)-**12** (73%, 96% ee) together with (1*R*,5*R*)-pulegol (**13**, 27%, >99% ee, Table 4, entry 1). Increasing catalyst loading to 1.0 mol% gave more **13** (69%), which is more advanced intermediate for the synthesis of (–)-menthol, with high enantioselectivity (>99% ee) and high diastereoselectivity (*cis*/*trans* >99:1, entry 2). In contrast to the reported Rh catalyst system where the *s-cis* C=C double bond was also reduced to afford a fully saturated ketone as a major over-reduced product,[16] the present Cu-catalyzed system did not reduce the *s-cis* C=C double bond.[17]

Table 4 Asymmetric Hydrogenation of Piperitenone (**11**)



11 **12** **13**

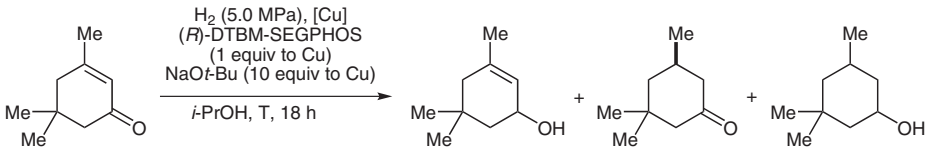
Entry	S/C	Conv. (%)[a]	**12**/**13**[a]	ee of **12** (%)[a]	ee of **13** (%)[a,b]
1	200	98	73[c]:27	96 (*R*)	>99 (1*R*,5*R*)
2	100	>99	31:69[d]	90 (*R*)	>99 (1*R*,5*R*)

[a] Determined by GC analysis.
[b] Only *cis*-isomer was observed on GC (*cis*/*trans* = >99:1)
[c] Isolated yield by silica gel chromatography was 52%.
[d] Isolated yield by silica gel chromatography was 50%.

In conclusion, we demonstrated that a Cu(I)-based system involving chiral chelating diphosphine ligands effectively catalyzed the asymmetric hydrogenation of several heteroaromatic ketones and enones with good to high enantioselectivity (up to 99% ee). The chemoselectivity and enantioselectivity of acyclic and cyclic enones highly depended on the chiral diphosphine ligands. In contrast to the general tendency that a Cu(I)-based system prefers a 1,2-selective reduction, this new Cu(I) system bearing the DTBM-SEGPHOS ligand catalyzed a 1,4-selective reduction with high enantioselectivity. Further investigation of the Cu(I)-based catalyst system for asymmetric hydrogenation of various functionalized alkenes, ketones, and imines is ongoing in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Table 3 Asymmetric Hydrogenation of Isophorone (**7**)



7 **8** **9** **10**

Entry	[Cu]	Temp (°C)	S/C	Conv. (%)[a]	**8**/**9**/**10**[a]	ee of **9** (%)[a]
1	$\{Cu(NO_3)[P(3,5\text{-xylyl})_3]_2\}$	30	200	16	0:97:3	98 (*R*)
2	$[Cu(NO_3)(PPh_3)_2]$	30	200	51	2:91:7	99 (*R*)
3	$[Cu(NO_3)(PPh_3)_2]$	50	200	72	4:82:14	98 (*R*)
4	$[Cu(NO_3)(PPh_3)_2]$	30	100	77	<1:84:16[b]	99 (*R*)
5	CuCl	30	100	59	<1:91:9	96 (*R*)

[a] Determined by GC analysis.
[b] Isolated yield of **9** by silica gel chromatography was 51% due to the relatively low boiling point of **9**.

References and Notes

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(14) The reaction using BDPP and SEGPHOS instead of DTBM-SEGPHOS under the reaction conditions of entry 2 resulted in low conversion and low chemoselectivity. (*S*,*S*)-BDPP: conv. 25%, **8/9/10** = 53:11:36. *R*-SEGPHOS: conv. 17%, **8/9/10** = 11:18:70.

(15) Asymmetric hydrogenation of 3-methylcyclohex-2-enone under the reaction conditions described in Table 3, entry 4 resulted in 51% conversion, allylic alcohol/sat. ketone/sat. alcohol = 2:61:37, 30% yield of sat. ketone, 92% ee (*R*) of sat. ketone (not optimized).

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