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Enantioselective Hydrogenation of 3-Alkylidenelactams: High-Throughput Screening Provides a Surprising Solution

Tai-Yuen Yue* and William A. Nugent*

Bristol-Myers Squibb Company, Process Research and Development Department, Chambers Works, P.O. Box 269, Deepwater, New Jersey 08023-0269

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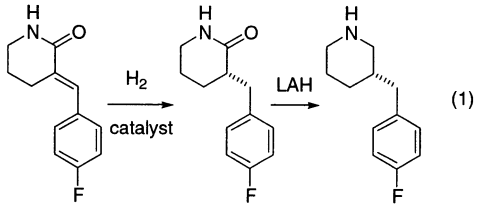
Enantiopure 3-alkylpiperidines are potent pharmacophores with applications in several areas of medicinal chemistry.[1] An attractive approach to these compounds would be asymmetric hydrogenation of a 3-alkylidenelactam followed by reduction of the carbonyl moiety as exemplified by eq 1. Unfortunately, there is little literature precedent regarding the asymmetric hydrogenation of N-unsubstituted lactams of this type.[2] In contrast, several catalytic systems have been reported for the asymmetric hydrogenation of acyclic and endocyclic enamides.[3]



A potential problem regarding eq 1 is the exocyclic nature of the C=C bond. The inability of this bond to rotate toward the carbonyl oxygen is expected to diminish the effectiveness of chelation of such substrates to the metal atom of a catalyst. Substrate chelation has long been recognized to be an important element in achieving highly enantioselective hydrogenations.[4]

A signficant advance in this area was reported by researchers at Merck.[5] They found that an N-unsubstituted 3-alkylidene-2-piperidone could be hydrogenated in 57% ee using (BINAP)$RuCl_2$ as catalyst. Moreover, when the piperidone nitrogen was substituted with a highly functional side chain, the ee could be increased to 93%. The increased selectivity was attributed to "internal chelation" by the side-chain functionality.[5]

Encouraged by this report, we sought an improved catalyst for asymmetric hydrogenation of 3-alkylidene-2-piperidones. Using the hydrogenation in eq 1 as a model system, we screened a set of 32 chiral phosphines and 8 metal precursors. Ruthenium precursors were generated in situ using protocols recently reported by Genet and co-workers.[6,7] The 6 most effective combinations of the 256 included in this study are listed in Table 1 (Chart 1). [For a complete list of phosphines and metal precursors and details of the screening protocol, see the Supporting Information.]

The highest enantioselectivity in Table 1 was observed for the combination of 2,4-bis(diphenylphosphino)pentane (BDPP) and $[(COD)_2Ir]BF_4$ (COD = 1,5-cyclooctadiene). This result was frankly surprising. Structural rigidity is often a beneficial feature of chelating diphosphines, and indeed other successful ligands in Table 1 − BICP,[8] PennPhos,[9] and the Josiphos type ligand Fc-PPh_2-P^tBu_2[10] − all share this structural feature. In contrast, the BDPP backbone is known to be highly flexible.[11] For a given enantiomer of BDPP, four possible conformers of a six-membered chelate ring are possible, two of which are "pseudo-achiral" chair conformations with the phenyl rings in an approximately achiral array.[12] Moreover, iridium complexes bearing BDPP ligands have proven especially problematic in this regard. The lower enantioselectivity observed for imine hydrogenations using Ir(COD)((*S*,*S*)-BDPP)$^+$ as compared with its rhodium analogue (0% ee versus 54% ee) led to the proposal that achiral chair conformations are prevalent in the iridium complex.[13]

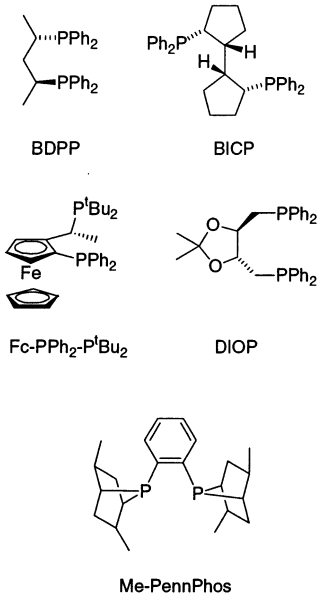
The iridium-BDPP catalyst is advantageous from the standpoint of process chemistry. Iridium is significantly cheaper than rhodium.

Table 1. Hydrogenation of 3-(*p*-Fluorobenzylidene)valerolactam[a]

metal precursor	diphosphine	conversion (%)	ee (%)
$[(COD)_2Ir]BF_4$	BDPP	100	91
$(COD)Ru(MeAll)_2 + 2HBr$[b]	BICP	30	85
$(COD)Ru(MeAll)_2 + 2HBr$[b]	Fc-PPh_2-P^tBu_2	98	70
$(COD)Ru(MeAll)_2 + BF_3$ /HBF_4[c]	Me-Pennphos	100	70
$[(COD)_2Rh]BF_4$	BDPP	100	69
$[(COD)_2Ir]BF_4$	DIOP	85	66

[a] Conditions: substrate/catalyst = 100:1, room temperature, 12 h, 65 psi H_2 in solvent ethanol; for details, see the Supporting Information. [b] $LRuBr_2$ was generated in situ from $(COD)Ru(methallyl)_2$ and HBr according to ref 6, run at 40 °C. [c] $[LRuH(COT)]BF_4$ was generated in situ from $(COD)Ru(methallyl)_2$, BF_3, and HBF_4 according to ref 7, run at 40 °C.

Chart 1. Structures of Diphosphine Ligands in Table 1



* To whom correspondence should be addressed. E-mail: william.nugent@bms.com.

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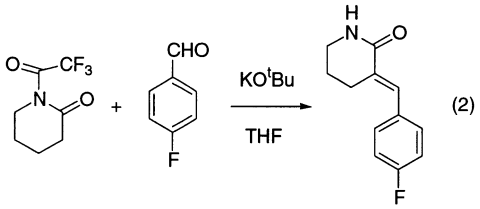
Table 2. Enantioselective Hydrogenation of 3-Alkylidenelactams with [(*S*,*S*)-BDPP]Ir(COD)]BF_4 According to Eq 3[a]

R	R′	*n*	yield (%)[b]	ee (%)
p-fluorophenyl	H	2	97	91
p-trifluoromethylphenyl	H	2	96	87
p-anisyl	H	2	92	90
2-furanyl	H	2	100	95
3-furanyl	H	2	98	95
n-propyl	H	2	93[c]	90
isopropyl	H	2	100	81
p-fluorophenyl	H	1	100	89
n-propyl	H	1	98	82
p-fluorophenyl	H	3	92	75
p-fluorophenyl	Me	2	97	67

[a] Conditions: substrate/catalyst = 200:1, room temperature, 24 h, 65 psi H_2 in solvent CH_2Cl_2/MeOH (1:1); for details, see the Supporting Information. [b] Isolated yield; conversion was quantitative except as noted. [c] Conversion was 95%.

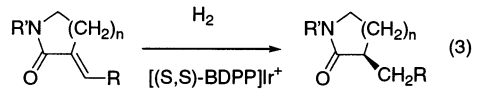
Both enantiomers of the BDPP ligand can be prepared inexpensively on a kilogram scale. The 3-alkylidenelactam substrate is conveniently prepared by aldol condensation[14] of valerolactam (trifluoroacetamide protecting group, lost during aqueous workup) as shown in eq 2. The stereochemistry of the exocyclic double bond is exclusively *E*.



(2)

As a demonstration of the practicality of this chemistry, eq 1 has been carried out on a 20 kg scale. Using (2*S*,4*S*)-BDPP as ligand at a substrate/catalyst ratio of 400:1, we obtained crude (*S*)-(+)-3-(*p*-fluorobenzyl)piperidine[1d] in 91% ee. The amine was then isolated as its (*R*)-mandelic acid salt in 99% ee. The overall yield for this three-step (hydrogenation, LAH reduction, salt formation) sequence was 79%.

It appears likely that the active catalyst precursor generated in situ from $[(COD)_2Ir]BF_4$ and (2*S*,4*S*)-BDPP is the known[13] cationic complex $[(BDPP)Ir(COD)]^+$. Because the isolated complex $[(BDPP)Ir(COD)]BF_4$ was found to give identical results in eq 1, it was utilized to explore the scope and limitations of this chemistry in eq 3.



(3)

As shown in Table 2, hydrogenation of 3-alkylidene-2-piperidones containing either aromatic or aliphatic R groups proceeded in synthetically useful ee's. The reaction appears relatively insensitive to electronic effects. For electronically similar substituents, sterically smaller groups afforded higher ee's (^{n}Pr > ^{i}Pr; furanyl > phenyl). The presence of a methyl substituent on nitrogen diminished enantioselectivity. Enantioselectivity was somewhat lower for pyrrolidinone substrates ($n = 1$) and was further reduced in the case of an alkylidenecaprolactam derivative ($n = 3$). Given the consistent order of elution of the products in Table 2 during chiral HPLC analysis, we tentatively assign the absolute stereochemistry as shown in eq 3 by comparison with the known[1d] structure of (*S*)-(+)-3-*p*-fluorobenzyl-2-piperidone.

Given the protean nature of BDPP ligation, we find its unique effectiveness as a ligand in these studies to be remarkable. As noted by Nobel laureate William Knowles in his 1983 review article,[4a] "Since achieving 95% ee only involves energy differences of about 2 kcal, which is no more than the barrier encountered in a simple rotation of ethane, it is unlikely that before the fact one can predict what kind of ligand structures will be effective." With Knowles we look forward to the day when computational techniques will allow the prediction of the optimal catalyst for novel applications. Until that day, high-throughput screening[15] will remain an invaluable tool for catalyst discovery.

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Supporting Information Available: Detailed experimental procedures and characterization of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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