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Asymmetric hydrogenation of aromatic compounds

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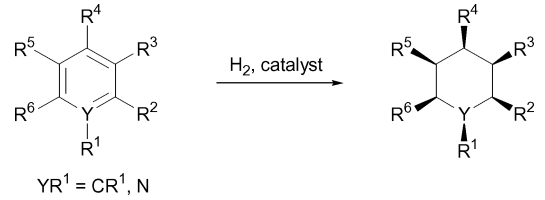
The asymmetric hydrogenation of aromatic and heteroaromatic compounds arguably presents one of the most attractive methods for the synthesis of six-membered cyclic compounds. In recent years, a number of promising stereoselective methods for the asymmetric hydrogenation of pyridines and related heterocycles have been reported.

Introduction

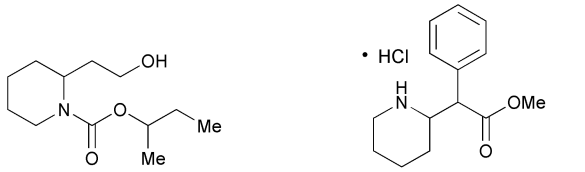
The asymmetric hydrogenation of unsaturated organic molecules often presents one of the most efficient methods for the preparation of enantiomerically pure organic compounds. Catalysts for the enantioselective hydrogenation of many different classes of substrates like enamides, β-ketoesters, imines or unfunctionalized olefins have been successfully developed.[1] Many of these processes are characterized by extraordinarily high levels of catalyst activity and selectivity and in the case of some substrates enantioselectivities of above 99% have become routine results. Still, the asymmetric hydrogenation of many other substrate classes like aromatic compounds (Scheme 1) has remained elusive.

The asymmetric hydrogenation of aromatics and heteroaromatics would lead to the formation of saturated cyclic compounds. The hydrogenation of pyridines would be especially important, since thousands of pyridine derivatives are commercially available and countless methods exist for their preparation.



Scheme 1 Asymmetric hydrogenation of aromatic compounds.

In addition, multiple stereocenters could be created in a single step and the resulting enantiomerically pure piperidines[2] are subunits of many biologically active compounds, even commercialized compounds like the insect repellent Bayrepel[3] or the drug Ritalin[4] for treatment of kids with attention-deficit-hyperactivity-disorder (Fig. 1). Therefore, a general method for the asymmetric hydrogenation of substituted pyridines and other aromatic compounds according to Scheme 1 would be highly desirable.



Bayrepel (Autan) | Methylphenidate Hydrochloride (Ritalin)

Fig. 1 Two chiral piperidines with distinct biological activity.

Partial hydrogenation of bicyclic heteroaromatic compounds

The enantioselective hydrogenation of 2-substituted quinoline derivatives was recently reported by Zhou *et al.*[5] and very recently with a related ligand by Fan and Chan.[6] In addition, methods for the partial hydrogenation of 2-methylquinoxaline[7] and of 2-[8a] and 3-substituted[8b] indoles have been reported resulting in the enantioselective formation of the corresponding benzene derivatives (Scheme 2). Analysis of these three types of substrate reveals striking similarities. In all cases, a benzene ring is annulated to a heteroaromatic ring (pyrazine, pyridine, pyrrole) resulting in a bicyclic heteroaromatic substrate. In these systems, the aromatic stabilization of the heteroaromatic ring is reduced, thus increasing the reactivity of these substrates towards hydrogenation. Besides this very important reactivity issue, selectivity is also affected by the benzene annulation. Compared to the monocyclic heteroaromatic parent compounds, the topology of these systems is changed. This seems to facilitate the differentiation of the two enantiotopic faces by the catalyst.

However, these excellent results are rather special since the substrate scope is limited to bicylic benzene derivatives. In

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Frank Glorius

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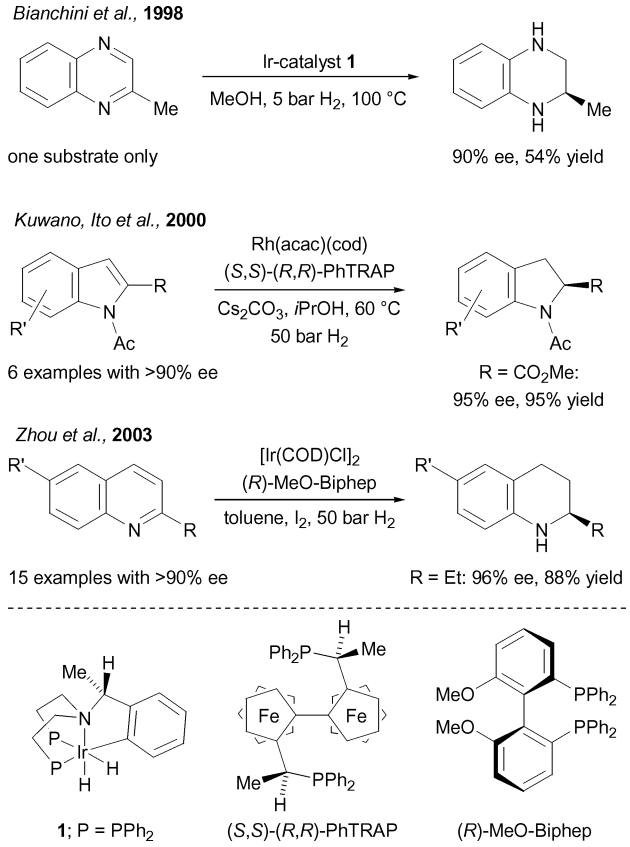
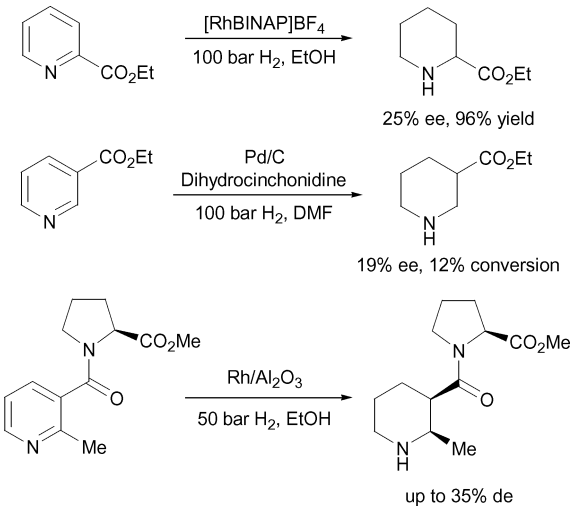


Scheme 2 Enantioselective hydrogenations of bicyclic substrates.

addition, the vast potential of hydrogenations of aromatic compounds to create multiple stereocenters is only barely scratched upon in these examples. Only one[8] or two[5,6,7] double bonds are hydrogenated in these substrates, resulting in the formation of a single stereocenter.

Asymmetric hydrogenation of pyridines

Success in the area of asymmetric pyridine hydrogenations has been rather limited for a long time. The best results obtained for pyridine hydrogenation, using a chiral homogeneous catalyst (up to 25% ee),[9] a cinchona alkaloid modified heterogeneous catalyst (up to 19% ee)[10] or employing auxiliary substituted pyridines (up to 35% de)[11] were not sufficient (Scheme 3).[12] In the following, two recent reports on the asymmetric hydrogenation of auxiliary-substituted pyridines[13,14] will be discussed that may eventually lead to more efficient catalytic methods.

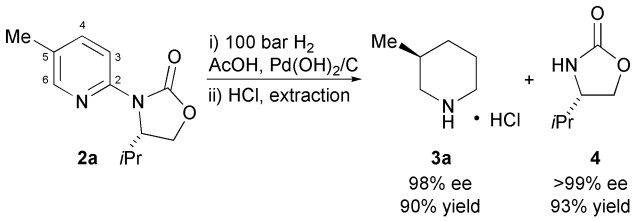


Scheme 3 Former state of the art asymmetric pyridine hydrogenations.

Asymmetric hydrogenation of auxiliary-substituted pyridines with achiral heterogeneous catalysts

An efficient method for the hydrogenation of 2-auxiliary-substituted pyridines using standard achiral heterogeneous hydrogenation catalysts has recently been developed.[13] Many attractive features arguably render this process to be one of the most efficient applications of chiral auxiliaries reported to date.

First of all, substrates **2** can be readily synthesized from 2-bromo- or chloropyridines and the oxazolidinone by copper catalysis.[13,15] For the hydrogenation of **2**, acetic acid was chosen as a solvent. First, the acid protonates and thereby activates the pyridine substrates. Second, it also protonates the piperidine products thus binding the piperidine's free electron pair and as a consequence, suppressing the catalyst poisoning property of the piperidines. The hydrogenation of 2-oxazolidinone-5-methyl-substituted pyridine **2a** with different heterogeneous catalysts under a hydrogen atmosphere of 100 bar generally resulted in the direct formation of (*S*)-3-methyl piperidine with high enantiomeric excess. Platinum, rhodium and palladium based catalysts resulted in complete conversion and high enantiomeric excess, with $Pd(OH)_2/C$ being the most selective one giving a remarkable enantiomeric excess of 98% (Scheme 4).[16] This method combines highly efficient chirality transfer and traceless cleavage of the auxiliary under the same conditions.

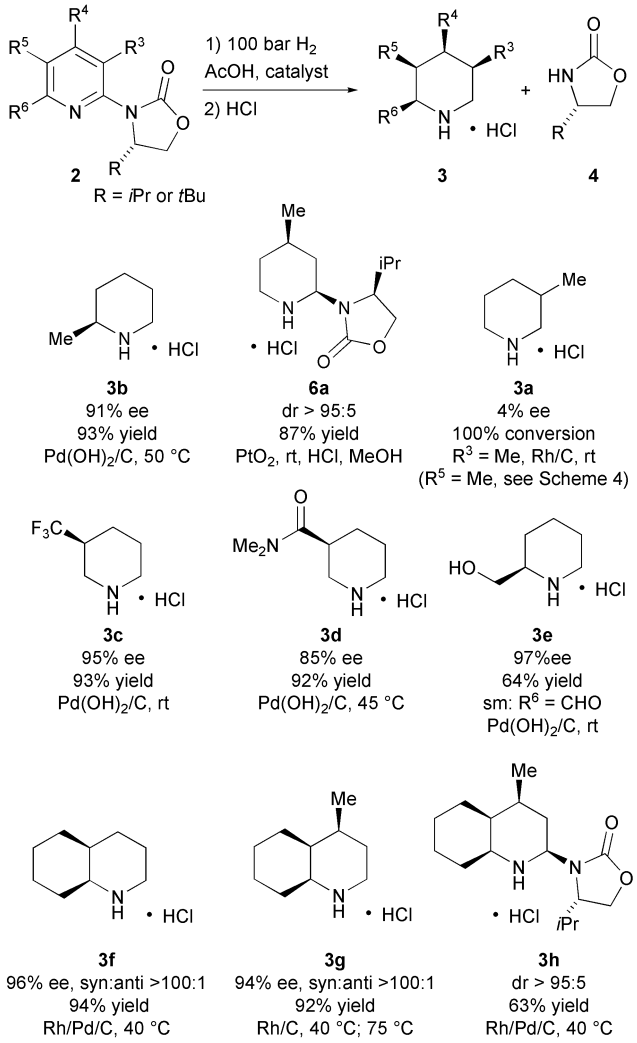


Scheme 4 Glorius' asymmetric hydrogenation of a 2-oxazolidinone substituted pyridine.

A simple purification procedure accompanies this chemical transformation. Hydrochloric acid was added to the crude reaction mixture, resulting in the formation of the corresponding piperidinium hydrochloride salts. As the piperidines are no longer volatile, acetic acid could be removed under reduced pressure. Subsequently, the more soluble auxiliary was separated from the less soluble piperidinium salt by simple extraction with ether/hexane mixtures, allowing for its recovery.

Several substrates were successfully hydrogenated using this stereoselective method (Scheme 5).[17] 6-, 5- and 4-methyl substitution on the pyridine ring is well tolerated resulting in high stereoselectivities. In the case of the 4-methyl substituted substrate, standard conditions would lead to the formation of the achiral 4-methyl piperidine. However, under a different set of conditions using MeOH/HCl as the solvent and PtO_2 as the catalyst, aminal **6a** was formed with a dr of >95 : 5. Only 3-substitution of the pyridine ring presents a limitation. First, the 3-methyl substituted substrate is much less reactive than the regioisomeric pyridines. Second, using a more reactive catalyst resulted in complete conversion, however, 3-methyl piperidine was formed with a disappointingly low ee of 4%. It seems that an unfavorable steric interaction between the 3-methyl group and the auxiliary results in significant shielding of both π-faces of the pyridine ring.

The efficacy of this novel pyridine hydrogenation was demonstrated by some additional attractive features. A number of functional groups are tolerated (**3c,d**) or can be selectively transformed (**3e**). Furthermore, the simultaneous creation of multiple stereocenters is realized. Up to four ring stereocenters can be formed with excellent selectivities (**3f,g,h**). In the presence of additives like acetaldehyde or acetic anhydride, an additional transformation can be performed in the same step, giving



Scheme 5 Optically active piperidine products.

(*S*)-*N*-ethyl 3-methyl piperidine in high yield and up to 95% ee (not shown).

Finally, this new method was successfully applied to natural product total synthesis (Fig. 2). Coniine, the poisonous alkaloid of hemlock, was directly prepared by asymmetric hydrogenation in 95% yield and 95% ee.[13] In addition, (*R*)-6-piperidin-2-yl-hexan-1-ol hydrochloride was prepared in 94% ee and skillfully used by Fürstner for the catalysis-based synthesis of the spermidine alkaloid (−)-isooncinotine.[18]

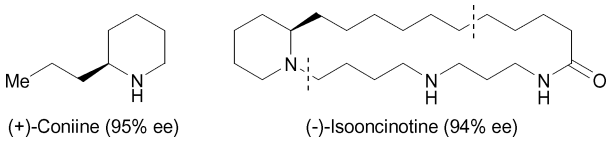


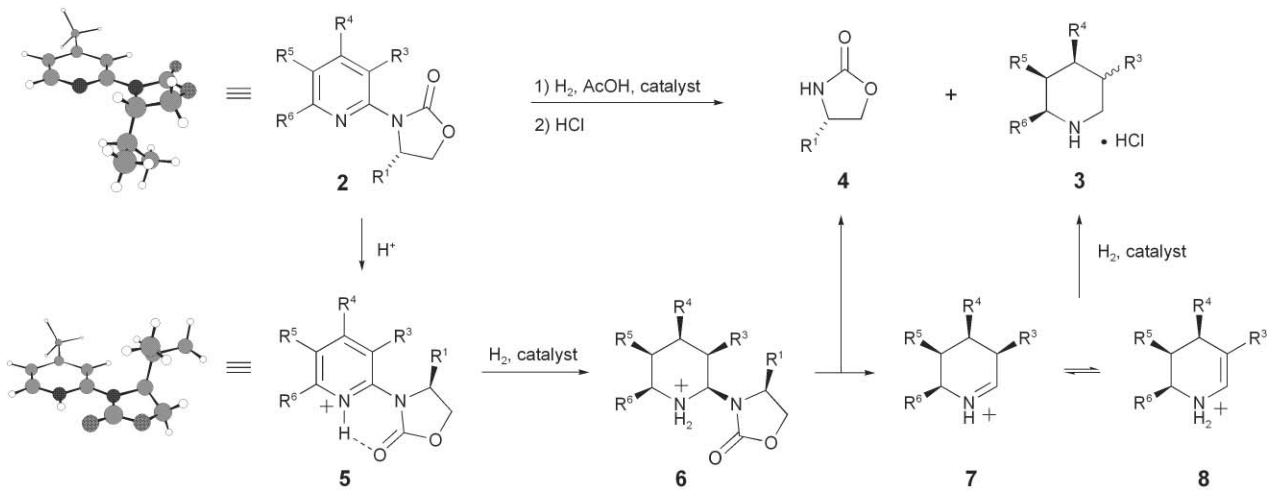
Fig. 2 Natural products synthesized by asymmetric pyridine hydrogenation.

A plausible mechanism for this stereoselective hydrogenation is depicted in Scheme 6, accounting for the observed selectivities. Protonation of the pyridine substrates under acidic conditions results in the formation of a relatively flat compound **5**, which is rigidified by a strong H-bond between the pyridinium and the oxazolidinone moiety. In this compound the R^1 group on the oxazolidinon shields the top face whereas the bottom face is accessible. Presumably, the unhindered π-face is adsorbed by the catalyst and hydrogen atoms transferred stepwise to this side, leading to the stereoselective formation of the aminal-type structure **6**. With the help of a free electron pair on the piperidine nitrogen, this compound can disintegrate to iminium **7** and the oxazolidinone **4**. However, under strongly acidic conditions (using HCl) the piperidine nitrogen is protonated leading to a stable compound that can be isolated. Using a weak acid-like acetic acid, not all piperidines **6** are protonated in the equilibrium and **7** can be formed. This iminium might be in equilibrium with the corresponding enaminium **8**. Hydrogenation of the resulting C=N or C=C-double bond would result in the formation of the observed piperidine products.

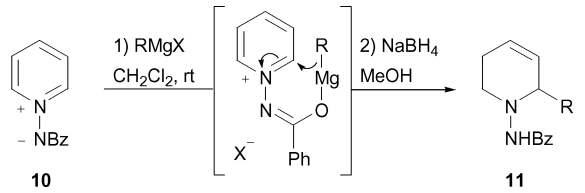
It is important to note that the rather high hydrogen pressure needed (100 bar) represents somewhat of a disadvantage for technical application of this method. First attempts to lower the hydrogen pressure significantly did not give satisfactory results.

Asymmetric hydrogenation of auxiliary-substituted pyridines with chiral homogeneous catalysts

An interesting activating and directing effect has previously been observed by Legault and Charette in the regioselective addition of Grignard reagents to substrates **10** (Scheme 7).[19] Complexation of the nucleophile by the NBz group enhances the electrophilicity of the ring and the limited tether length promotes the highly selective formation of the 1,2-addition adducts. The rather unstable dihydropyridines were reduced *in situ* leading to the tetrahydropyridine products **11**. This selective addition process was the root of a remarkable asymmetric pyridine hydrogenation.



Scheme 6 Mechanistic proposal for asymmetric hydrogenation of 2-oxazolidinone substituted pyridines **2**.



Scheme 7 Complexation promoted addition of Grignard reagents.

Using an Ir-BINAP catalyst, the Charette group made the interesting finding that of the different pyridine type substrates shown in Fig. 3 only *N*-iminopyridinium ylide **10** is hydrogenated.[14] Based on this result an exciting enantioselective hydrogenation of substrates **10** was developed, in which the benzoylimino group (NBz) obviously acts as an activating achiral auxiliary (Scheme 8).

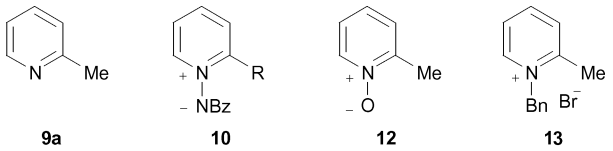


Fig. 3 Pyridine-type substrates.

Optimization of the asymmetric hydrogenation of substrates **10** to piperidine derivatives **14** revealed a number of interesting facts. First of all, iridium complexes were found to be best suited for this reaction, whereas other metal complexes were inactive, like $[Rh(COD)Cl]_2$, or not as active. Secondly, the use of catalytic amounts of iodine is very important for achieving high yields. Interestingly, the same observation has been made by Zhou in the quinoline hydrogenations (Scheme 2).[5] Presumably, iodine helps in the conversion of an Ir(I) to a catalytically active Ir(III) species.[20]

In analogy to iridium catalyzed olefin or imine hydrogenations,[21] the non-coordinating tetrakis(3,5-bis(trifluoromethyl)-phenyl)borate (BArF) was found to be the best counterion. Furthermore, many chiral ligands were screened and the highest enantioselectivities were obtained with iridium complexes of phosphinooxazolines[22] like **16** (Fig. 4).

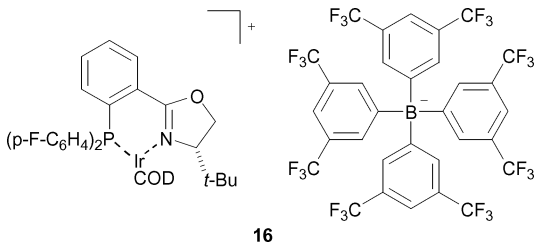


Fig. 4 Most selective catalyst **16**.

Table 1 Hydrogenation of *N*-benzoyliminopyridinium ylides

Entry	R	Yield **14** (%)[a]	ee **14** (%)[b]	Products
1	2-Me	98	90	**14a**
2	2-Et	96	83	**14b**
3	2-*n*Pr	98	84	**14c**
4	2-Bn	97	58	**14d**
5	$2\text{-}CH_2OBn$	85	76	**14e**
6	$2\text{-}(CH_2)_3OBn$	88	88	**14f**
7	$2,3\text{-}Me_2$	91 [>95 : 5]	54	**14g**
8	$2,5\text{-}Me_2$	92 [57 : 43]	86 : 84	**14h**, **14h′**

[a] Diastereomeric ratios are shown in brackets. [b] Determined by HPLC.

Considering the stability of aromatic compounds, it is rather counterintuitive that their hydrogenations can stop at intermediate stages, leading to the formation of partially reduced products. Intriguingly, even though the conversions of substrates **10** were complete, in some cases, tetrahydropyridines were formed in small amounts. Therefore, a hydrogenation of the crude reaction mixtures over Pd/C was advantageous.

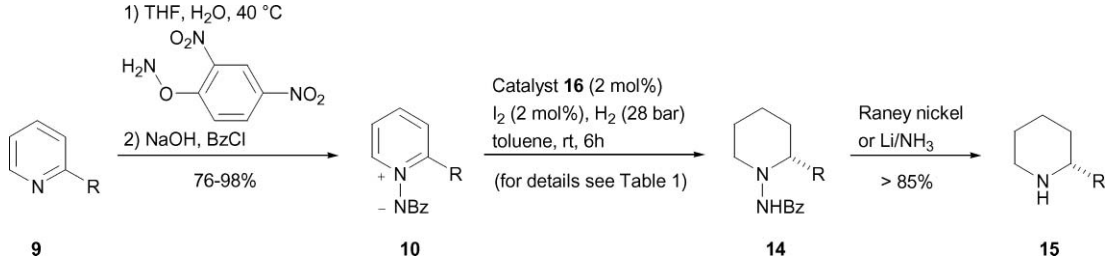
Charette's method is best suited for enantioselective hydrogenation of 2-substituted *N*-benzoyliminopyridinium ylides **10** giving good enantioselectivities for a variety of substrates (Table 1). Even though the enantioselectivities are generally below 90% this process represents a breakthrough since comparable methods give much lower selectivities (Scheme 3). Moreover, it was demonstrated that the optical purity of the resulting *N*-benzamide substituted piperidines **13** can be readily improved by a single recrystallization from EtOAc (97% ee for **14a**), significantly increasing the attractiveness of this process.

The use of doubly substituted substrates results in the formation of two new stereocenters, however, with somewhat lower selectivity (entries 7, 8). 3-Substitution appears to present a limitation of this method since low yields and enantioselectivities were obtained for the 3-methyl-substituted pyridinium ylide (not shown).

The usefulness of an auxiliary-based method strongly depends on the ease of introduction and removal of the auxiliary. In this case, the pyridinium ylides can be readily prepared from the corresponding pyridines by a one-pot amination/benzoylation procedure. In addition, the hydrogenation adducts can easily be converted to the piperidine derivatives **15** by a high yielding N–N bond cleavage using Raney nickel or lithium in ammonia (Scheme 8).

Conclusion

To date, no satisfactory method for the catalytic asymmetric hydrogenation of unmodified aromatic substrates exists. The developments discussed in this article are promising and should be stimulating for further research. However, it is especially important to point out that these methods are still rather limited. Understanding the underlying principles of these reactions might eventually lead to general asymmetric hydrogenation methods for aromatic compounds.



Scheme 8 Charette's enantioselective hydrogenation of *N*-iminopyridinium ylides.

Acknowledgements

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16 Of the catalysts tested, only Ru on C was not reactive enough. Other catalysts gave full conversion and the following selectivities: PtO_2 85% ee, Pt/C 85% ee, Rh/C 86% ee, Rh/Pd/C 94% ee, Pd/C 97% ee, $Pd(OH)_2$/C 98% ee.

17 Differently substituted oxazolidinones can be used in this process. It was found that *t*Bu substitution often results in slightly improved ee values relative to those obtained with a *i*Pr group. Phenyl and Benzyl substitution also result in high selectivities, however, these substituents are not inert under reaction conditions, resulting in the formation of reduced oxazolidinones.

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