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# Asymmetric Hydrosilylation of Ketones Catalyzed by Zinc Acetate with Hindered Pybox Ligands

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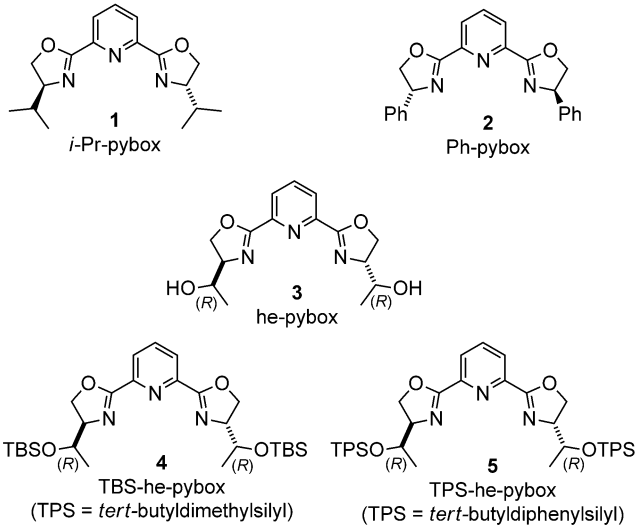
**Abstract:** A highly efficient asymmetric hydrosilylation (AHS) of a wide variety of prochiral aryl ketones catalyzed by zinc acetate with TPS-he-pybox (*tert*-butyldiphenylsilyl hydroxyethyl pybox) ligand has been successfully developed. Cheap and readily available chiral Lewis acids based on zinc salts have been used as promising catalyst for the reduction of aryl ketones under mild conditions at room temperature leading to chiral alcohols in excellent yields and good to high enantioselectivities (up to 85% *ee*).

**Keywords:** asymmetric synthesis; chiral alcohols; metal complexes; reduction; zinc

Asymmetric hydrosilylation (AHS) of prochiral ketones represents one of the most efficient methods for the preparation of chiral secondary alcohols. Although the asymmetric hydrosilylation using catalysts based on expensive precious metals such as ruthenium, rhodium or iridium is well established,[1] an efficient means to access chiral alcohols by using cheaper and more environmentally friendly metals still remains a significant challenge. Noteworthy recent contributions in this field have emerged by utilizing chiral iron[2] and copper[3] complexes. Despite some advances, the demand for less expensive, environmentally more benign zinc-based catalytic systems for the asymmetric hydrosilylation of ketones is still an urgent need and of great significance because of the broad availability and biomimetic nature of zinc. Surprisingly, only few studies have been presented in this field, mostly utilizing zinc catalysts made of unstable and hazardous dialkylzinc compounds.[4] Synthesis and application of these organometallic species is dangerous and inconvenient, especially for industrial or large-scale use. Therefore, considerable efforts should be directed towards the development of cheap, reliable and safe zinc complexes for asymmetric hydrosilylation.

For the first time an inorganic zinc salt was applied for asymmetric hydrosilylation by Nishiyama et al. in 2009.[5] These authors demonstrated that ketones can undergo reduction in an asymmetric manner with *ee*s ranging at about 80% (one example with 92% *ee*) by using zinc acetate complexes with a ligand based on chiral diaminocyclohexane (DACH). Recently Lai[6] applied a similar zinc-based catalyst with chiral DACH ligands containing furan rings.

In 2012 Beller and co-workers[7] used chiral *i*-Pr-(**1**) and Ph-pybox (**2**) ligands (Scheme 1) with either zinc acetate or diethylzinc. These authors showed that both of these catalysts can induce stereoselectivity in the reduction of acetophenone, but the reactions catalyzed by $Zn(OAc)_2$–pybox led to poor *ee*s and conver-




**Scheme 1.** Structures of pybox-type ligands used in this work: *i*-Pr-pybox, Ph-pybox and he-pyboxes.

sions in comparison with those promoted by $Et_2Zn$ complexes with the same chiral ligands.

In spite of the previous unpromising application of zinc salts with pybox ligands, we decided to further explore this field as successful applications of pybox ligands in various areas of asymmetric synthesis are well documented.[8] The reason of this success derives from the simple preparation of modified pybox that makes the preparation of new derivatives easily realizable.

In this paper we describe a convenient application of hindered *tert*-butyldiphenylsilyl-hydroxyethyl-pybox (TPS-he-pybox) (**5**, Scheme 1) complex with zinc acetate as highly efficient and stereoselective catalysts for hydrosilylation of prochiral ketones. $Zn(OTf)_2$–TPS-he-pybox has been previously used to catalyze asymmetric Mukaiyama-aldol reactions carried out in a water environment, but has never been applied for the asymmetric reduction of ketones.[9]

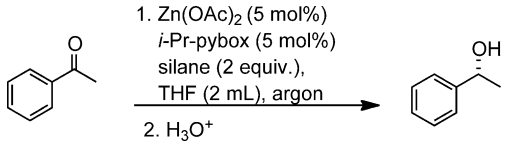
Initial optimization of the reaction conditions was carried out for commercially available *i*-Pr-pybox (**1**). From among the tested zinc salts (acetate, chloride, bromide, triflate and trifluoroacetate) applied for the reduction of acetophenone, only zinc acetate complexes have shown the expected high activity in THF solution with diethoxymethylsilane as hydrogenating agent (Table 1).[10] For this particular reduction, only low enantioselectivity was observed for the $Zn(OAc)_2$–*i*-Pr-pybox catalyst (38% *ee*, Table 1, entry 2) but the observed outstanding substrate conversion at low temperature encouraged us for further research. Similar conversion and *ee* were observed for triethoxysilane at 20 °C while the reaction with polymethylhydrosiloxane (PMHS) failed.

Although we observed better conversions and yields in the presence of commercial pybox ligand when compared to previously published results [$Zn(OAc)_2$–Ph-pybox, 60 °C],[7] the low level of enantioselectivity still left much to be desired.

To address this issue, a family of hydroxyethyl pybox ligands (**3**–**5**) was evaluated in association with $Zn(OAc)_2$ to identify the most enantioselective and reliable catalytic system. Essential results observed for the reduction of acetophenone are collected in Table 2. Initial application of hydroxyethyl-pybox **3**[11] resulted in poor enantioselectivity (Table 2, entry 1), while the application of pybox ligands with hindered siloxy substituents (TBS-he-pybox **4**[11] and TPS-he-pybox **5**,[9a] Scheme 1) turned out to be far more successful and stereoselective (Table 2, entries 2 and 3). The best performance (conversion: 99%, 68% *ee*) was observed for 5 mol% catalyst loading in THF solution (Table 2, entry 3). The ability to carry out the reaction at low temperature without unnecessary heating of the reaction mixture was an important and distinctive feature of this newly elaborated catalytic system.

Again, among four tested silanes, the best enantioselectivity was observed for $(EtO)_2MeSiH$ (68% *ee*, Table 2, entry 3) at room temperature. Our further

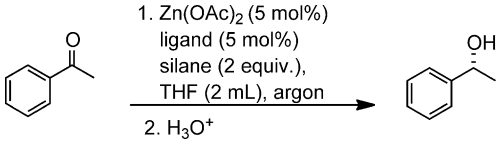
**Table 1.** Conversion and enantiomeric excess of acetophenone hydrosilylation catalyzed by Zn–*i*-Pr-pybox.[a]




| Entry | Silane | Temp. [°C] | Time [h] | Conv. [%][b] | *ee*[c] |
|---|---|---|---|---|---|
| 1 | $(EtO)_2MeSiH$ | 20 | 20 | >99 | 32 |
| **2** | **$(EtO)_2MeSiH$** | **4** | **20** | **>99** | **38** |
| 3 | $(EtO)_3SiH$ | 20 | 20 | >99 | <5 |
| 4[d] | $(EtO)_3SiH$ | 20 | 20 | >99 | 34 |
| 5[d] | $(EtO)_3SiH$ | 4 | 46 | >99 | 22 |

[a] *Reaction conditions:* the catalyst was synthesized by stirring zinc acetate (5 mol%) with pybox ligand (**1**, 5 mol%) in THF (2 mL) at room temperature under argon. Acetophenone (1 mmol) and silane (2 mmol) were added and the reaction mixture was stirred at the mentioned temperature for 20–46 h.
[b] Conversion and *ee* were determined by HPLC methods.
[c] The absolute (*R*)-configuration of the product was determined by comparing the optical rotation and HPLC analysis with literature data.
[d] Catalyst was preformed under reflux.

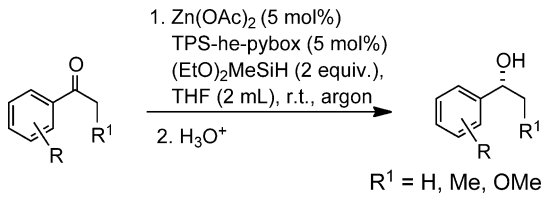
**Table 2.** Conversion and enantiomeric excess of acetophenone hydrosilylation catalyzed by Zn–TPS-pybox.[a]




| Entry | Silane/Ligand | Temp. [°C] | Time [h] | Conv. [%][b] | *ee*[c] |
|---|---|---|---|---|---|
| 1 | $(EtO)_2MeSiH$/**3** | 20 | 20 | 73 | 11 |
| 2 | $(EtO)_2MeSiH$/**4** | 20 | 20 | > 99 | 64 |
| 3 | $(EtO)_2MeSiH$/**5** | 20 | 20 | > 99 | 68 |
| **4** | **$(EtO)_2MeSiH$/5** | **4** | **70** | **94** | **74** |
| 5 | $(EtO)_3SiH$/**5** | 20 | 20 | > 99 | 16 |
| 6 | PMHS/**5** | 20 | 20 | 0 | – |
| 7 | $PhSiH_3$/**5** | 20 | 20 | > 99 | 0 |

[a] *Reaction conditions:* the catalyst was synthesized by stirring zinc acetate (5 mol%) with pybox ligand (**3**–**5**, 5 mol%) in THF (2 mL) at room temperature under argon. Acetophenone (1 mmol) and silane (2 mmol) were added and the reaction mixture was stirred at the mentioned temperature for 20-46 h.
[b] Conversion and *ee* were determined by HPLC methods.
[c] The absolute (*R*)-configuration of the product was determined by comparing the optical rotation and HPLC analysis with literature data.

**Table 3.** Enantioselective hydrosilylation of prochiral ketones by $(EtO)_2MeSiH$ catalyzed by $Zn(OAc)_2$–TPS-pybox.[a]



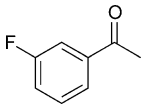
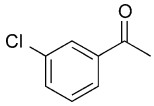
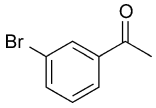
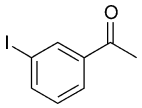
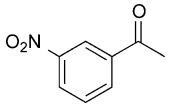
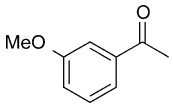
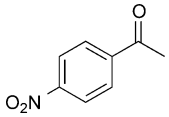
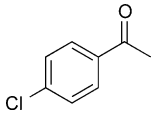
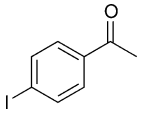
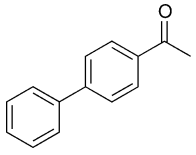
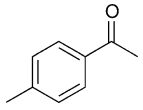
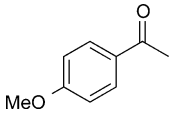
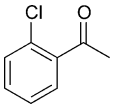
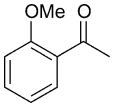
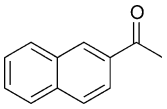
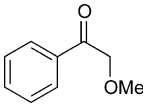
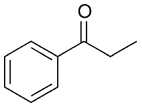

| Entry | Ketone | Time [h] | Conv. [%] | Yield [%][c] | *ee*[b] |
|---|---|---|---|---|---|
| 1 |  | 20 | >99 | 69 | 84 (*R*)[d] |
| 2 |  | 20 | >99 | 71 | 83 (*R*) |
| 3 |  | 20 | >99 | 68 | 85 (*R*) |
| 4 |  | 20 | >99 | 76 | 83 (*R*) |
| 5 |  | 46 | >99 | 83 | 80 (*R*) |
| 6 |  | 70 | >99 | 67 | 61 (*R*) |
| 7 |  | 46 | >99 | 92 | 77 (*R*) |
| 8 |  | 20 | >99 | 96 | 73 (*R*) |
| 9 |  | 20 | >99 | 78 | 62 (*R*) |
| 10 |  | 20 | 54 | 71 | 60 (*R*) |
| 11 |  | 20 | >99 | 70 | 52 (*R*) |
| 12 |  | 70 | >99 | 84 | *rac.* |

**Table 3.** (Continued)

| Entry | Ketone | Time [h] | Conv. [%] | Yield [%][c] | *ee*[b] |
|---|---|---|---|---|---|
| 13 |  | 20 | >99 | 90 | 54 (*R*) |
| 14 |  | 20 | >99 | 93 | 37 (*R*) |
| 15 |  | 20 | >99 | 97 | 80 (*R*) |
| 16 |  | 20 | >99 | 81 | 14 (*S*)[e] |
| 17 |  | 20 | >99 | 80 | 50 (*R*) |

[a] *Reaction conditions:* the catalyst was synthesized by stirring zinc acetate (5 mol%) with pybox ligand (**5**, 5 mol%) in THF (2 mL) at room temperature under argon. Ketone (1 mmol) and silane (2 mmol) were added and the reaction mixture was stirred at the mentioned temperature for 20–46 h.

[b] Conversion and *ee* were determined by HPLC methods.

[c] Isolated yield.

[d] The absolute (*R*)-configuration of the product was determined by comparing the optical rotation and HPLC analysis with literature data.

[e] Opposite (*S*)-configuration results from the CIP convention only.

effort was to find the best conditions for Zn–TPS-pybox-promoted reactions, especially in terms of temperature and catalyst loading. Application of diethoxymethylsilane in combination with TPS-he-pybox at lower temperature (4 °C) increased the *ee* up to 74% (Table 2, entry 4). Reduction of the catalyst amount from 5 to 2.5 mmol% does not affect the yields, but the *ee* drops to 24%. Interestingly, increasing the catalyst amount to 7.5 mmol% did not result in any change, thus 5 mol% catalyst loading was taken to be the best.

Although Ozasa[12] demonstrated that zinc acetate itself is a good catalyst for non-asymmetric reduction of miscellaneous ketones by using $PhSiH_3$, we found the reducing agent to be active yet unselective in the presence of chiral Lewis acids. The popular PMHS does not react with the Zn-based catalyst and confirmed the only previous observations of Lai[6] and Nishiyama.[5]

Having the best catalyst and conditions in hand, we tested the scope of the reduction to other prochiral ketones. As shown in Table 3, a broad range of aryl

ketones was investigated to demonstrate the scope of our procedure and also clarify the influence of various substituents differently placed at the phenyl ring.

To our delight, for most of the substrates, complete hydrosilylation was achieved in the presence of 5 mol% of the $Zn(OAc)_2$/pybox within 20 h at room temperature. The isolated yields were substantial and besides such excellent efficiency, many of the studied reactions provided alcohols with high stereoselectivity (up to 85% *ee*) favoring formation of the (*R*) isomer. Absolute configurations of the resulting alcohols have been revealed by comparison of the HPLC analysis on a chiral stationary phase of the products with that reported in the literature.

The best results in terms of high enantioselectivity have been observed for ketones that possess electron-withdrawing groups placed in a *meta* position (entries 1–5). For all of these substrates the *ee*s exceed 80%. Interestingly, AHS of 3′-methoxyacetophenone gave a lower enantiomeric excess of 61% (entry 6). This phenomenon suggests that the catalyst is the most selective for the *meta*-substituted substrates with lower electron density in the aromatic rings. Interestingly, applications of the *meta*-substituted aryl ketones have not been widely studied in the literature.

*para*-Substituted acetophenones demonstrated a similar tendency in terms of reactivity, although they underwent reduction less selectively. Electron-withdrawing substituents at the *para* position did not affect the enantioselectivity too much (entries 7–9). Ketones containing deactivating groups such as nitro and halogens were reduced with higher yields and *ee* values among all studied *para*-substituted derivatives. Again, the donating effect of methoxy group has an adverse impact on stereoselectivity and reduction of *para*-methoxyacetophenone resulted in the formation of racemic alcohol (entry 12). A similar tendency was previously reported by other authors. Observed enantioselectivity in asymmetric hydrosilylation was significantly diminished when a *p*-MeO group was present in the substrate.[2h] This tendency was also visible for zinc-based catalytic systems.[4]

*ortho*-Substituted substrates have been also reduced with high yield but with lower selectivity (entries 13 and 14) probably because of steric hindrance between catalysts and ketone.

The last tested representative of methyl aryl ketones, i.e., β-acetonaphthone was also easily converted to the appropriate alcohol with 80% *ee* (entry 15).

Some other ketones were also reduced in the presence of the new zinc catalyst $Zn(OAc)_2$–TPS-pybox. The α-methoxyacetophenoene was fully converted but the *ee* value is rather poor. The propiophenone was reduced with 50% of *ee* only (entry 17).

Initial application of the elaborated catalytic system to alkyl ketones was unsuccessful, unfortunately. Reduction of tetralone led to a racemic product while reduction of alkyl methyl ketones delivered alcohols in *ca.* 15–20% *ee* although the observed conversion was excellent (> 99%).

Formation of an equimolar complex between TPS-he-pybox and $Zn(OAc)_2$ was confirmed by ESI HR-MS. In the mass spectrum the peak of a 1:1 complex in which one acetate anion is tightly bound with $Zn^{2+}$ cation within a complex molecule is found exclusively.[10]

In summary, we have presented an efficient protocol for the asymmetric hydrosilylation of aryl ketones in the presence of an inexpensive and easy to handle zinc catalyst. The newly elaborated $Zn(OAc)_2$–TPS-he-pybox complex can be directly used for enantioselective reduction of a wide variety of alkyl aryl ketones at room temperature. Such observed high *ee* values along with the high level of substrate conversion at ambient temperature have never been previously presented for a catalyst composed of a zinc salt with a pybox ligand. It is also at least comparable to previously published catalysts based on zinc acetate[5] and chloride.[6] A family of *meta*-substituted aryl ketones, mostly neglected in previous studies, has been detected as the most suitable substrates for zinc-based asymmetric AHS reactions.

We have also shown that the asymmetric induction strongly depends on the size of substituents at the oxazoline ring of pybox. Further research on the synthesis of other pyboxes with bulky substituents and their applications in AHS are ongoing in our laboratory and will be reported in due course.

## Experimental Section

### Enantioselective Hydrosilylation of Prochiral Ketones (Table 3)

The catalyst was prepared by stirring the solution of TPS-he-pybox[9,10] (**5**, 0.043 mmol, 33.2 mg) with $Zn(OAc)_2$ (0.043 mmol, 7.6 mg) in 2 mL of THF under argon at room temperature. To the homogenous solution of the catalyst both ketone (1 mmol) and silane (2 mmol) were added with 15 min intervals, respectively. The reaction progress was controlled by TLC analysis using plates with a silica matrix and a (1:4) mixture of ethyl acetate and hexane. When the reaction was completed the solution was cooled to *ca.* 0 °C and quenched with 2 mL of 1 M HCl and stirred for 1 h. After this time organic compounds were extracted 3 times with ethyl acetate. The combined organic phases were then washed with concentrated $NaHCO_3$ and brine and then dried over anhydrous $Na_2SO_4$. After filtration of the desiccant, the organic solvent was removed by vacuum evaporation. The crude mixture was separated from catalyst by short column chromatography on silica gel (1:4 ethyl acetate-hexane) and the blend of desired alcohol and eventually rest of ketone was subjected to HPLC analysis to determine the conversion and enantiomeric excess and to elucidate the configuration of the enantiomer existing in excess.

## Acknowledgements

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