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Synthesis of asymmetric iron–pybox complexes and their application to aziridine forming reactions

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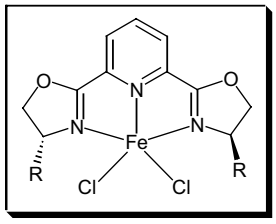
Abstract—The synthesis of a series of iron–pybox complexes and their employment in the catalytic asymmetric aziridine forming reaction is presented. When $AgSbF_6$ is used as an initiator, the *i*-pr- and *t*-bu-pybox complexes produce 47% of the *cis*-aziridine in moderate ee's with the bulk of side products consisting of the *trans*-isomer and β-amino-α,β-unsaturated esters (AUE's).

Methods for obtaining asymmetric aziridines by catalysis generally proceed through one of two principal routes: transfer of a nitrogen group to an olefin, or transfer of a carbenoid to an imine. While the former approach is more prevalent in the literature, increasing attention has been given to the latter in recent years.[1] Other recent work by Brookhart and co-workers,[2] Gibson and co-workers,[3] and Nomura and co-workers[4] has suggested that iron–pybox complexes of the type **1** (Fig. 1) might be effective candidates for the asymmetric aziridine forming reaction between imines and ethyl diazoacetate.

The pybox ligands[5] were synthesized from the commercially available amino alcohol in three steps.[6] 2,6-Pyridine dicarboxylic acid was refluxed with thionyl chloride and isolated. The residue was treated with the amino alcohol in chloroform at 0 °C, followed by in situ addition of thionyl chloride to yield the pybox ligand (generally as a hydrochloride salt). Neutralization of the salt was achieved by stirring a methanolic solution of the salt with aqueous sodium hydroxide at room temperature for 3 days. Recrystallization from ethyl acetate and pentane yielded the free pybox ligand as long, white needles (Scheme 1).

The iron–pybox complexes were prepared by stirring a THF solution of pybox ligand and iron(II) chloride until



1a, R = *i*-pr
1b, R = *t*-bu
1c, R = ph

Figure 1. Iron–pybox complexes **1**.

all the solids were observed to dissolve (Scheme 2).[7] In the cases of the isopropyl and *tert*-butyl pybox complexes (**1a** and **1b**, respectively), the resultant solution turned a dark blue-violet color instantly, and all solids dissolved within a few minutes. In the complexation of the phenyl pybox ligand, the solution was a deep magenta color, and the magenta solid (**1c**) began to precipitate as stirring continued.

The iron complexes exhibited different solubilities throughout the series: both the isopropyl and *tert*-butyl pybox complexes dissolved readily to form solutions in dichloromethane, whereas the complex **1c** did not unless under high dilution (greater than 1000 times the amount of solvent required to dissolve compared to the other complexes). ^{1}H NMR analysis of the crude **1a** indicated a paramagnetic complex, along with resonances corresponding to the uncomplexed ligand. Repeated washing of the crude solid with diethyl ether removed the uncomplexed ligand, and subsequently the NMR spectrum displayed only highly shifted resonances appearing as

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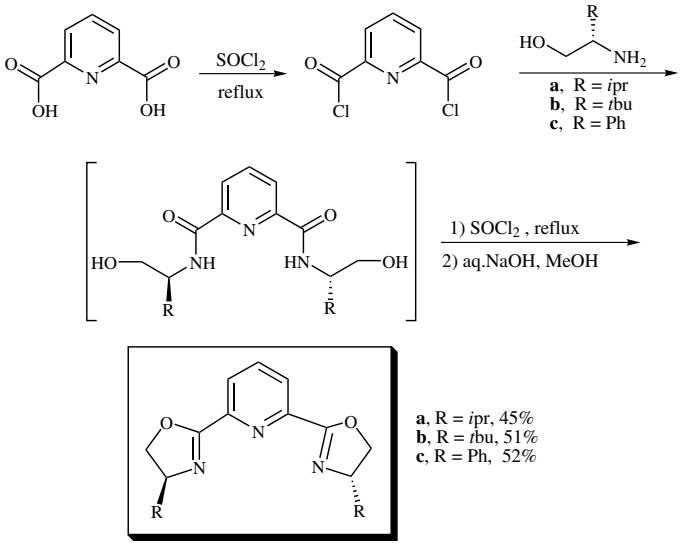
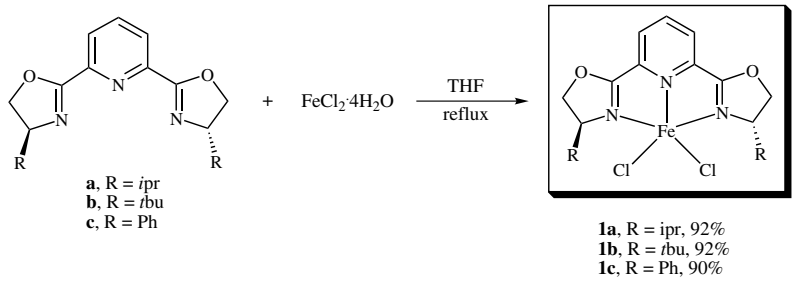


Scheme 1. Synthesis of the pybox ligands.



Scheme 2. Synthesis of the iron–pybox complexes.

broad singlets between 60 and 30 ppm for the coordinated pybox ligand. The other complexes displayed similar behavior when analyzed by NMR. In an attempt to achieve a higher incidence of ligand coordination, the reaction was run again in refluxing THF, and allowed to stir for up to 48 h. ^{1}H NMR analysis of the reaction progress showed no appreciable complexation occurring after 5 min. When the reaction was repeated at 0 °C, again, no change in the reaction profile was observed by NMR.

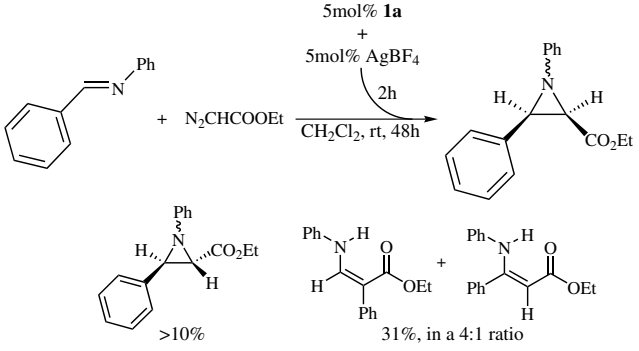
The complex **1a** was employed in an aziridine forming reaction of *N*-benzylideneaniline and ethyl diazoacetate (EDA), no consumption of the imine was observed by TLC over 48 h. The reaction was ceased, and only starting materials were recovered (Table 1, entry 1). Another reaction was attempted (Scheme 3); however, before the iron–pybox complex was added to the imine, it was stirred in the presence of 1 equiv of $AgBF_4$ for 2 h. The solution was then filtered under nitrogen into the flask containing the imine, and EDA was added to the solution. After 48 h, imine conversion was no longer detected by TLC, and the reaction was halted.[8] ^{1}H NMR analysis of the crude reaction mixture revealed the *cis*-aziridine,[9] plus small amounts of the *trans*-isomer in a *cis*/*trans* ratio of 85:15. HPLC analysis of the crude reaction mixture revealed a 43% ee for the reaction. After workup, the reaction yielded 41% of the *cis*-aziridine, with the major byproducts being β-amino-α,β-unsaturated esters (AUE's) as a 4:1 mixture (entry 2).

Different amounts and types of initiator were attempted (entries 3–6). In each case, NMR analysis of the crude reaction mixture revealed small amounts of the *trans*-isomer in a *cis*/*trans* ratio of approximately 85:15. Increasing the amount of initiator increased the yield of the reaction, but at the expense of the enantioselectivity. The best results were obtained with the use of 1 equiv of $AgSbF_6$ (entry 5). The reaction was also attempted in differing solvents (entries 7–10), and the results are listed in Table 1. The best overall solvent for the reaction appeared to be dichloromethane, although THF produced a better yield (38% vs 32%), and nitromethane gave better enantioselectivity (49% vs 42%). Results were poor in both yields and ee categories when methanol was used as the solvent. A catalyst loading of 5 mol% was used for the remainder of the iron–pybox catalyzed reactions. There appears to be little correlation between the relative concentrations of the substrates and either the yield or the enantioselectivity (entries 11–13). Nor was enhancement in ee observed in any of the reactions with the addition of extra equivalents of pybox ligand to the

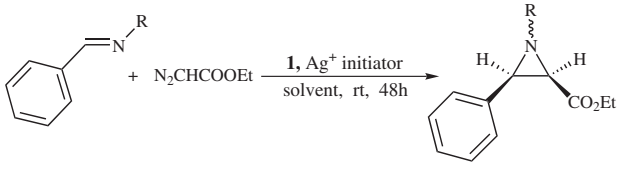
Table 1. Iron–pybox catalyzed aziridine forming reactions of imines and ethyl diazoacetate (Scheme 4)

Entry	R	Catalyst (mol%)	Ag^+ Initiator (mol%)	Equiv. EDA[a]	Solvent	Yield[b] *cis*-aziridine (%)	%ee[c]	Combined yield AUE's (%)[b]
1	Ph	**1a** (5)	—	1	CH_2Cl_2	0	—	—
2	Ph	**1a** (5)	$AgBF_4$ (5)	1	CH_2Cl_2	41	43	31
3	Ph	**1a** (5)	$AgBF_4$ (10)	1	CH_2Cl_2	49	30	Not det'd
4	Ph	**1a** (5)	AgOTf (5)	1	CH_2Cl_2	20	32	Not det'd
5	Ph	**1a** (5)	$AgSbF_6$ (5)	1	CH_2Cl_2	47	45	Not det'd
6	Ph	**1a** (5)	$AgSbF_6$ (10)	1	CH_2Cl_2	54	31	Not det'd
7	Ph	**1a** (2)	$AgBF_4$ (2)	1	CH_2Cl_2	32	42	Not det'd
8	Ph	**1a** (2)	$AgBF_4$ (2)	1	NO_2Me	21	49	Not det'd
9	Ph	**1a** (2)	$AgBF_4$ (2)	1	THF	38	35	Not det'd
10	Ph	**1a** (2)	$AgBF_4$ (2)	1	MeOH	14	20	Not det'd
11	Ph	**1a** (5)	$AgBF_4$ (5)	0.85	CH_2Cl_2	28[d]	40	Not det'd
12	Ph	**1a** (5)	$AgBF_4$ (5)	1.2	CH_2Cl_2	34	28	Not det'd
13	Ph	**1a** (5)	$AgBF_4$ (5)	1.5	CH_2Cl_2	42	31	Not det'd
14[e]	Ph	**1a** (5)	$AgBF_4$ (5)	1	CH_2Cl_2	40	40	Not det'd
15[f]	Ph	**1a** (5)	$AgBF_4$ (5)	1	CH_2Cl_2	37	32	Not det'd
16[g]	Ph	**1a** (5)	$AgBF_4$ (5)	1	CH_2Cl_2	30	15	Not det'd
17[h]	Ph	**1a** (5)	$AgBF_4$ (5)	1	CH_2Cl_2	28	40	Not det'd
18	Ph	**1b** (5)	$AgSbF_6$ (5)	1	CH_2Cl_2	47	49	34
19	Ph	**1c** (5)	$AgSbF_6$ (5)	1	CH_2Cl_2	15[i]	5	8
20	$CHPh_2$	**1a** (5)	$AgSbF_6$ (5)	1	CH_2Cl_2	25[i]	20	6
21	$CHPh_2$	**1b** (5)	$AgSbF_6$ (5)	1	CH_2Cl_2	39[i]	28	9
22	$CHPh_2$	**1c** (5)	$AgSbF_6$ (5)	1	CH_2Cl_2	9[i]	0	>2

[a] Relative to imine.
[b] Isolated yield.
[c] Enantiomeric excess of the *cis*-aziridine was determined using a (*S,S*) Whelk-O column. The %ee of the *trans*-isomer was not determined.
[d] Yield based on EDA.
[e] An additional 5 mol% pybox ligand added to substrate flask.
[f] An additional 10 mol% pybox ligand added to substrate flask.
[g] An additional 25 mol% pybox ligand added to substrate flask.
[h] Reaction run at 0 °C.
[i] Incomplete consumption of the imine.



Scheme 3. Reaction of complex **1a** with *N*-benzylideneaniline and EDA.

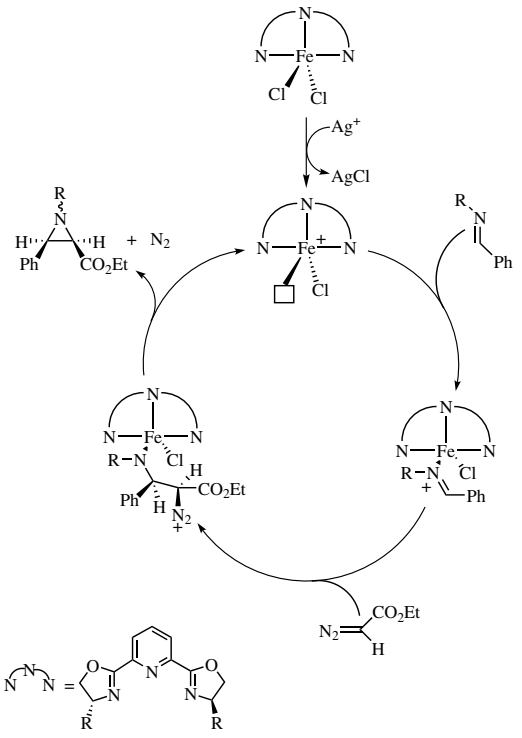


Scheme 4. Iron–pybox catalyzed aziridine-forming reaction.

substrate solution (entries 14–16).[6b,10] When the reaction was attempted at 0 °C, the yield was decreased to 28%, without improvement in the ee (entry 17).

Using the optimal set of conditions from the test reaction, the entire series of pybox complexes were employed in two aziridine forming reactions with either *N*-benzylideneaniline or *N*-benzylidene-*N*-(diphenyl-methyl)amine (benzhydryl imine) as the substrate (Scheme 4 and Table 1, entries 18–22). In reactions where *N*-benzylideneaniline is the substrate, conversion of the imine into products is essentially complete, with the AUE's comprising the bulk of non-aziridine product. As expected, the formation of AUE's is reduced when the more electron-rich benzhydryl imine is used;[1b,c] however, yield of *cis*-aziridine and ee are both reduced in those reactions. In addition, unreacted benzhydryl imine was recovered in all trials where it was the substrate, and letting the reaction proceed for additional time (72 h, 96 h) did not improve percent conversion. The best overall results came when the *tert*-butyl pybox catalyst was used, although results obtained with the isopropyl pybox catalyst are very similar. It is interesting to note that in both reaction types, the efficacy of the phenyl pybox complex is markedly different than either of the other two complexes. These results, coupled with the differing physical properties of the phenyl pybox complex, warranted further analysis of the pybox complexes, which is underway.

A proposed catalytic cycle for the reaction is given in Scheme 5. Initiation with 1 equiv of Ag^+ ion creates an open site for coordination of the imine to the Lewis acid.



Scheme 5. Proposed mechanism of monochelated iron–pybox complexes.

Attack of the diazo compound occurs enantioselectively; approach from one side is significantly more hindered by the isopropyl or *tert*-butyl side chains. Backside ring closure and expulsion of a molecule of nitrogen creates the aziridine ring, which disassociates to reform the active catalyst.

Further analysis to determine the nature of the pybox complexes and the mechanism of the origin of enantioselectivity in the reaction is currently in progress.

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7. *General procedure for the preparation of the iron–pybox complexes*: A 100 mL side armed flask was charged with the 1.5 mmol pybox ligand, followed by 1.5 mmol iron(II) chloride tetrahydrate. The solids were dissolved in THF, and stirred at room temperature for 1–2 h. The solvent was removed under reduced pressure, and the powder was washed with cold ether to provide near-quantitative yields of the iron–pybox complexes.
8. *General procedure for the synthesis of aziridines:* A side armed flask was prepared and charged with 0.1 mmol iron–pybox Lewis acid. The solid was dissolved in 2 mL CH_2Cl_2. A separate side armed flask was charged with silver salt initiator and suspended in 3 mL CH_2Cl_2. The silver salt suspension was transferred over to the iron–pybox solution via cannula and stirred in absence of light for 2 h. The solution was then stick-filtered through a cotton plug to a side armed flask containing 2.0 mmol imine. The diazo compound was added after stirring for 10–15 min, and the reaction was allowed to proceed for 1–2 days. The reaction solution was filtered through a plug of silica and eluted with ether or EtOAc into a 100 mL flask. The solvent was removed by rotary evaporation, and the crude product was analyzed by HPLC. After HPLC analysis, the crude product was separated by column chromatography (0–10% EtOAc/pentane) and the compounds were identified by matching their ^{1}H NMR with those of known compounds.[1b,c,9]
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