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A Metallocene-Pyrrolidinopyridine Nucleophilic Catalyst for Asymmetric Synthesis

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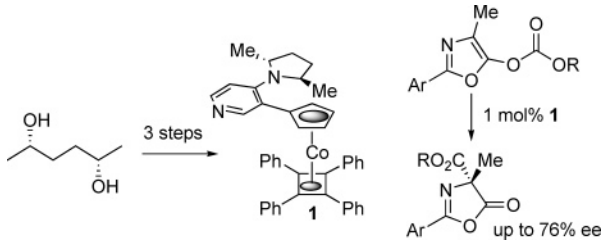
ABSTRACT



A highly active chiral 4-aminopyridine nucleophilic catalyst, available in three steps from (*S*,*S*)-hexane-2,5-diol, was applied to the asymmetric Steglich rearrangement of *O*-aceylated azlactones (1 mol % loading, up to 76% ee).

Since its introduction by Litvinenko and Steglich in the late 1960s,[1] 4-(dimethylamino)pyridine (4-DMAP) and the more active 4-pyrrolidinopyridine (4-PPY) have been extensively employed as nucleophilic catalysts for acyl transfer reactions.[2] The high activity of these systems is exemplified by the 3.4×10^8 rate enhancement of alcohol acylation (by benzoyl chloride) in the presence of a stoichiometric quantity of 4-DMAP.[3] As a consequence, the 4-aminopyridine moiety has been incorporated into a variety of acyl transfer catalysts for application in asymmetric synthesis (Figure 1). When considering how to introduce chirality into these catalysts it is important not to attach a substituent at the pyridine 2-position, as this significantly attenuates nucleophilicity (e.g., **A**).[4] The challenge is to introduce a substituent at the 3-position (e.g., **B**)[5] or even more remotely (e.g., **C**)[6] and yet maintain an asymmetric environment about the active pyridine nitrogen. The only exceptions to this requirement are planar chiral ferrocene derivatives such as **D**,[7] where the balance of fair reactivity[8] and high selectivity in many different reactions comes at the cost of a lengthy synthesis

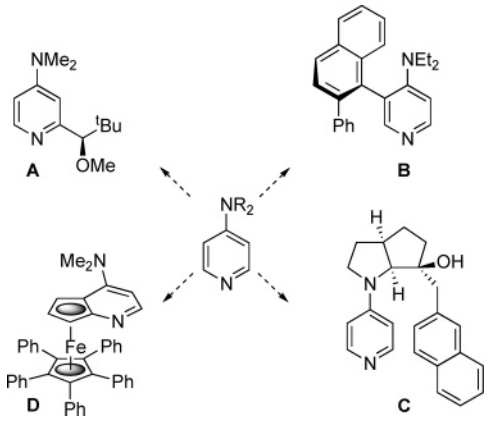


Figure 1. Known chiral 4-aminopyridine nucleophilic catalysts.

(1) (a) Litvinenko, L. M.; Kirichenko, A. I. *Dokl. Chem.* **1967**, 763; *Dokl. Akad. Nauk SSSR Ser. Chim.* **1967**, *176*, 97. (b) Steglich, W.; Höfle, D. *Angew. Chem.* **1969**, *81*, 1001; *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.

(2) (a) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129. (b) Grondal, C. *Synlett* **2003**, 1568. (c) Murugan, R.; Scriven, E. F. V. *Aldrichimica Acta* **2003**, *36*, 21.

(3) Bondarenko, L. I.; Kirichenko, A. I.; Litvinenko, L. M.; Dmitrenko, I. N.; Koberts, V. D. *J. Org. Chem. USSR (Engl. Transl.)* **1981**, 2310; *Zh. Org. Khim.* **1981**, *17*, 2588.

(4) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809.

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and the need for subsequent chromatographic resolution to obtain the enantiopure catalyst.[9]

We reasoned that an alternative and potentially much simpler approach to a chiral acyl transfer catalyst would be to relay the stereochemistry of a readily synthesized enantiopure C_2-symmetric pyrrolidine through to the pyridine nitrogen by use of a bulky metallocene substituent (Figure 2). Attachment of this to the 3-position should ensure the

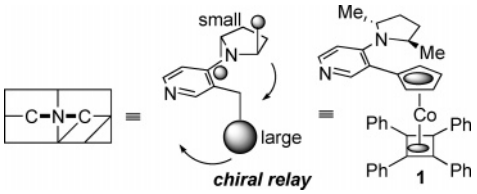


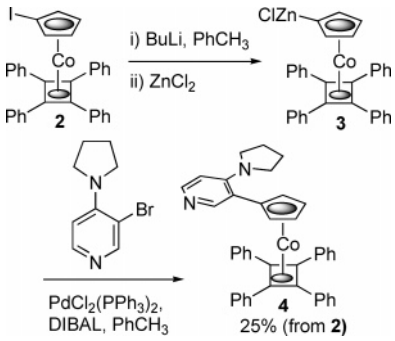
Figure 2. Design rationale for **1**.

maintenance of high nucleophilicity, while placing the pyridine nitrogen in an asymmetric environment by projection of the tetraphenylcyclobutadiene moiety into one of the quadrants surrounding the pyridine nitrogen. In this Letter we report on the synthesis and properties of metallocene catalyst **1** and on the application of this to the asymmetric Steglich rearrangement.

We first established a simple procedure for the synthesis of achiral 3-substituted 4-PPY derivative **4**, utilizing a Negishi cross-coupling to generate the key metallocene-pyridine C−C bond. (Scheme 1). As it did not prove possible to lithiate the parent metallocene directly, the known iodo derivative **2**[10] was subjected to halogen−lithium exchange and transmetalation with zinc chloride to give the organozinc intermediate **3**. This was not isolated and was instead cross-coupled with 3-bromo-4-pyrrolidinopyridine[11] to give the novel metallocene **4** as an air-stable yellow crystalline solid.

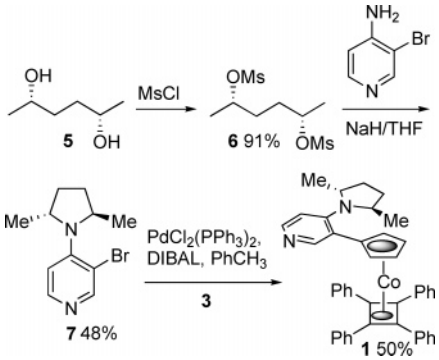
Adaptation of this methodology for the synthesis of a chiral complex began with commercially available (*S*,*S*)-hexane-2,5-diol,[12] which was converted via an intermediate dimesylate into (*R*,*R*)-pyrrolidinopyridine **7** (Scheme 2).[13] Use of

Scheme 1. Synthesis of an Achiral 3-Substituted PPY Nucleophilic Catalyst



this as a reaction partner in the Negishi cross-coupling protocol gave the novel chiral nucleophilic catalyst **1**.

Scheme 2. Asymmetric Synthesis of a Chiral 3-Substituted PPY Nucleophilic Catalyst



Of the two metallocene-substituted nucleophilic catalysts, we have so far only been successful in obtaining the X-ray crystal structure of the achiral derivative **4** (Figure 3).[14] This revealed that the size and proximity of the two pyridine substituents results in (a) a 29° tilt of the pyridine ring with respect to the cyclopentadienyl ring, (b) a twist in the pyrrolidine group moving the methylene C(42) away from the adjacent cyclopentadienyl ring, and (c) the pyridine carbon C(38) is bent 25° above the plane (as viewed) defined by C(42)−N(2)−C(39), indicative of some sp^3 character in the pyrrolidine nitrogen. In addition, this structure illustrates the projection of the cyclobutadiene phenyl groups under one face of the pyridine.

An asymmetric catalyst requires selective differentiation between the two pyridine faces. To examine if **1** displays this requirement, we next examined the conformational

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(6) (a) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc*. **1997**, *119*, 3169. (b) Priem, G.; Pelotier, B.; Macdonald, S. J. F.; Anson, M. S.; Campbell, I. B. *J. Org. Chem*. **2003**, *44*, 3844. (c) Spivey, A. C.; Maddaford, A.; Fekner, T.; Redgrave, A. J.; Frampton, C. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3460. (d) Naraku, G.; Shimomoto, N.; Hanamoto, T.; Inanaga, J. *Enantiomer* **2000**, *5*, 135.

(7) Fu, G. C. *Acc. Chem. Res*. **2004**, *37*, 542.

(8) As an indicatior of the relative activity of **D** versus 3-substituted-4-aminopyridines, the former are generally used at 0 °C to catalyze alcohol acylation, whereas the latter may be employed at −78 °C.

(9) (a) Ruble, J. C.; Fu, G. C. *J. Org. Chem*. **1996**, *61*, 7230. (b) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc*. **1997**, *119*, 1492.

(10) Rausch, M. D.; Genetti, R. A. *J. Org. Chem*. **1970**, *35*, 3888.

(11) Spivey, A. C.; Fekner, T.; Spey, S. E.; Adams, H. *J. Org. Chem*. **1999**, *64*, 9430.

(12) Lieser, J. K. *Synth. Commun*. **1983**, 765.

(13) Compound **7** was synthesized using a procedure developed for related C_2-symmetric 2,5-disubstituted pyrrolidines; see ref 6c.

(14) **Crystal Data for 4**. $C_{42}H_{36}CoN_2O_{0.50}$, $M = 635.66$, monoclinic, $a = 18.5614(3)$, $b = 34.2968(8)$, $c = 10.4254(2)$ Å, $\alpha = 90°$, $\beta = 107.7760(10)°$, $\gamma = 90°$, $V = 6319.9(2)$ Å^3, space group $C2/c$, $Z = 8$, $D_c = 1.336$ Mg/m^3, $\mu = 0.579$ mm^{-1}, reflections measured 22082, reflections unique 7187 with $R_{int} = 0.0438$, $T = 120(2)$ K, final R indices [$F^2 > 2\sigma(F^2)$] R1 = 0.0385, wR2 = 0.0880 and for all data R1 = 0.0605, wR2 = 0.0971.

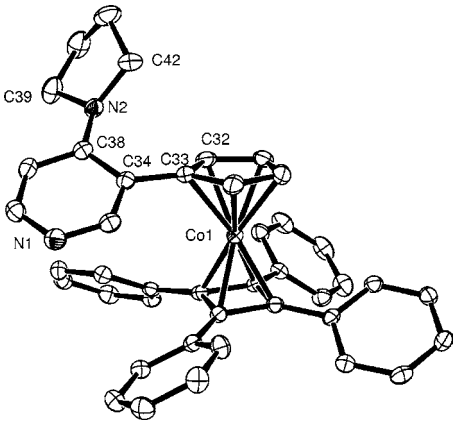


Figure 3. Representation of the X-ray crystal structure of **4** (water of crystallization removed for clarity). Key bond angles and torsions: C(39)−N(2)−C(42) = 110.11(15)°, C(39)−N(2)−C(38) = 119.58(15)°, C(38)−N(2)−C(42) = 122.33(15)°, C(32)−C(33)−C(34)−C(38) = 29.0°, C(34)−C(38)−N(2)−C(39) = −164.5°, C(34)−C(38)−N(2)−C(42) = 49.7°

properties of this complex by NMR spectroscopy (Figure 4). A gradient-enhanced nuclear Overhauser enhanced spec-

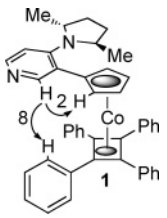
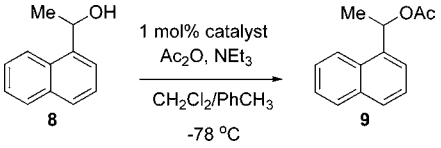


Figure 4. GOSEY connectivity and percentage enhancements for **1**.

troscopy experiment (GOSEY) revealed connectivity between the pyridine H-2 singlet and only one of the two diastereotopic α-hydrogens of the cyclopentadienyl group.[15,16] That this is drawn as the pro-$_p$*S* hydrogen is based on the assumption that the pyrrolidine methyl substituent adjacent to the Cp-ring is orientated away from the metallocene.

All of the points (a−c) made in the discussion of the X-ray structure of **4** could potentially reduce the effectiveness of this as a nucleophilic catalyst. One method to estimate activity is by comparison of the chemical shift of the pyridine *β*-hydrogen(s) in the ^{1}H NMR spectra (Table 1).[17] This indicated that **4** should have an activity similar to that of

Table 1. Determination of Catalyst Activity



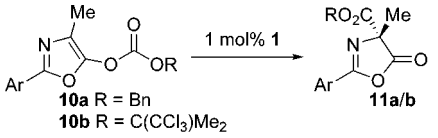
catalyst	time (h)	conversion to **9**[a] (%)	catalyst δ(^{1}H) β-H[b] (ppm)
4-PPY	5	68	6.38
4-DMAP	5	53	6.48
4	5	71	6.44
1	18	38[c,d]	6.61

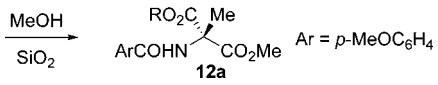
[a] Determined by ^{1}H NMR spectroscopy. [b] Determined in $CDCl_3$. [c] Recovered (*S*)-**8** = 17% ee (*s* = 2.1). [d] Use of *i*-Pr_2O gave a 50% conversion with recovered (*S*)-**8** = 32% ee (*s* = 2.6).

4-DMAP, with the chiral species **1** being slightly less active. This was verified by application of these catalysts to the acetylation of 1-(1-naphthyl)ethanol **8**. The conversion obtained with **4** was similar to that obtained with 4-PPY and 4-DMAP, whereas **1** required a longer reaction time to achieve a lower conversion. Subsequent analysis of the recovered alcohol from this last reaction indicated that this catalyst is not suitable for application in secondary alcohol kinetic resolution.

Instead we chose to examine the Steglich rearrangement[18] of enol carbonates **10**, precursors to azlactones **11** containing a quaternary stereogenic center.[19] Addition of 1 mol % of **1** to **10a** resulted in clean rearrangent at 0 °C (Table 2, entry

Table 2. Asymmetric Steglich Rearrangement with Catalyst **1**[a]





entry	R	solvent	temp (°C)	time (h)	conv to **11** (%)[b]	ee (%)[c]
1	Bn	$PhCH_3$	0	48	100	72 (**12a**)
2	Bn	CH_2Cl_2	0	72	100	45 (**12a**)
3	Bn	*t*-amyl alcohol	0	72	70	0 (**12a**)
4[d]	Bn	$PhCH_3$	−20	156	85	75 (**12a**)
5	$C(CCl_3)Me_2$	$PhCH_3$	0	48	100	76 (**11b**)

[a] 1 mol % unless otherwise stated. [b] Determined by ^{1}H NMR after removal of the catalyst by filtration through a SiO_2 plug. [c] Determined by HPLC (Chiralcel OD). [d] 3 mol % **1**.

1). Because of the instability of **11a** toward chiral HPLC analysis, we found it more convenient to determine the

(15) Irradiation of pyridine H-2 (7.76 ppm) at 298 K resulted in a pro-$_p$*S* (4.92 ppm) to pro-$_p$*R* (5.14 ppm) enhancement ratio of >23:1 (the latter was not observed).

(16) An alternative way to consider the stereochemical environment of the pyridine moiety is to regard it as being in an environment of virtual planar chirality. See: Jones, G.; Richards, C. J. *Organometallics* **2001**, *20*, 1251.

(17) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069.

(18) (a) Steglich, W.; Höfle, G. *Chem. Ber.* **1969**, *102*, 883. (b) Steglich, W.; Höfle, G. *Chem. Ber.* **1971**, *104*, 3644. (c) Höfle, G.; Prox, A.; Steglich, W. *Chem. Ber.* **1972**, *105*, 1718.

enantioselectivity following ring opening to diester **12a**. This revealed an enantiomer ratio of 86:14, and the configuration of the major isomer was determined by comparison of the rotation of **11a** to the literature value.[19] Use of dichloromethane as the reaction solvent significantly reduced the enantioselectivity (entry 2), and use of *tert*-amyl alcohol resulted in no enantioselectivity (entry 3). This latter result was suprising as this solvent has previously been determined to maximize enantioselectivity for reactions of this type.[5c,19] Returning to toluene and lowering the reaction temperature resulted in a 75% enantiomeric excess, though at the expense of a higher catalyst loading and a longer reaction time (entry 4). Essentially the same enantioselectivity was achieved with 1 mol % of **1** and the bulkier 2,2,2-trichloro-1,1-dimethylethyl group[20] of substrate **10b**, rearranged azlactone **11b** subsequently being isolated in 65% yield.

In summary, we have demonstrated a short synthesis of a highly active 4-aminopyridine nucleophilic catalyst from a commercially available chiral starting material. Use of a bulky cobalt metallocene to relay the stereochemistry of the pyrrolidine results in a defined chiral environment about the pyridine nitrogen. Preliminary investigations into the use of this catalyst have resulted in greater than 7:1 enantioselectivity for the rearrangement of an *O*-acylated azlactone.

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Supporting Information Available: Synthesis, characterization, and ^{1}H NMR spectra of **1**, **4**, **7**, **10b**, **11b** and **12a**; methods of ee determination; and details of the X-ray crystal structure of **4** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc*. **1998**, *120*, 11532.

(20) This has previously been successfully applied to the related rearrangement of *O*-acylated oxindoles, see: Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921.