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Asymmetric synthesis of oxindoles containing a quaternary stereogenic centre by catalytic *O*/*C*-carboxyl rearrangement

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ABSTRACT

A catalysed *O*/*C*-carboxyl rearrangement generates the all-carbon stereogenic centre in phenyl 1,3-dimethyl-5-methoxy-2-oxoindoline-3-carboxylate (up to 57% ee). Crystallisation and removal of racemic crystals enhance the ee to 95%. The X-ray crystal structure of the cobalt metallocene–pyrrolidinopyridine nucleophilic catalyst employed is reported.

A number of oxindole-based naturally occurring alkaloids contain an all-carbon quaternary stereogenic centre at C-3. Examples include (−)-horsifiline **1**[1a] (Fig. 1) and more complex compounds containing additional stereogenic centres such as gelsemine,[1b] welwitindolinone A[1c] and spirotryprostatins A[1d] and B.[1e] Related pyrroloindoline alkaloids containing a C-3 quaternary stereogenic centre that also display biological activity have long attracted the interest of synthetic chemists. In addition to (−)-physostigmine **2a**[2a] and its congeners (−)-phenserine **1b**[2b] and (−)-esermethole **1c**,[2a] related examples include (−)-pseudophrynaminol[2c] and (−)-flustramine B.[2d]

Asymmetric catalysis may be used to control the absolute configuration at C-3 during the synthesis of these natural products, with methods employed ranging from palladium-catalysed Heck[3a] and molybdenum-catalysed allylic alkylation reactions,[3b] to iminium ion catalysis.[2d] Chiral 4-aminopyridine-based nucleophilic catalysts have been extensively developed in recent years for enantioselective acyl and carboxyl transfer reactions.[4] Although the focus of this research has been largely on chiral secondary alcohol kinetic resolution, success has also been achieved with enantioselective *O*/*C*-carboxyl transfer reactions for the synthesis of quaternary stereogenic centres (Scheme 1).[5,6]

To this end we recently reported the synthesis of a cobalt metallocene–pyrrolidinopyridine nucleophilic catalyst **3**, available in three steps (22% unoptimised yield) from commercially available (*S*,*S*)-hexane-2,5-diol (Scheme 2).[7] Use of 1 mol % of this catalyst resulted in the quantitative *O*/*C*-carboxyl rearrangement of azlactone-derived enol carbonates in up to 76% ee. We now report on the application of **3** to the generation of the C-3 stereogenic centre of a 3-methyl-5-methoxyoxindole building block that has the potential to be employed in the synthesis of natural products and related compounds.

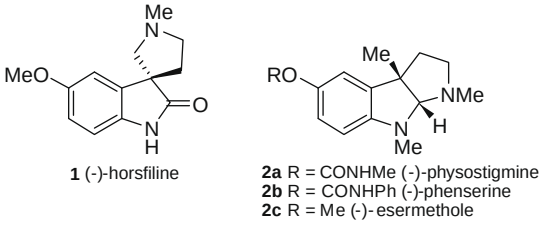
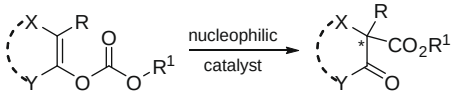


Figure 1. Representative oxindole and pyrroloindoline alkaloids containing an all-carbon quaternary stereogenic centre.



Scheme 1. *O*/*C*-Carboxyl rearrangement for the synthesis of quaternary stereogenic centres.

Starting with commercially available *N*-methyl-4-methoxyaniline **4**, oxindole **5** was synthesised using a literature procedure (Scheme 3).[8] Subsequent deprotonation with potassium hexamethyldisilazide followed by chloroformate addition gave enol carbonates **6a**–**d**.[9] The very low yield of **6c** was mainly due to the preferential formation of 3-benzyl-1,3-dimethyl-5-methoxy-2-oxoindoline.[2a] This was also the major product when triethylamine or sodium hydride was used with benzyl chloroformate, these reactions also resulted in a very low yield (<2%) of **6c**.

Addition of 5 mol % of catalyst **3** to **6a** in toluene/dichloromethane (the latter solvent being required to completely solubilise the substrate) resulted in clean rearrangement and isolation of **7a** in 48% ee (Table 1, entry 1). Repetition of the reaction at 0 °C resulted in no reaction (entry 2) and the use of dichloromethane alone also

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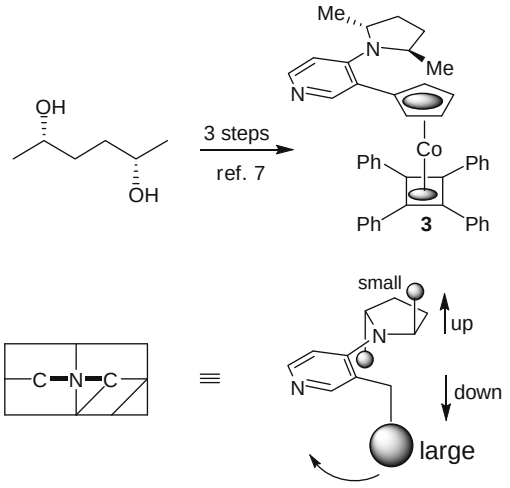
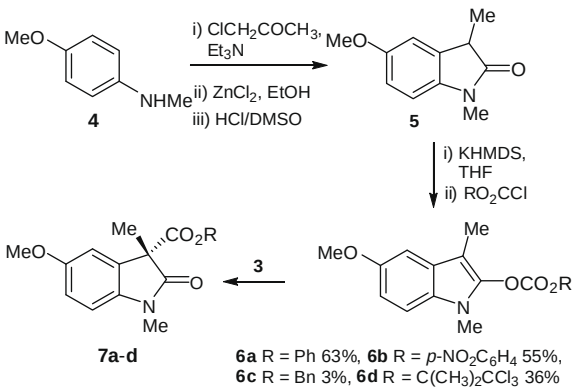


Scheme 2. Chiral nucleophilic catalyst **3** and the mechanism of chirality transfer to the pyridine nitrogen environment of **3**.

gave an ee of 48% (entry 3).[10] This increased to 57% in THF, albeit with a significantly longer reaction time and lower yield (entry 4). The replacement of the phenyl carbonate **6a** with the *p*-nitrophenyl and benzyl congeners **6b** and **6c** resulted in essentially no enantioselectivity (entries 5 and 6). In contrast the trichloro-*tert*-butyl analogue **6d** gave a 50% ee in toluene (with 10 mol % **3**, entry 7), but much lower enantioselectivities in hexane/dichloromethane or THF (entries 8 and 9).[11] Following lithium hydroxide-mediated hydrolysis of enantioenriched esters **7a** and **7d**, the resulting acids were determined to contain the same major enantiomer by chiral HPLC analysis. The absolute configuration of the major enantiomer of **7a** and **7d** is tentatively assigned as *S* by comparison with the major enantiomer resulting from the rearrangement of azlactone-derived enol carbonates with catalyst **3**.[7] Other catalysts applied to the rearrangement of enol carbonates derived from both azlactones and oxindoles have resulted in the same sense of enantioselectivity.[5a–d]



Scheme 3. Synthesis and rearrangement of oxindole-derived enol carbonates **6a**–**d**.

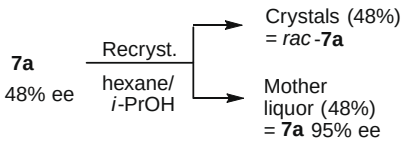
Table 1
Rearrangement reactions of enol carbonates **6** with nucleophilic catalyst **3**[a]

Entry	Substrate/ product	Mol % **3**	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**6a/7a**	5	PhMe/ CH_2Cl_2[e]	24	83	48
2[d]	**6a/7a**	5	PhMe/ CH_2Cl_2[e]	36	0	—
3	**6a/7a**	5	CH_2Cl_2	18	50	48
4	**6a/7a**	5	THF	72	43	57
5	**6b/7b**	5	PhMe/ CH_2Cl_2[f]	48	70	5
6	**6c/7c**	5	PhMe/ CH_2Cl_2[f]	36	78	5
7	**6d/7d**	10	PhMe	24	61	50
8	**6d/7d**	10	Hexane/ CH_2Cl_2[f]	48	48	15
9	**6d/7d**	3	THF	24	43	7

[a] All reactions at 25 °C unless otherwise stated.
[b] After isolation by chromatography.
[c] Determined by HPLC.
[d] At 0 °C.
[e] 5:2 Ratio.
[f] 4:1 Ratio.

Recrystallisation of **7a** (48% ee) from hexane/*i*-PrOH gave crystalline racemic **7a** and a mother liquor consisting almost exclusively of the major enantiomer (Scheme 4).[12] The use of preferential crystallisation to separate the enantiomers of a racemic compound (as opposed to a racemic mixture that forms a conglomerate) has recently been demonstrated, and requires the use of an enantioenriched mixture of enantiomers.[13] Thus, although the enantioselectivity of the *O*/*C*-carboxyl rearrangement is relatively modest, this crystallisation procedure provides a highly scalemic intermediate for the synthesis of alkaloids of general structure **2**.

The X-ray crystal structure of **3**[14] (Fig. 2) reveals the operation of the chiral relay effect as represented in Scheme 2. That this conformation, with respect to rotation about the pyridine–cyclopentadienyl bond, is maintained in solution has previously been established by NMR (GOSEY) analysis.[7] The deviation from co-planarity of the pyridine and cyclopentadienyl rings is 38°, which is at least in part due to the avoidance of interaction between the cyclo-



Scheme 4. Enantiomeric enrichment of **7a**.

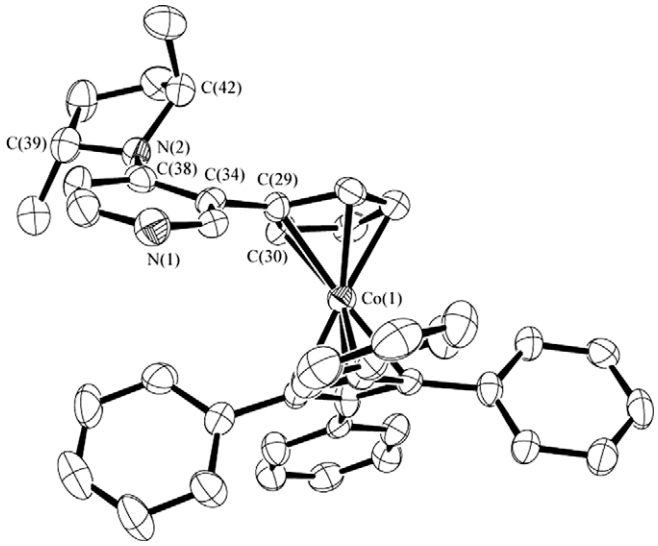


Figure 2. ORTEP representation of the X-ray crystal structure of **3**. Key bond angles and torsions: C(39)–N(2)–C(42) = 108.3(4)°, C(39)–N(2)–C(38) = 118.4(4)°, C(38)–N(2)–C(42) = 117.7(4)°, C(30)–C(29)–C(34)–C(38) = −37.6(8)°, C(34)–C(38)–N(2)–C(39) = 168.2(5)°, C(34)–C(38)–N(2)–C(42) = −58.3(7)°.

pentadienyl and pyrrolidine moieties. The latter adopts an envelope conformation with the out-of-plane carbon [C(42)] adjacent to the cyclopentadienyl group, towards which is projected an equatorial hydrogen. The pyridine carbon C(38) is bent 36° out of the plane defined by C(42)–N(2)–C(39) which is indicative of some sp^3 character in the pyrrolidine nitrogen. This deviation from the sp^2 pyrrolidine nitrogen of 4-pyrrolidinopyridine (PPY), and the resulting reduction in the magnitude of the $n_N \rightarrow \pi^*_{(C=C)}$ interaction, accounts for the reduction in the activity of **3** compared to PPY and 4-dimethylaminopyridine (DMAP) as catalysts in alcohol acetylation reactions.[7,15] The steric impediment of a cyclobutadiene-appended phenyl group may also be a factor. However, it must be stressed that **3** is still a very active nucleophilic catalyst and the relatively high catalyst loading of 5 mol % required for the rearrangement of oxindole-derived enol carbonates is a consequence of the low activity and challenging nature of this class of substrate.

In summary, we have demonstrated that the synthetically accessible chiral nucleophilic catalyst **3** is applicable to the asymmetric rearrangement of an oxindole-derived enol carbonate, and in particular to the generation of highly scalemic phenyl 1,3-dimethyl-5-methoxy-2-oxoindoline-3-carboxlate following enantioenrichment by recrystallisation. The utilisation of this building block for the synthesis of indole alkaloids and related compounds is currently in progress.

Acknowledgements

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References and notes

1. (a) Pellegrini, C.; Strässler, C.; Weber, M.; Borschberg, H.-J. *Tetrahedron: Asymmetry* **1994**, *5*, 1979; (b) Yokoshima, S.; Tokuyama, H.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 4073; (c) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394; (d) Edmondson, S. D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1138; (e) von Nussbaum, F.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2175.
2. (a) Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.* **1991**, *56*, 872; (b) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043; (c) Kawasaki, T.; Ogawa, A.; Takashima, Y.; Sakamoto, M. *Tetrahedron Lett.* **2003**, *44*, 1591; (d) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5482.
3. (a) Ashimori, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949; (b) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590.
4. Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570.
5. (a) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532; (b) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921; (c) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368; (d) Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925; (e) Busto, E.; Gotor-Fernández, V.; Gotor, V. *Adv. Synth. Catal.* **2006**, *348*, 2626; (f) Duffey, T. A.; Shaw, S. A.; Vedejs, E. *J. Am. Chem. Soc.* **2009**, *131*, 14.
6. *N*-Heterocyclic carbene and amidine catalysts have also been applied to the rearrangement of oxindole derived enol carbonates: (a) Thomson, J. E.; Kyle, A. F.; Gallagher, K. A.; Lenden, P.; Concellón, C.; Morrill, L. C.; Miller, A. J.; Joannesse, C.; Slawin, A. M. Z.; Smith, A. D. *Synthesis* **2008**, 2805; (b) Joannesse, C.; Simal, C.; Concellón, C.; Thomson, J. E.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 2900.
7. Nguyen, H. V.; Butler, D. C. D.; Richards, C. J. *Org. Lett.* **2006**, *8*, 769.
8. Underwood, R.; Prasad, K.; Repic, O.; Hardtmann, G. E. *Synth. Commun.* **1992**, *22*, 343.
9. *Synthesis of* **6a**: A solution of 1,3-dimethyl-5-methoxyindolin-2-one (0.592 g, 3.1 mmol) in THF (4 mL) was added slowly to a solution of KHMDS (0.743 g, 3.7 mmol) in THF (4 mL) at −78 °C. The solution was stirred at −78 °C for 30 min, then transferred via cannula to a solution of phenyl chloroformate (0.47 mL, 3.7 mmol) in THF (5 mL) at −78 °C. The solution was allowed to warm to rt, then poured into 0.1 M HCl, and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 20–60 μm) with EtOAc/hexane (5:95) as the eluent, yielding **6a** as a colourless crystalline solid (0.61 g, 63%): Mp 59–61 °C; IR (Nujol) ν_{max} 1781 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44–7.39 (2H, m), 7.33–7.25 (3H, m), 7.13 (1H, d, J = 7.1 Hz), 6.97 (1H, d, J = 1.5 Hz), 6.86 (1H, dd, J = 7.1, 1.5 Hz), 3.84 (3H, s), 3.60 (3H, s), 2.20 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 2 × 154.6, 151.3, 139.4, 2 × 130.0, 128.0, 126.8, 2 × 120.8, 111.8, 110.1, 101.5, 96.6, 56.3, 28.8, 7.7. HRMS (m/z, EI): found for MH^+ 312.1234. $C_{18}H_{18}NO_4$ requires 312.1230. Analytical TLC, EtOAc/hexane (3:7), R_f = 0.65.
10. *Synthesis of* **7a**: A solution of catalyst **3** (5.1 mg, 0.008 mmol) in dichloromethane (5.0 mL) was added to **6a** (50 mg, 0.16 mmol). After 18 h, the solution was concentrated in vacuo. The crude residue was dissolved in dichloromethane and purified by flash column chromatography with CH_2Cl_2/hexane (90:10) to yield **7a** (50% yield, 48% ee): Mp 114–116 °C; IR (Nujol) ν_{max} 1761 (C=O), 1717 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.27–7.23 (2H, m), 7.14–7.10 (1H, m), 6.91–6.86 (3H, m), 6.82 (1H, dd, J = 7.8, 1.5 Hz), 6.75 (1H, d, J = 7.8 Hz), 3.75 (3H, s), 3.21 (3H, s), 1.69 (3H, s). ^{13}C NMR (100 MHz) δ 174.6, 168.6, 156.5, 150.6, 137.4, 131.3, 2 × 129.5, 126.3, 2 × 121.4, 113.7, 110.5, 109.3, 56.1, 26.9, 20.3. HRMS (m/z, EI): found for MH^+ 312.1233. $C_{18}H_{18}NO_4$ requires 312.1230. HPLC (Chiralcel OD, 0.46 cm × 25 cm, 95:05 hexane/*i*-propanol, 1.0 mol/min) T_R = 19.6 min (minor), T_R = 23.5 min (major). Analytical TLC, 35% EtOAc/hexane, R_f = 0.31.
11. HPLC data for **7d** (Chiralcel OD, 0.46 cm × 25 cm, 98:2 hexane/*i*-propanol, 1.0 mL/min). T_R = 19.6 min (major), T_R = 22.3 min (minor). Analytical TLC, 30% EtOAc/hexane, R_f = 0.54.
12. *Recrystallisation of* **7a**: A solution of **7a** (25 mg, 48% ee) in 4 mL of HPLC grade hexane/*i*-propanol (6:1) was allowed to stand open to the atmosphere for one week at room temperature. Pale yellow square shaped crystals surrounded by a viscous liquid were obtained. The crystals were washed with a little amount of hexane followed by a little amount of methanol. HPLC (Chiralcel OD) revealed the crystals (12 mg, 48%) to be a perfect racemate of **7a,** and the evaporated mother liquor (12 mg, 48%) to be **7a** with 95% ee.
13. (a) Lorenz, H.; Polenske, D.; Seidel-Morgenstern, A. *Chirality* **2006**, *18*, 828; (b) Polenske, D.; Lorenz, H.; Seidel-Morgenstern, A. *Cryst. Growth Des.* **2007**, *7*, 1628.
14. *Crystal data* **3**: $C_{44}H_{39}CoN_2$, M = 654.70, orthorhombic, a = 10.7478(13), b = 11.808(2), c = 26.305(5) Å, α = 90°, β = 90°, γ = 90°, V = 3338.4(9) $Å^3$, space group $P2_12_12_1$, Z = 4, D_c = 1.303 Mg/m^3, μ = 0.549 mm^{-1}, reflections measured 15287, reflections unique 6527 with R(int) = 0.0976, T = 120(2) K, final R indices [$F^2 > 2\sigma(F^2)$] R_1 = 0.0658, wR_2 = 0.1059 and for all data R_1 = 0.1683, wR_2 = 0.1337. Absolute structure parameter = 0.02(2). CCDC No. = 720582.
15. Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436.