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An Efficient Catalytic Asymmetric Route to 1-Aryl-2-imidazol-1-yl-ethanols

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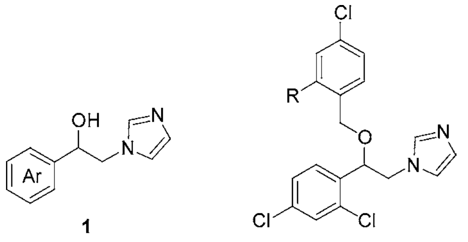
Abstract:

The asymmetric hydrogenation of 1-aryl-2-imidazol-1-yl-ethanones offers a concise route to homochiral 1-aryl-2-imidazol-1-yl-ethanols. Catalytic asymmetric transfer hydrogenation with formic acid using [(*R*,*R*)-TsDPEN]Ru(Cymene)Cl as precatalyst was shown to be effective in this transformation. Preliminary process development showed that the hydrogenation could be carried out under mild conditions at a molar substrate-to-catalyst (*S*/*C*) ratio of 1000−2000.

Chiral alcohols are fundamentally important building blocks in the pharmaceutical and fine chemical industry. There is a constant need to discover and develop new methods capable of supplying such building blocks containing an increasingly diverse range of structural features.

The authors recently became interested in developing a route to 1-phenylethanols bearing an imidazolyl substituent α- to the alcohol **1**. Racemic alcohols of this type have found widespread use in topical fungicides such as econazole **2a** and miconazole **2b** (Figure 1).[1]

While the use of racemic chiral alcohols is suitable for some of the existing topical applications, the trend within the pharmaceutical industry is to utilise single isomer chiral material;[2] therefore, a route to such chiral alcohols in high enantiomeric excess is desirable.[3] Although the resolution of some 2-(imidazol-1-yl)-1-(aryl)ethanols via the formation of diastereomeric salts has been demonstrated,[4] an asymmetric synthesis offers a potentially more general and efficient route to compounds such as **1**. While there are many synthetic approaches that furnish chiral alcohols in high enantiomeric excess, catalytic asymmetric hydrogenation offers several advantages as it can easily be applied to a wide range of substrates, the utilisation of material is high, and waste and byproducts can be drastically reduced. Two outstanding catalytic asymmetric hydrogenation technologies have been developed in recent years for the enantioselective reduction of ketones. First, bisphosphino ruthenium diamine complexes have been shown to be very efficient catalysts for the hydrogenation of simple prochiral ketones with gaseous hydrogen, furnishing the desired alcohols with very high enantioselectivity.[5] Second, monosulfonated diamino ruthenium arene complexes, which utilise hydrogen donors such as propan-2-ol and formic acid as hydrogen sources, have been used to reduce ketones with similarly high enantioselectivities.[6]



1

R = H econazole **2a**
R = Cl miconazole **2b**

Figure 1. **1-Aryl-2-imidazol-1-yl-ethanol 1 and azole antifungal agents 2.**

3 4

Figure 2. **1-Phenyl-2-imidazol-1-yl-ethanone 3 and 1-(2,4-dichloro-phenyl)-2-imidazol-1-yl-ethanone 4.**

Two imidazolyl acetophenone substrates were chosen to gain an understanding of the hydrogenation reaction of this type of substrate; 1-phenyl-2-imidazol-1-yl-ethanone **3** was synthesised from 2-bromoacetophenone and imidazole. 1-(2,4-Dichloro-phenyl)-2-imidazol-1-yl-ethanone **4** was made in a similar fashion from 2,2′,4′-trichloroacetophenone and imidazole.

Bisphosphino ruthenium diamine complexes have been shown to give extremely high catalyst efficiency demonstrated in the hydrogenation of simple acetophenone derivatives.[5] In light of these results this class of catalyst was examined in the first instance. Using the standard literature conditions no hydrogenation was observed using [((*S*)-XylylPhanePhos)Ru((*R*,*R*)-DPEN)Cl_2].[7] The use of triisopropyl borate as an additive has been shown to be effective in promoting the hydrogenation of acetylpyridines.[8] It is

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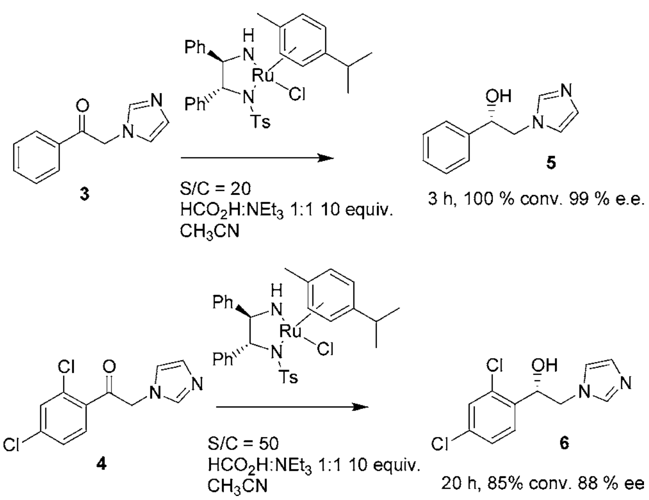
Scheme 1. **Preliminary results for the catalytic asymmetric transfer hydrogenation of 1-aryl-2-imidazol-1-yl-ethanones**



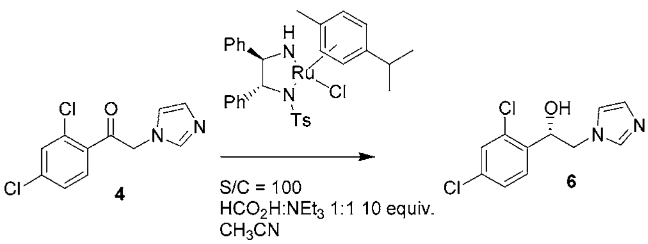
believed that the borate catalytically removes the β-amino alcohol from a postulated ruthenium adduct which lacks activity. However, for the hydrogenation of these substrates the addition of a borate ester did not promote the reaction.

When standard conditions for catalytic asymmetric transfer hydrogenation using [(*R*,*R*)TsDPEN]Ru(cymene)Cl as the catalyst precursor were applied, both ketones were reduced to the corresponding 1-aryl-2-imidazol-1-yl-ethanols. The hydrogenation of 1-phenyl-2-imidazol-1-yl-ethanone **3** proceeded to completion yielding (*S*)-2-imidazol-1-yl-1-phenylethanol **5** with a 99% ee.[9] Under very similar conditions the hydrogenation of 1-(2,4-dichloro-phenyl)-2-imidazol-1-yl-ethanone proceeded to 85% conversion and 88% ee (Scheme 1). Bearing in mind the incomplete reaction and the high catalyst loading used, there was obviously considerable scope for optimising the reaction conditions for the formation of **6**.

To improve catalyst utilisation the reaction for substrate **4** was repeated at higher temperatures (Table 1). As can be seen from these results, the reaction will tolerate a range of temperatures and the alcohol is stable to the reaction conditions even when held at 70 °C for 20 h. The selectivity appears to fall slightly as temperature is increased; however, these variations are similar in magnitude to the variability of the analytical method. It is more significant that at the higher temperatures unidentified impurities become apparent in the ^{1}H NMR spectra of the crude reaction products. At 40 °C complete conversion could be achieved for overnight reactions at significantly lower catalyst loadings (Table 2, entries 6 and 7).

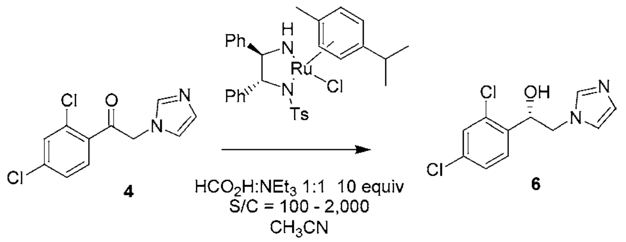
The choice of solvent in which the reaction is run had a dramatic effect on selectivity, catalyst utility, and rate (Table 3). Acetonitrile gave the highest reactivity but with modest selectivity (entry 7). Although DMF gave rise to a high initial conversion (37% in 2 h), the reaction slowed considerably and after 20 h had only reached 76% conversion (entry 4). Dichloromethane emerged as the pre-eminent solvent giving one of the best selectivities and nearly complete conversion within 20 h at *S*/*C* = 1000 (entry 3).

Table 1. **Effect of temperature on conversion and selectivity for the catalytic asymmetric transfer hydrogenation of 1-(2,4-dichloro-phenyl)-2-imidazol-1-yl-ethanone 4**



entry	temp °C	conversion %		ee %	
		2 h	20 h	2 h	20 h
1	25	84	100	86	85
2	40	100	100	84	85
3	55	100	100	82	84
4	70	100	100	83	83

Table 2. **Effect of temperature on conversion and selectivity for the catalytic asymmetric transfer hydrogenation of 1-(2,4-dichloro-phenyl)-2-imidazol-1-yl-ethanone 4 at reduced catalyst loading**



entry	molar *S*/*C*	temp °C	conversion %		ee %
			2 h	20 h	
1	100	25	89	100	85
2	200	25	59	100	81
3	300	25	47	100	86
4	400	25	35	100	87
5	600	25	24	100	86
6	1000	40	50	100	81
7	2000	40	36	100	81

By increasing the overall reaction concentration, the amount of formic acid and triethylamine could be reduced to 5 equiv while still obtaining complete conversion at a reasonable catalyst loading within a practical reaction time frame. These conditions (*S*/*C* 1000, 40 °C, CH_2Cl_2) were reproduced on a 16 g input of 1-(2,4-dichloro-phenyl)-2-imidazol-1-yl-ethanone, the rate and selectivity observed in the smaller scale reaction was maintained for the larger scale reaction with complete conversion achieved in 26 h and the product obtained in 91% ee. The optimised conditions were also applied at a higher catalyst loading (*S*/*C* = 200) to the asymmetric transfer hydrogenation of 1-phenyl-2-imidazol-1-yl-ethanone which gave (*S*)-1-phenyl-2-imidazol-1-yl-ethanol in 97% ee.

In conclusion, we have demonstrated the application of catalytic asymmetric transfer hydrogenation to the synthesis of an interesting and challenging class of substrates, where

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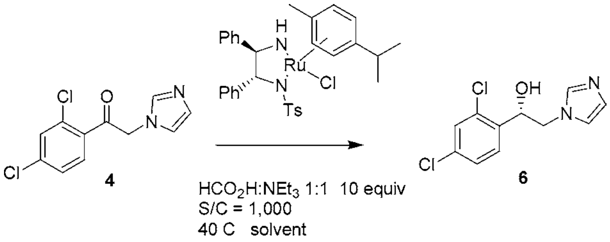
(9) Stereochemistry is assigned on the basis of the rotation compared to literature data for the (*R*)-enantiomer: Kotsuki, H.; Wakao, M.; Hayakawa, H.; Shimanouchi, T.; Shiro, M. *J. Org. Chem.* **1996**, *61*, 8915.

Table 3. **Effect of solvent on conversion and selectivity for the catalytic asymmetric transfer hydrogenation of 1-(2,4-dichloro-phenyl)-2-imidazol-1-yl-ethanone 4**



entry	solvent	conversion % 2 h	20 h	90 h	ee %
1	MTBE	13	75	97	92
2	toluene	11	59	97	92
3	CH$_2$Cl$_2$	30	98		93
4	DMF	37	76		87
5	^{i}PrOH	7	33	30	93
6	EtOAc	15	74	99	89
7	CH$_3$CN	50	>98		81

the bisphosphino ruthenium diamine complexes were found to be ineffective. During the preliminary process development, conditions were discovered that allowed for efficient utilisation of catalyst and reagents and thus furnish a practicable synthetic route.

Experimental Section

1-(2,4-Dichlorophenyl)-2-imidazol-1-yl-ethanone 4: A solution of 2,2′,4′-trichloroacetophenone (36.9 g, 0.12 mol) in dichloromethane (50 mL) was added dropwise over 30 min to a suspension of imidazole (24.5 g, 0.36 mol) in dichloromethane (100 mL). The mixture was heated to 40 °C for 2 h and then overnight at room temperature. The reaction mixture was washed with water (2 × 100 mL) and brine (100 mL) and dried (MgSO$_4$), and solvent was removed under vacuum to give a red oil. The oil was recrystallised twice from hot methanol (120 mL) to give the product as a white powder (17.73 g, 58% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.34 (s, 2H), 6.93−6.95 (m, 1H), 7.13 (br, 1H), 7.38 (dd, J = 8 and 2 Hz, 1H), 7.51 (d, J = 2 Hz, 2H), 7.57 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 55.5, 120.0, 127.9, 129.8, 130.8, 131.1, 132.5, 134.1, 138.1, 139.2, 193.7.

(*S*)-1-(2,4-Dichlorophenyl)-2-imidazol-1-yl-ethanol 6: A flask was charged with 1-(2,4-dichlorophenyl)-2-imidazol-1-yl-ethanone (16.3 g, 63.9 mmol) and [(*R*,*R*)-TsDPEN Ru-(Cymene)Cl (40 mg, 63 μmol). A nitrogen atmosphere was established, and dichloromethane (50 mL) and triethylamine (44 mL, 0.32 mol) were added. Formic acid (12.5 mL, 0.32 mol) was added over a period of an hour via syringe pump. During the addition, the temp rose slowly to 30 °C. The mixture was heated at 40 °C for 26 h. NaHCO$_3$ (saturated solution, 100 mL) was cautiously added, and the organic layer was separated and washed with water (100 mL), NaHCO$_3$ (100 mL), water (100 mL), and brine (100 mL) and dried (MgSO$_4$). Solvent was removed to give a red glassy mass which crystallised on standing to give the product (16.1 g, 98% yield, 91% ee). ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.84 (dd, J = 8 and 14 Hz, 1H), 4.19 (dd, J = 2 and 14 Hz, 1H), 5.21 (dd, J = 2 and 8 Hz, 1H), 6.81 (br, 1H), 6.89 (br, 1H), 7.30 (dd, J = 2 and 8 Hz, 1H), 7.36 (br, 1H), 7.39 (d, J = 2 Hz, 1H), 7.60 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 58.4, 69.7, 120.4, 128.0, 129.1, 129.3, 132.3, 134.4, 137.9. $[\alpha]^{25}_{D}$ = +83.8 (c = 0.998, MeOH, 91% ee), lit.[10] +88 (c = 1.06, MeOH, 98.8% ee); Chiral analytical assay: Chiralpak AS-H 250 × 4.6 mm × 5 μm, mobile phase heptane/ethanol 90/10, flow rate 1 mL/min, temp ambient, detector 220 nm, retention times 6.77 min (*S*)-(+) and 8.70 min (*R*)-(−), starting material 19.6 min.

1-Phenyl-2-imidazol-1-yl-ethanone 3: 2-Bromoacetophenone (11.89 g, 59.7 mmol) was added in portions to a solution of imidazole (8.63 g, 127 mmol) in dichloromethane (100 mL) (exothermic). After stirring at room temperature for 3 h, the reaction was quenched with water (100 mL). The organic layer was washed with brine during which time a white solid formed which was removed by filtration. Solvent was removed under vacuum, the residue was dissolved in ethyl acetate and (150 mL) filtered, and the solvent was removed again to give a light brown solid (7.54 g, 68%, yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.41, (s, 2H), 6.96 (br, 1H), 7.15 (br, 1H), 7.51−7.57 (m, 3H), 7.64−7.70 (m, 1H), 7.96−8.00 (m, 2H).

(*S*)-1-Phenyl-2-imidazol-1-yl-ethanol 5: A solution of [(*R*,*R*)-TsDPEN]Ru(Cymene)Cl[11] (3.5 mg, 5.5 μmol) in dichloromethane (5.5 mL) was prepared in a Schlenk tube under nitrogen. A 1 mL aliquot (1 μmol) was taken for the hydrogenation reaction. A solution of 1-phenyl-2-imidazol-1-yl-ethanone (0.186 g, 1 mmol) in dichloromethane (2 mL) was prepared under nitrogen, and triethylamine (1.4 mL, 9 mmol) and catalyst solution (1 mL) were added followed by formic acid (0.4 mL, 9 mol). The mixture was stirred at 40 °C for 22 h. Sodium bicarbonate solution (saturated, 10 mL) was added, and the product was extracted into dichloromethane. The organic layer was washed with water (10 mL) and dried (MgSO$_4$); the removal of solvent gave the product as a white solid 97% ee. ^{1}H NMR (400 MHz, d_6-DMSO) δ 4.08 (dd, J = 8 and 14 Hz, 1H), 4.18 (dd, J = 4 and 14 Hz, 1H), 4.83−4.89 (m, 1H) [4.08, 4.18 and 4.86 signals ABX system], 6.88 (br, 1H), 7.16 (br, 1H), 7.29−7.34 (m, 1H), 7.34−7.42 (m, 4H), 7.54 (br, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 53.9, 72.4, 120.4, 126.4, 127.7, 128.1, 128.4, 138.1, 143.0. $[\alpha]^{25}_{D}$ = +46.1 (c = 0.98, EtOH, 97% ee, lit.[9] −47.6 for (*R*)-enantiomer); Chiral analytical assay: Chiracel OD-H 250 × 4.6 mm × 5 μm, mobile phase heptane/ethanol 92/8, flow rate 1 mL/min, temp ambient, detector 210 nm, retention times 21.8 min (*S*)-(+) and 24.3 min (*R*)-(−).

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