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Catalytic asymmetric oxonium ylide - [2,3] sigmatropic rearrangement with diazocarbonyl compounds : First use of C_2-symmetry in Rh(II) carboxylates.

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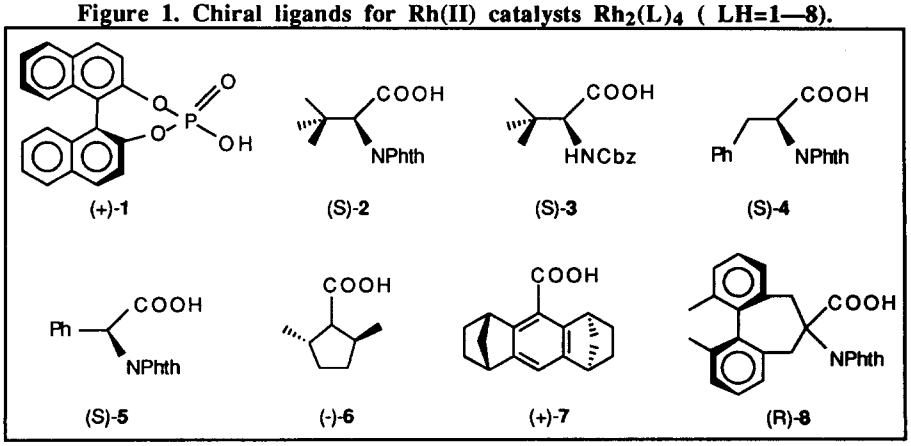
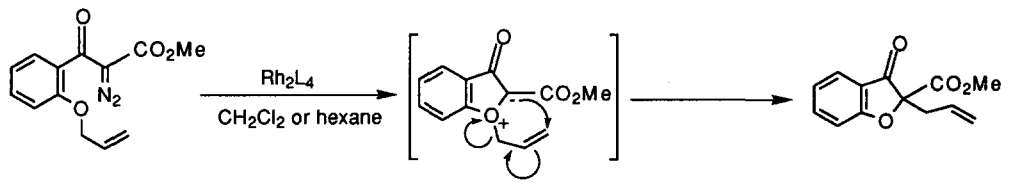
Abstract: Several new chiral rhodium(II) catalysts have been synthesised for evaluation as catalysts in asymmetric oxonium ylide-[2,3] sigmatropic rearrangement of diazocarbonyl substrates; a catalyst derived from (*S*)-*tert*-leucine afforded a chiral benzofuranone derivative with an ee of 60 %. © 1997 Elsevier Science Ltd.

Metal carbenes derived from α-diazocarbonyl compounds add to nitrogen, oxygen and sulfur-containing substrates to form ylides whose subsequent reactions have found many useful applications in the synthesis of complex molecules.[1,2] Of particular interest is the combination of catalysed intramolecular ylide formation and [2,3] sigmatropic rearrangement in allylic systems leading to heterocycles.[3] The usefulness of this tandem process would be significantly enhanced if it could be conducted as an enantioselective asymmetric synthesis through the use of chiral catalysts. Several other characteristic metal-catalysed diazocarbonyl processes, notably cyclopropanation and C-H insertion[1], are capable of high levels of enantioselectivities. Earlier work from our laboratory has shown that the Rh(II)-phos **1**[4] (Figure 1) is an efficient catalyst for oxonium ylide-[2,3] sigmatropic rearrangement with substrates of the type shown in scheme 1. Although modest, the enantiocontrol (30% ee) observed in this reaction indicated for the first time that the catalyst and its ligands are not fully dissociated from the ylide prior to bond formation in the sigmatropic rearrangement step.

Figure 1. Chiral ligands for Rh(II) catalysts $Rh_2(L)_4$ (LH=1—8).



We have completed a more extensive survey of the use of chiral catalysts for this transformation and we now report the performance of rhodium (II) carboxylates[5,6] (Figure 1) derived from N-phthaloyl and N-Cbz-(*S*)-*tert*-leucine, **2**[7] and **3**, N-phthaloyl-(*S*)-phenylalanine **4**[7], and N-phthaloyl-(*S*)-phenylglycine **5**. N-phthaloyl amino acids have emerged as ligands of choice for some intramolecular aromatic substitution reactions of diazoketones.[7] We have also synthesised a new family of rhodium(II) carboxylates **6** - **8** containing features of C_2 symmetry, including one derived from the recently reported α-amino acid[8] whose chirality results from the presence of a C_2 biaryl grouping. Its phthaloyl derivative **8**, obtained in 96% yield following a standard procedure[9], was used as the ligand. Carboxylic acid **6**[10,11] was prepared from (*S*,*S*)-2,5-hexanediol[12] via the corresponding ditosylate, and the C_2 symmetric benzoic acid **7** was prepared from the corresponding aldehyde[13] via potassium permanganate oxidation in benzene catalysed by 18-crown-6.[14,15]



9 **10**

Scheme 1

Table. Dirhodium(II) catalysed asymmetric oxonium ylide-[2,3] sigmatropic rearrangement of (**9**) to (**10**).

Ligands(L)	Solvent	Temperature	Yield %	ee / %[a]	Major isomer[b]
2	CH_2Cl_2	40 °C	97	47	(-)-A
2	Hexane	69 °C	86	60	(-)-A
2	Hexane	20 °C	96	60	(-)-A
3	CH_2Cl_2	20 °C	83	15	(+)-B
3	Hexane	20 °C	88	27	(+)-B
4	Hexane	69 °C	94	21	(-)-A
5	Hexane	69 °C	95	27	(-)-A
6	CH_2Cl_2	40 °C	98	3	(-)-A
6	Hexane	69 °C	92	4	(-)-A
7	CH_2Cl_2	40 °C	94	18	(-)-A
7	Hexane	20 °C[c]	96	29	(-)-A
8	CH_2Cl_2	40 °C	45[d]	17	(+)-B
8	Hexane	69 °C	73	25	(+)-B

[a]Enantiomeric excesses were measured by ^{1}H NMR shift study using europium (III) tris[3-(heptafluoropropylhydroxymethylene) (+)-camphorate] ($Eu(hfc)_3$).

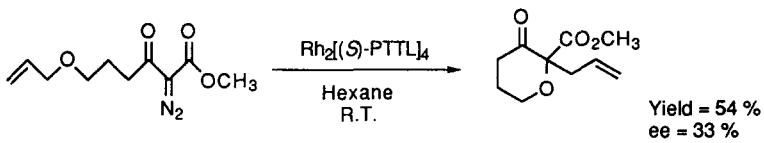
[b]Major isomer refers to the chemical displacement observed by ^{1}H NMR spectroscopy using chiral shift reagent: "A" is the peak of higher ppm; "B" is the peak of lower ppm.

[c]Reaction carried out at room temperature for 2 days, then completed under reflux for 1h.

[d]This reaction did not go to completion.

The realisation of catalytic asymmetric oxonium ylide-[2,3] sigmatropic rearrangement reactions with diazo keto ester **9**[16] using these diverse chiral dirhodium (II) catalysts is evident from the table. All reactions were carried out in CH_2Cl_2 or hexane at room temperature and also under reflux to give the product **10** (Scheme 1) in excellent yield (Table). As previously established by Davies[17] and Doyle[18] in cyclopropanation, a beneficial effect on the asymmetric induction in [2,3]-sigmatropic rearrangement was observed when hexane was used as a solvent, but a temperature effect was less evident. This was the case with catalyst **2** (table) in hexane where the same enantiomeric excess (60%) was observed both at room temperature and at 69 °C.

Although C_2-symmetric chiral catalysts from **6-7** were chemically very active, modest ee values were observed (up to 29% ee). Among the N-protected amino acids ligands, the N-phthaloyl-*tert*-leucinate **2** provided the highest levels of enantiocontrol (60% ee); using the N-Cbz-*tert*-leucinate, the ee value decreased to 27%. The encouraging results also obtained with the new ligand **8** should allow this new family of rhodium (II) carboxylates with ligands using C_2-symmetry to play an interesting role in terms of the future of asymmetric induction in catalysed decomposition of diazocarbonyl compounds. The potential of these new catalysts is being applied to some synthetically more demanding cyclic ethers found in natural products.



11 **12**

Scheme 2

Following the work of Pirrung and coworkers[19] on the cyclisation of diazoester **11** with rhodium(II) acetate, we prepared this compound (Scheme 2) as a precursor for asymmetric oxonium ylide-[2,3] sigmatropic rearrangement. The reaction was carried out using Rh(II) N-phthaloyl-*tert*-leucinate **2** as catalyst and the first enantiomeric excess has been obtained for this type of six-membered cyclic ethers (**12**). Although the ee was moderate (33% ee), we are continuing to explore ways of enhancing the enantioselectivity of these Rh(II) catalysts in carbenoids transformations.

References and Notes

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9. A stirred solution of (R)-6-amino-1,11-dimethyl-6,7-dihydro-5H-dibenzo[a,c] cycloheptene-6-carboxylic acid[8] (50 mg, 1.77×10^{-4} mol), phthalic anhydride (27.6 mg, 1.86×10^{-4} mol) and triethylamine (catalytic amount) in dry toluene (2.5 ml) was refluxed under argon for 12 h; the water

evolved from the reaction was separated and collected by a Dean Stark apparatus. The solution was evaporated to dryness before it was taken up in CH_2Cl_2 (6 ml) and washed with water (1.5 ml), HCl 2M (1.5 ml) and brine (1.5 ml). The organic layer was dried over $MgSO_4$ and evaporated, affording 70 mg (96 % yield) of pure compound (R)-**8** as a white crystalline powder. mp 281-282 °C; $[\alpha]^{20}_D$ = + 177.8 (c 0.5, $CHCl_3$); ^1H (300 MHz, $CDCl_3$, 25 °C) : δ (ppm): 2.18 (s, 3H, CH_3); 2.20 (s, 3H, CH_3); 3.08 (d, 1H, J = 13.7 Hz, C(H)H); 3.12 (d, 1H, J = 14.5 Hz, C(H)H); 3.23 (d, 1H, J = 14.5 Hz, CH(H)); 4.35 (d, 1H, J = 13.7 Hz, CH(H)); 6.8 (br d, 1H, J = 7.8 Hz, Ar); 7.07 (m, 2H, Ar); 7.25 (m, 3H, Ar); 7.73 (m, 2H, Ar (Phth)); 7.81 (m, 2H, Ar (Phth)); ^{13}C (500 MHz, $CDCl_3$, 25 °C) : δ (ppm): 19.78 (CH_3); 19.83 (CH_3); 36.61 (CH_2); 37.93 (CH_2); 72.34 (HOOC*C*NPhth); 123.35 (Ar (Phth)); 126.12, 126.75, 127.16, 127.36, 129.59, 129.76 (Ar); 131.37, 134.25 (Ar (Phth)); 134.50, 135.13, 136.09, 136.24, 138.03, 138.37 (Ar); 168.81 (C=O (Phth)); 173.92 (COOH); ν_{max} (KBr)/cm^{-1} 1713, 1779 and 1760; M^+ calcd for $C_{26}H_{21}NO_4$: 411.1470; Found : 411.1458.

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11. Compound **6**: Colourless crystal. mp 45-47 °C; $[\alpha]^{20}_D$ = -63.8 (c 1.035, acetone); ^1H (300 MHz, $CDCl_3$, 25 °C) : δ (ppm) : 0.97 (d, J = 6.7 Hz, 3H, CH_3); 1.04 (d, J = 6.2 Hz, 3H, CH_3); 1.18 (m, 1H, C(*H*)H); 1.35 (m, 1H, C(*H*)H); 1.93 (m, 2H, CH(*H*)); 2.40 (m, 3H, CH);^{13}C (500 MHz, CDCl3, 25 °C): δ (ppm) : 17.09 (CH_3); 20.08 (CH_3); 33.35 (CH_2); 33.76 (CH_2); 35.92 (*C*HCH_3); 36.71 (*C*HCH_3); 55.83 (*C*HCOOH); 179.28 (COOH); ν_{max} (film)/cm^{-1} 1702; Anal. calcd for $C_8H_{14}O_2$: C 67.55; H 9.92. Found: C 67.71; H 9.70.
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15. To a vigourously stirred suspension of $KMnO_4$ (79 mg,5x10^{-4} mol) in benzene (15 ml), at room temperature, 18-crown-6 (132 mg, 5x10^{-4} mol) was added and the solution became purple. Then, (+)-1,2,3,4,5,6,7,8-octahydro-1:4,5:8-dimethanoanthracene-9-carboxaldehyde[13] (90mg, 3.78x10^{-4} mol) in benzene (5 ml) was introduced. The reaction was monitored by thin layer chromatography which revealed that it was completed after 3 days. The very dark mixture was filtered and the solid potassium salt was dissolved in KOH aq. 5%; the aqueous solution obtained was treated with some sodium sulfite to destroy the excess of $KMnO_4$ and filtered again. The aqueous phase was extracted once with ether to remove traces of crown ether and acidified with concentrated HCl. The precipitate formed was filtered, washed with cold water and dried to afford the pure compound (+)-**7** as a white solid (75mg, 78 % yield). mp 210-216 °C, decomp.; $[\alpha]^{20}_D$ = +131.8 (c 0.22, $CHCl_3$); ^1H (500 MHz, $CDCl_3$, 25 °C) : δ (ppm) : 1.15 (m, 4H); 1.46 (m, 2H); 1.68 (m, 2H); 1.90 (m, 4H); 3.30 (br s, 2H); 4.06 (br s, 2H); 7.15 (s, 1H); ^{13}C (500 MHz, $CDCl_3$, 25 °C) : δ (ppm) : 26.35, 26.98 (CH_2); 43.69, 43.72 (CH); 48.82 (CH_2); 116.70, 117.98, 146.60, 146.91 (Ar); 171.48 (COOH); ν_{max} (KBr)/cm^{-1} 1676; M^+ calcd for $C_{17}H_{18}O_2$: 254.1306; Found 254.1311.
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