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Parallel Synthesis Techniques in the Identification of New Chiral Dirhodium(II) Carboxylates for Asymmetric Carbenoid Insertion Reactions

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Abstract: New chiral dirhodium(II) carboxylate catalysts for asymmetric carbenoid Si-H insertion reactions have been identified using solution phase parallel synthesis techniques.

The principles of combinatorial and parallel synthetic techniques have already found application beyond the confines of the pharmaceutical industry and the search for new therapeutic agents.[1] The benefits of the approach have been demonstrated for chiral catalysts,[2] the identification of novel co-ordination complexes[3] and the preparation of superconductors.[4] The majority of contributions in the area of asymmetric synthesis have concentrated on parallel techniques since this methodology improves efficiency without introducing complex analysis and a deconvolution process to identify the catalyst of interest. A number of groups have published studies involving the preparation of ligands on a solid-support and evaluation of their potential as ligands either as bound or free species.[5] The limitations of these approaches include: (i) the lack of diversity in non-peptidic ligands, (ii) the introduction of a functional group on the ligand which acted as a point of attachment to the resin, and (iii) the potential variation between solid bound and free ligand. In this paper we demonstrate the potential of a parallel solution phase approach to optimisation of non-peptidic chiral ligands for a rhodium(II) catalyst used in the enantioselective Si-H insertion reaction of diazoesters with silanes.[6]

The development of chiral catalysts for asymmetric reactions of metal carbenoids has been widely studied of late, and a number of copper and rhodium based catalysts developed.[7] In continuation of our own work in the area of carbenoid insertion reactions of silanes, preliminary studies using methyl 2-(diazo)phenylethanoate and dimethylphenylsilane demonstrated a marked increase in enantioselectivity from 8% to 30% on changing the ligand from mandelic acid to α-methoxy-α-(trifluoromethyl)phenylacetic acid.[8] To further enhance the enantioselectivity,[9] a systematic search of alternative chiral carboxylic acid ligands was required, and parallel array technology allowed a wide variety of acids to be evaluated efficiently. The commercially available carboxylic acids, *ca.* 30,000 compounds (of which *ca.* 10,000 possess a "chiral flag"), contained within the Available Chemical Directory were identified and filtered to identify the mono-carboxylic acids containing no incompatible functional groups (*e.g.* primary amines). The resulting set, *ca.* 2000 compounds, was then clustered and the centroid of each of 80 clusters selected as a representative acid. The singletons produced during the process were not evaluated further because of the self-evident limitation on second generation arrays.

The representative chiral carboxylic acid ligand from one of each of the 80 clusters then underwent ligand exchange with a previously prepared dirhodium(II) carbonate species.[10] Typically, 20 chiral acids were subjected to the reaction conditions in parallel. Subsequent parallel vacuum filtration followed by drying allowed the isolation of the desired chiral dirhodium(II) carboxylate catalysts. The structures were confirmed by automated ^{1}H NMR and mass spectrometry analysis. From the original 80 acids used, 69 chiral dirhodium(II) carboxylate catalysts were isolated in this manner, the remaining chiral carboxylic acid ligands were recovered as unreacted starting material. Subsequently a dichloromethane solution of methyl 2-(diazo)phenylethanoate (10

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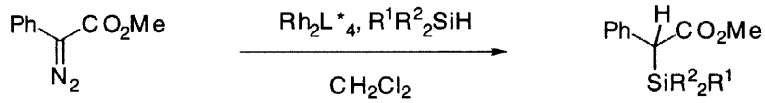
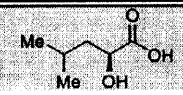
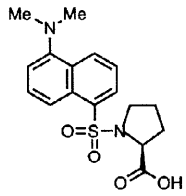
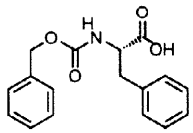
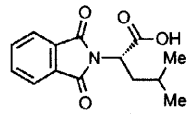
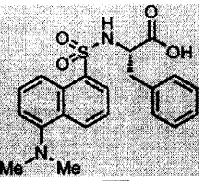
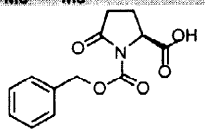
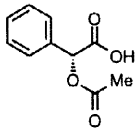
mg) and one of 3 silanes, with a varying degree of steric bulk, was then treated with one of each of the 69 previously prepared chiral dirhodium(II) carboxylate catalysts to effect the carbenoid Si-H insertion reaction (Scheme 1). Of the 69 chiral dirhodium(II) carboxylate catalysts used, 47 catalysed the desired Si-H insertion and gave the expected product, the remaining rhodium species showing no catalytic activity. Parallel purification through a small silica column (BondElut®) allowed the isolation of sufficient material for the determination of the enantioselectivities of the Si-H insertion products by automated chiral HPLC (Table 1).[11]



Scheme 1

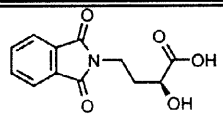
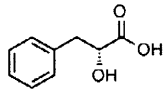
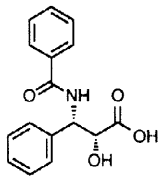
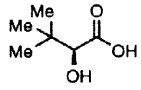
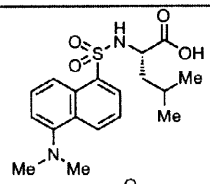
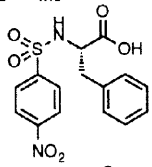
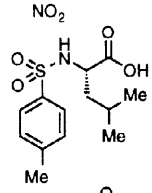
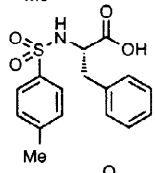
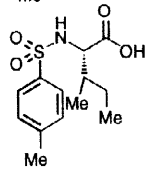
Table 1. Parallel screening of dirhodium(II) carboxylate catalysts; best 7 of initial 69

LIGAND (L*)	ENANTIOSELECTIVITY (%ee)		
	Me_2PhSiH	$^tBuMe_2SiH$	$^iPr_3SiH$
	23	39	53
	23	36	47
	32	41	43
	23	32	41
	25	43	48
	27	32	35
	15	17	15

This identified two chiral carboxylic acid ligands (α-hydroxyisocaproic acid and *N*-dansylphenylalanine) of significant interest, and hence a second generation array was constructed from the original 80 clusters to

identify further derivatives based on these two ligands. The results of these sets of parallel reactions are shown in Table 2.

Table 2. Parallel screening of dirhodium(II) α-hydroxycarboxylates and dirhodium(II) *N*-arenesulfonyl α-aminocarboxylates in silane insertion reactions

LIGAND (L*)	ENANTIOSELECTIVITY (%ee)			
	Me_2PhSiH	$^tBuMe_2SiH$	$^iPr_3SiH$ at rt	$^iPr_3SiH$ at -78 °C
	29	42	46	54
	15	26	41	30
	30	32	39	31
	11	24	34	30
	32	57	61	–
	23	48	55	64
	21	44	49	76
	21	35	39	56
	7	27	42	73

The second set of parallel reactions identified further dirhodium(II) carboxylate catalysts capable of effecting enantioselective Si-H insertion reactions, with the *N*-arenesulfonyl α-aminoacid set showing better selectivity than the α-hydroxyacids. In some, but not all cases, carrying out the reactions at -78 °C resulted in further improvement of the enantioselectivity; for example, from 49 to 76%ee in the case of *N*-(toluene-4-sulfonyl)-*L*-leucine as the chiral carboxylic acid ligand.

It is interesting that catalysts based on α-hydroxyacids and *N*-arenesulfonyl α-aminoacids were among the earliest chiral dirhodium(II) carboxylate catalysts investigated,[7] although the first studied ligands, mandelic acid and *N*-benzenesulfonylprolinate, give relatively poor results in our silane insertion reactions (8 and 12 %ee respectively for Me_2PhSiH).[8] However, the use of parallel synthesis techniques has resulted in the rapid identification of improved catalysts for enantioselective Si-H insertion reaction of diazoesters with silanes. Work is underway to optimise the enantioselectivity by using the newly identified ligands as lead structures, and applying conventional chemistry to synthesise other derivatives for improved enantioselectivity.

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