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Novel isomenthone-derived 1,3-diol ligands identified through parallel synthesis and screening catalyse an asymmetric aldol reaction†

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A library of new (+)-isomenthone-derived 1,3-diol ligands, containing 5 contiguous stereocentres (3 fixed, 2 variable), was prepared in 2 steps by parallel synthesis. Evaluation in parallel identified several different ligands from the library for catalysing a Mukaiyama aldol reaction with 87–90% e.e.

The application of parallel or combinatorial methods to identify new chiral catalysts has been the subject of considerable attention in recent years.[1] Solid-supported ligand synthesis has been one significant area, with amide and imine systems being popular constructs.[2] Solution-phase approaches have included screening arrays of pre-prepared or commercially available ligands against a target metal and process,[3] screening ligand arrays with metal and/or conditions variability,[4] and the evaluation of mixed ligand combinations.[5] Recent years have seen particularly important strides in analytical methods for detecting catalytic activity, such as IR thermography, which have potentially wide applicability and support the parallel approach.[6]

Almost all approaches use divergent ligand assembly but with common ligating functionality types within ligand structural diversification, and generate stereochemical diversity through isomer combinations. We were interested in evaluating an approach which used a chiral scaffold starting point to develop solution phase parallel diversification of ligand functionality types to 2 or 3 different ligating atom combinations, and which concurrently introduced limited stereochemical randomness (Fig. 1). The protocol was directed towards allowing generation of ligand subsets which would then be directly screenable against several different catalytic target reactions. Our choice of ligand scaffold was based on (+)-isomenthone derivatives which have been almost completely unexplored as a source of potential reagents, auxiliaries or ligands, although terpenoids in general have proven a rich source of efficient chiral controllers.[7] We envisaged that isomenthone chemistry could be extended to (−)-isopinocamphone as a pseudo-enantiomeric analogue.[8]

We had previously established that (+)-isomenthone **1** undergoes aldol reactions which are diastereoselective at C6 with universally exclusive *R* configuration to give **2** (established through a series of X-ray structure analyses) (Scheme 1). The side chain centre is obtained with variable diastereoselectivity dependent on the structure of R, and also the conditions employed.[8,9] To evaluate the facility for different elaborations from this entry point, several new types of isomenthyl derivatives have been prepared both through reactions at the ring carbonyl (variable diastereoselectivity§) and through elaboration of the side chain hydroxy functionality.[9]

This offers the possibility of generating diverse ligand structures from this scaffold, based on:

(1) variations in R (from aldol)

(2) post-aldol elaborations of the ring carbonyl (herein, reduction to give **3**)

(3) post-aldol elaborations of the side chain hydroxyl

(4) introduction of diastereochemical diversity specifically at 1 or 2 of the 5 contiguous stereocentres of (+)-isomenthone-derived ligands.

Our aim was to develop a protocol enabling generation of small ligand libraries from a large virtual library¶ (with wide variations in R, and different elaborations of both carbonyl and hydroxyl, with stereochemical flexibility), and which could be screened directly as subsets. These subsets were envisaged as being available for screening against multiple processes to amplify the total screening available without additional synthesis. Herein we report a protocol for parallel aldol synthesis (to **2**), followed by reduction (to **3**) which then allows for direct catalyst screening in parallel. This provides lead ligands catalyzing a model Mukaiyama aldol reaction with up to 90% e.e.

Synthesis of aldol products was optimized for parallel chemistry,‖ allowing 12-member aldol library generation in a reaction carousel. The aldol products were then reduced in parallel directly with LAH, and a minimum work-up afforded the diol ligands **3** of sufficient chemical purity for screening. Several of the ligands were formed as diastereomeric mixtures** (at either or both the hydroxyl-bearing centres) but these were not separated for the initial screening reactions. The reaction vessels were charged with toluene to provide solutions of the individual ligands for direct catalysis evaluation in parallel.

These members of the diol ligand library were screened in parallel against a Mukaiyama aldol reaction (Scheme 2),[10,11] using Et_2AlCl and ligand at 20 mol% catalyst loading, at

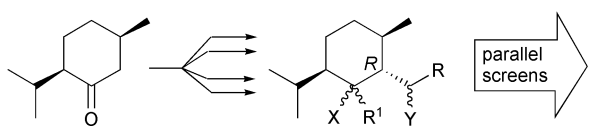
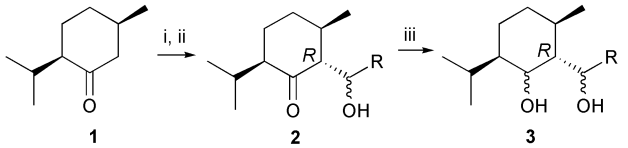
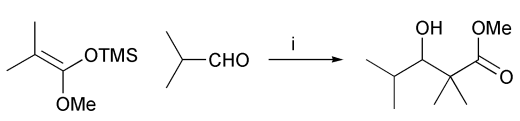


Fig. 1



Scheme 1 *Reagents and conditions*: i, LDA; ii, RCHO; iii, $LiAlH_4$.



Scheme 2 *Reagents and conditions*: i, Et_2AlCl, ligand library, 2 h, PhMe.

† Electronic supplementary information (ESI) available: HPLC data for Mukaiyama aldol products. NMR data for a pure reference sample of Mukaiyama aldol product, independently prepared selected examples of isomenthone aldol constituents and the diols included in the ligand array. See http://www.rsc.org/suppdata/cc/b2/b212769p/

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Table 1 Parallel screen using catalyst **3** for synthesis of **6**

Entry	R	e.e. (%)[a]
1	*p*-bromophenyl	89
2	2,5-dichlorophenyl	63
3	isopropyl[b]	35
4	2-pyridyl	88
5	*E*-2-phenylvinyl	84
6	phenyl	19
7	2-thiophenyl	72
8	*E*-crotyl	90
9	*p*-methoxyphenyl	87
10	2-naphthyl	72
11	3,4-methylenedioxyphenyl	77
12	2-furyl	77

[a] Absolute configuration preferred not determined. The sense of selectivity is, however, the same with all library members as determined by chiral HPLC. [b] Only this system screened as a single diastereomer.

ambient temperature (Table 1). The products were analyzed by chiral HPLC,†† and as shown in Table 1 four ligand systems catalyzed the reaction with 87–90% e.e. (entries 1, 4, 8, 9). Clearly, parallel evaluation could be iteratively employed to screen other reaction parameters such as solvent, ligand and catalyst loadings and ratio for further optimization for these ligands, or for other ligand sets using this same basic protocol.

Since most of the diol ligand solutions screened contained diastereomeric mixtures of a given ligand **3**, the likelihood is that enhanced e.e. could be achieved by using purified diastereomeric ligands. The alternative possibility is that non-linear diastereomeric ligand cooperativity effects may be observed, which, although less likely, is not unprecedented.[12] Future work will evaluate the diastereoisomeric ligand effects by diastereomer separation prior to screening.

This work demonstrates the viability of generating new ligand diversity from the (+)-isomenthone skeleton, and provides a practicable protocol for generating new ligands directly for catalysis screening. The library synthesis method can be extended to other aldol libraries, and to larger arrays with appropriate equipment. The initial work reported here identifies new chiral ligand leads with good e.e. In addition to this work, we have elaborated such aldol products in several other ways into different bi- and trifunctional ligand types, which will extend the applicability of screening these ligand systems to bi- and trifunctional arrays.[9]

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Notes and references

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§ Addition of hydride or various types of *C*-nucleophiles show a range of selectivities, some with complete (*S*)-preference.

¶ This approach could be extended to prepare and screen larger libraries (by using alternative equipment).

‖ The isomenthone enolate was generated over 5 mins (in THF), aldehyde added and the reaction quenched by addition of Amberlyst® 15 resin. Filtration allowed direct reuse of the product solutions for LAH reduction. Work-up involved addition of a minimal volume of water and NaOH (aq.), filtration, and sample evaporation before recharging with new solvent to provide ligand solutions for catalyst screening.

** TLC indicated complete consumption of isomenthone (stage 1) and complete reaction of aldols (stage 2). Pure aldol diastereoisomers from cinnamaldehyde and benzaldehyde (entries 5 and 6, Table 1) were isolated and X-ray structures obtained. Accurate diastereoisomeric ratios were not obtained for library members due to NMR overlap or HPLC co-elution.

†† Chiralpak A5; 90 : 10 hexane : propan-2-ol; 3.3 min; 4.1 min. No other materials observed.

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