Supramolecular Protecting Groups Can Impart Prosthetic Stereoselectivity to Catalytic Systems Employing Unmodified Achiral Heterogenous Catalysts.

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Abstract:

Use of homogeneous catalysis – typically based on scarce precious metals – remains a dominant approach to afford good yields of enantiopure compounds. Combining typical strengths of heterogenous catalysts (low cost, sustainable, recyclable) with those of precious metal-mediated homogenous catalysis (amenability to design for selectivity) is desirable: several approaches have been demonstrated (chiral material surfaces, modification of surfaces with chiral auxiliaries, immobilisation of chiral catalysts), but it remains a challenge. Here we present a systems catalysis approach, with a heterogenous material providing catalytic activity, and a separate host species controlling access to the catalyst to impart 'prosthetic' chiral selectivity. Since this non-covalent analogue to conventional covalent protecting group strategies is modular, the same substrate/host combination may be applied to a range of catalytic surfaces. The potential of this approach to achieve effective kinetic resolution is demonstrated in stereoselective synthesis of the drug (*R*)-cinacalcet.

Keywords: supramolecular chemistry, supramolecular protecting group, heterogenous catalysis, asymmetric catalysis, molecular recognition.

Introduction

Catalysis is fundamental to the making of the modern world, with the manufacture of most consumer products involving some form of catalysis. Efficient, selective, asymmetric (chiral) catalysis in particular is paramount in the manufacture of fine chemicals (e.g. pharmaceutical and agrochemical products) and, increasingly, advanced materials. Archetypal stereoselective chemical catalysts consist of well-defined, soluble (homogenous), metal-ligand complexes.[1–5] These require careful design and are often difficult to develop/produce, making them expensive. Furthermore, many incorporate precious metals like platinum and palladium,[6] deposits of which are limited, leading to sustainability concerns,[7] which are only partially addressed by a movement to earth-abundant metals.[8] Alternative approaches to homogenous catalysis include selective chiral 'poisoning' of catalysts,[9] organocatalysis,[10–15] reaction inside molecular containers ("Supramolecular Catalysts"),[16–24] and the use of enzymes:[25–30] all can offer some measure of selectivity, activity, and sustainability, but often to varying degrees beyond a narrow range of reactions, substrates, or conditions.

By contrast, heterogeneous (insoluble/solid) catalysts are widely used in industrial chemistry, and typically are relatively cheap, sustainable, stable, recyclable, and easy to produce/obtain.[31] However, heterogenous catalysts typically lack precisely-defined sterically-controlled active sites, akin to those which mediate control in homogenous catalysts, making design for (stereo)selectivity challenging.[26,32–38]

Attempts to achieve "the best of both worlds" – the selectivity of homogenous precious metal complexes, with the low cost and recyclability of heterogenous catalysts – have been numerous, but their success and adoption limited. Approaches to impart selectivity to catalytic surfaces by modifying them have included tethering otherwise-soluble

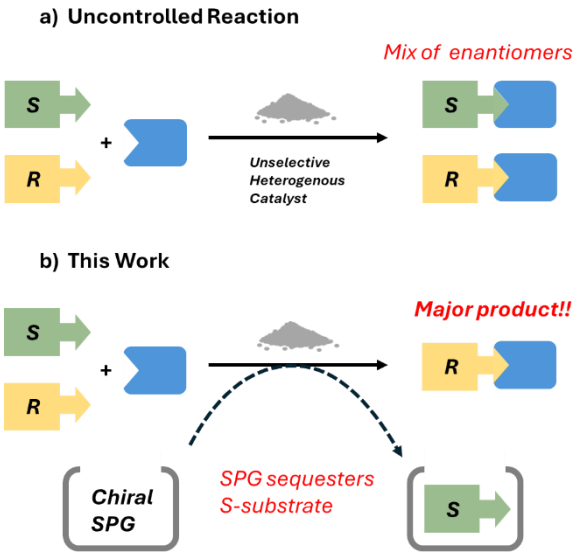
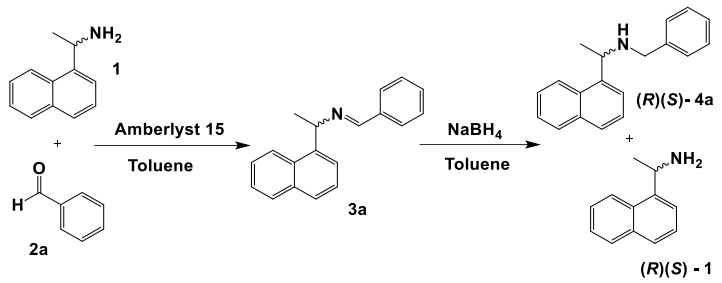


Figure 1. Supramolecular Protecting Groups (SPGs) impart prosthetic enantioselectivity to reactions mediated by unmodified achiral solid catalysts. In this work (b) a chiral SPG selectively recognises one enantiomer of substrate (*S*-enantiomer), allowing only one enantiomer to access catalyst.



Scheme 1. Model reductive amination reaction, which may be carried out over a range of temperatures (see SI, Section 2).

metal complexes to surfaces,[39] or depositing chiral compounds on their surface,[26,32–38] have met with some success, but are not widely reported in routine use. In all these approaches, the catalyst – or catalytic surface – is engineered for selectivity: a costly and laborious process, even when successful.

In this work, we explore an alternative: a modular systems approach, where instead of engineering the catalytic species for selectivity, we separate the roles of catalysis and selection (Fig. 1). A non-selective catalyst may be used, and "prosthetic" selectivity (selectivity not mediated by the catalyst) is imparted by molecular recognition of one enantiomer by a Supramolecular Protecting Group (SPG), preventing its reaction in a manner analogous to a covalently-bound protecting group. Using SPGs to control reactivity, where molecular recognition prevents access of reagents or catalysts to a substrate – or a region of a substrate – has been reported for some time,[40] including for regioselectivity[41–43] and kinetic resolution reactions,[44,45] particularly following a landmark publication by Gibb *et al.* applying this principal to control a simple, otherwise-unselective, ester hydrolysis reactions.[44] Indeed, the approach might be more well-recognised but for the diverse range of terms used to describe it ('Supramolecular Inhibitors', 'Noncovalent Auxiliaries', 'Shadow Mask', among others).[46] However we are not aware of examples incorporating this into a catalytic system employing an unselective solid catalyst, which may be recycled.

Specifically, here we demonstrate how a Supramolecular Protecting Group may be applied to impart stereoselectivity to an otherwise-achiral catalytic system, a reductive amination: a common reaction in pharmaceutical synthesis.[47] We employ an unmodified, commercially-available, solid acid catalyst, which is active, but not stereoselective, and an established host molecule (a modified β-cyclodextrin) which provides stereoselectivity by recognising one enantiomer of the starting material selectively, preventing its reaction. We demonstrate this system in kinetic resolution in a model reductive amination reaction, and in the stereoselective synthesis of the drug *(R)*-cinacalcet, sold under the names Sensipar®, Mimpara®, or Regpara® in enantiopure form,[48,49] from a racemic amine.

Results and Discussion

Catalysis Of Model Reductive Amination By Unselective Solid Catalyst

To establish our approach, we chose a model reductive amination of racemic 1-(1-napthyl)ethylamine (**1**), initially reacting with an aldehyde (**2**) to produce an imine (**3**), which can then be reduced to form the amine product (**4**).

The amine, **1**, was chosen, as a stereoselective host/SPG (6-O-triisopropylsilylated β-cyclodextrin, "**TIPS-β-CD**", see Fig. 2) for this amine is already established by Kida *et al,*[45] achieving stereoselective recognition of the ***(S)*-1** and kinetic resolution in more simple model reactions at low temperatures (-20 °C). *Amberlyst 15*, a polymeric resin with strongly acidic sulfonic acid groups, with was chosen as an available, affordable, achiral, and reusable solid acid catalyst.[50,51]

Exploring reaction conditions in the absence of **TIPS-β-CD**, in toluene (see SI, Table S1; in the absence of protic solvents) we found that the imine (**3a**) formation reaction proceeds only in the presence of the *Amberlyst 15* catalyst (Brønsted acid) at reduced temperatures (Table S1, Entries 4 & 5). Furthermore, the subsequent reduction of the imine (without isolation) to yield the amine (**4a**) product requires the catalyst, even at room temperature (Table S1, Entries 7 & 8): likely as the catalyst acts as a source of H^+ (4.7 mmol H^+ per g)[52] for the initiation of the reduction in the presence of $NaBH_4$ in an aprotic solvent.[53] Taken together, in the low temperature conditions required for selective recognition of ***(S)*-1** by **TIPS-β-CD**, the model reaction only proceeds when catalysed by *Amberlyst 15*.

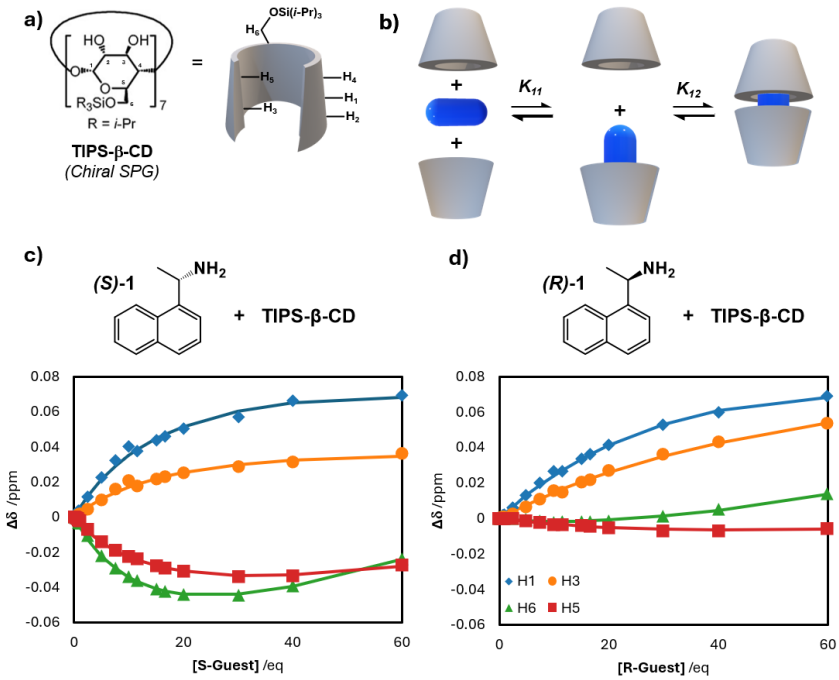


Figure 2. (a) Structure of **TIPS-β-CD**, with key protons labelled, and (b) schematic representation of 2:1 complexation of **1** by **TIPS-β-CD** (to yield **1**⊂**TIPS-β-CD**$_2$). (c and d) ^{1}H NMR chemical shift of **TIPS-β-CD** (0.05 M) protons on titration with ***(S)*-1** (c) and ***(R)*-1** (d) in d$_8$-toluene at room temperature (*ca.* 298 K); lines correspond to fitting to stepwise 2:1 binding [see SI, Section 5].

An important advantage of solid catalysts is recyclability. To screen the recyclability of the *Amberlyst 15*, two reactivation processes were applied to the material after catalysing reaction between **1** and **2a** at in our reaction conditions (see Fig. S1). While reuse of the catalyst after simple washing with an organic solvent (CH_2Cl_2) led to decreased activity in subsequent reactions, an addition wash with dilute hydrochloric acid maintained the efficiency of the catalyst for at least three subsequent reactions (likely due to the presence of organic material on the surface, which is eliminated after acid treatment).

Selective Recognition Of Amine *(S)*-1 In Reaction Conditions.

To confirm and explore enantioselective recognition of the substrate, **1**, by **TIPS-β-CD** (see Fig 2a) in our model reaction's solvent, toluene, we synthesised the host (in a modification of reported procedures for microwave reaction, see SI, Section 4)[54] and performed ^{1}H NMR binding titrations with both enantiomers of amine **1**.

At room temperature, progressive changes in the chemical shift of the well-resolved host proton resonances (H1, H3, H6, H5, see Fig. 2 and SI Section 5) on guest addition reveals binding with a fast exchange regime, in contrast to reports of **1**/**TIPS-β-CD** binding in cyclohexane/benzene which observed slow exchange.[45] Some preference for binding of ***(S)*-1** at room temperature is observable in binding response of H1, consistent with reports in other solvents.[45] Consistent with reports of **1**/**TIPS-β-CD** binding in cyclohexane or benzene, a Job's plot suggests 2:1 host:guest binding (see SI Section 5), however, observing chemical shift changes at multiple host protons, we did not find exclusively monotonic responses, inconsistent with the concerted 2:1 binding model applied elsewhere.[45,54] Instead, we applied a more orthodox stepwise 2:1 binding model to fit binding (see SI, Section 5), finding increased first and second binding constants for ***(S)*-1** (estimating K_{11} as 0.22 M and K_{12} as 2000 M), relative to ***(R)*-1** (estimating K_{11} as 0.08 M and K_{12} as 1220 M). A Rotating Frame Overhauser Effect Spectroscopy (ROESY) NMR spectrum of the *(R/S)*-**1** recognition by and **TIPS-β-CD** in the same conditions (see SI, Section 5) further demonstrates inclusion, with interactions between the aromatic protons of **1** and cavity protons (H-3 and H-5) of **TIPS-β-CD** observable.

Furthermore, comparing chemical shift changes at multiple host protons shows that the nature of binding of ***(S)*-1** and ***(R)*-1** is distinct qualitatively. While binding of ***(S)*-1** leads to marked changes in all four protons plotted in Figs 2c and 2d, binding of ***(R)*-1** affects H5 (deeper in the cyclodextrin cavity) rather less, suggesting a distinct binding conformation for ***(R)*-1** resulting from a poorer 'fit' in the host**.** Since our reaction was intended to be

performed at -20 °C (-253 K), a series of ^{1}H spectra were acquired at this temperature (see SI, Fig. S6). Unusually, while all room-temperature spectra manifest fast guest exchange regimes, these spectra suggest slow guest exchange for the binding of ***(S)*-1**, but fast exchange of ***(R)*-1**: promising for selective ***(S)*-1** protection, while allowing ***(R)*-1** to react in these conditions.

SPG-Mediated Kinetic Resolution With An Achiral Catalyst

Bringing together our model reaction, and selective recognition of amine ***(S)*-1**, we evaluate the **TIPS-β-CD** as an SPG in the reaction between racemic **(*R*/*S*)-1** and benzaldehyde (**2a)** in presence of *Amberlyst 15* at different temperatures (see Fig 3, and SI, Table S2).

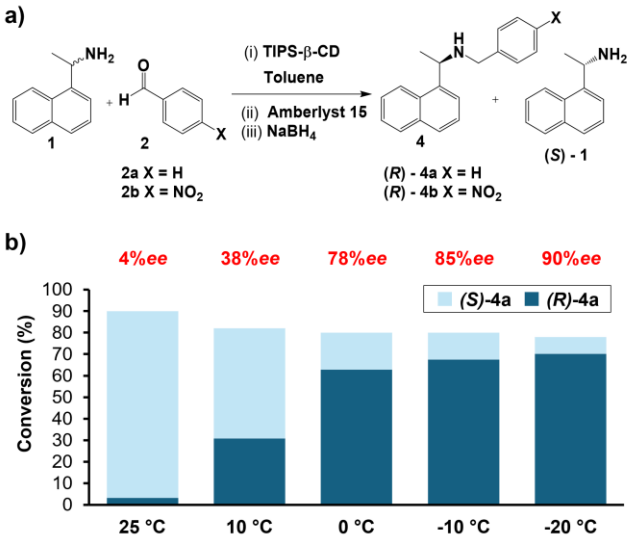


Figure 3. (a) Model kinetic resolution reactions scheme. [(i) amine **1** (0.1 mmol), aldehyde **2a** (0.05 mmol), TIPS-β-CD (0.4 mmol) and toluene (2 mL), 15 min. (ii) Amberlyst 15 (50% mmol), 1 h. (iii) $NaBH_4$ (0.20 mmol), 1h.] (b) Results for varying temperature of reaction between amine **1** and aldehyde **2a**, showing increasing enantioselectivity as temperature decreases. [Conversion of aldehyde **2a** to **4a,** and %*ee* of product **4a** determined by HPLC (see SI, Section 6), with yield of ***(R)*-4a** shaded dark, and ***(S)*-4a** shaded light.]

In our initial experiment, the reaction was conducted with 2 equivalents of **(*R*/*S*)-1** at room temperature (relative to aldehyde **2a**), and we obtained 90% conversion observed with 3.6% enantiomeric excess (*ee*). Progressively lowering temperature lead to progressively increasing chiral selectivity in product **4a**, up to 90% *ee*, with only a minimal drop in conversion (ca. 80%). Decreasing the amount of limiting reagent added (aldehyde) to 0.2 eq at the lowest temperature led to only a modest increase in selectivity (*ee* = 91.4%), and the use of a different aldehyde (**2b**, 4-Nitrobenzaldehyde) provided similarly high yield and selectivity profiles to **2a** (see SI, Section 6).

Modular Substitution Of Catalyst

An important advantage of our approach, separating the roles of catalytic activity and selectivity, is the modular nature of the system. In such modular catalytic systems, it should be possible to vary the catalytic species, and maintain selectivity (though activity may vary).

Table 1. Scope of reaction with different solid acids.[a]

Entry	Aldehyde	Catalyst	Conv. (%)[b]	%*ee*[b]
1	**2a**	Amberlyst 15	78	**90.0**
2	**2a**	Graphene oxide	28	**87.8**
3	**2a**	Montmorillonite	20	**87.6**
4	**2a**	MCM-41	-	**-**
5	**2a**	SiO2	-	**-**

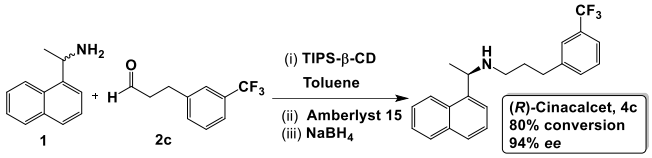
[a] Reagents: (i) Amine **1** (0.1 mmol), aldehyde **2a** (0.05 mmol), TIPS-β-CD (0.4 mmol) and toluene (2 mL), 15 min; (ii) Solid acid (50% mmol), 1 h; (iii) $NaBH_4$ (0.20 mmol), 1h at -20 ˚C. [b]The conversion of **2a** to **4**, and %*ee* of product **4a** was determined by HPLC (see SI, Section 6).

To establish this, we performed a series of reactions employing a range of solid acid catalysts (Montmorillonite, Graphene Oxide, MCM-41, SiO_2), without further optimisation of conditions. We observe that in all cases where measurable yield is observed, selectivity remains almost constant, at around 90% *ee*. Very similar results were observed on varying the aldehyde to **2b** (see SI, Table S2). While selectivity is unaffected, yield varies to a great extent, reflecting the optimisation of conditions/catalyst loading for *Amberlyst 15*. This is demonstrates the modularity of the system.

Stereoselective Synthesis Of *(R)*-Cinacalcet

To demonstrate the usefulness of our approach to catalytic selectivity, we applied it to the synthesis of the drug (*R*)-cinacalcet (**4c**), which is approved for the treatment of secondary hyperparathyroidism and hypercalcaemia.[49] In almost all reported syntheses of this API, enantiopure ***(R)*-1** has been used as a starting material (typically obtained by enzymatic resolution) to ensure only one enantiomer is produced[48] (one exceptional report employs another enantiopure feedstock, *(R)*-tert-butanesulfinamide, to introduce an asymmetric C-N bond).[55] Here we use our SPG-mediated approach to perform the stereoselective synthesis from a racemic starting material – the amine ***(S/R)*-1**and an a achiral aldehyde (**2c**) reported in a number of syntheses of (*R*)-cinacalcet – and achiral *Amberlyst*

15 as the catalyst for the enantioselective bond-forming step.



Scheme 2. Synthesis of *(R)*-Cinacalcet using SPG to impart selectivity. i) Amine **1** (0.1 mmol), aldehyde **2c** (0.05 mmol), TIPS-β-CD (0.4 mmol) and toluene (2 mL), 15 min; (ii) Solid acid (50% mmol), 1 h; (iii) $NaBH_4$ (0.20 mmol), 1h at -20 ˚C.

Following the approach developed in our model reactions, we implemented the reaction as shown in Scheme 2. Varying conditions (see SI, Table S4), we find similar responses to temperature: at room temperature no enantioselectivity is observed in the system. Lowering temperature to favour **TIPS-β-CD** acting as an SPG for ***(S)*-1** (preventing access to catalyst and reagents), we are able to produce (*R*)-cinacalcet (**4c**) in good yield and high enantiopurity (up to 94% *ee* with 80% aldehyde conversion) from the racemic amine.

Conclusions

Our approach of separating the roles of catalytic activity and selectivity in a system, using an established Supramolecular Protecting Group to impart selectivity to catalytic reactions, can produce chiral products (over 90% *ee*) from racemic feedstocks, employing otherwise-unselective (low-cost and recyclable) solid catalysts. We have also demonstrated that these low-cost catalysts can be recycled, that modular 'catalyst swapping' does not hinder selectivity, and that all this can be used in an unprecedented synthesis of the chiral drug (*R*)-cinacalcet from a racemic starting material. We note that this SPG approach is distinct to Supramolecular Catalysis,[24] as molecular recognition is employed to prevent reaction (just as covalent protecting groups are distinct from covalent chiral auxiliaries).

While we are not aware of previous applications to systems employing solid catalysts, we have noted that the use of Supramolecular Protecting Groups to control reactivity is not a new phenomenon (though nomenclature may vary). Since early reports,[40] however, concepts and implementation of catalytic systems for synthesis have developed enormously. Where refining/engineering catalysts (the selectivity and activity of singles species) was long the overarching focus, increasingly catalytic systems are becoming accessible. Whether they employ multiple enzymes in a 'cascade',[28] chemo-enzymatic combinations,[56] or the use of multiple chemical catalysts,[57] all these approaches share the division of roles into modules, comprising a (catalytic) system.[58] We suggest that the value of SPGs is not as stand-alone alternatives to 'traditional' selective catalysts, but promising modules for incorporation into developing approaches to catalytic systems.

Supporting Information

The authors have cited additional references within the Supporting Information.[45]

Acknowledgements

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Author Contributions

Conceptualization and methodology were by AJS and JAMS. Investigation, data curation, formal analysis were by BIVA and JAMS. Funding acquisition and writing – review & editing were by AJS, JAMS and BIVA.

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