Kinetic resolution of racemic pyrrolidine-2,5-diones using chiral oxazaborolidine catalysts†

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Kinetic resolution of racemic C-3 substituted pyrrolidine-2,5-diones has been achieved for the first time using highly efficient oxazaborolidine catalysts derived from *cis*-1-amino-indan-2-ol.

Asymmetric catalysis is perhaps one the most useful methods available to the modern organic chemist, allowing the transformation of an achiral material into an enantioenriched one.[1] Chiral catalysts have been developed for use in various types of organic transformations, with one of the most widely used for the asymmetric reduction of prochiral ketones being chiral oxazaborolidines, initially reported by Itsuno *et al.* then championed by Corey and co-workers.[2] Oxazaborolidines have also been employed in the kinetic resolution of racemic esters giving enantioenriched products.[3]

Our group has used various B-substituted oxazaborolidines **1** (Fig. 1), derived from *cis*-1-amino-indan-2-ol, as chiral catalysts for the asymmetric reduction of prochiral ketones.[4] Subsequently, various N-substituted oxazaborolidines **1**–**3** were probed as catalysts for the desymmetrisation of *meso*-imides, demonstrating that unsubstituted oxazaborolidines **2** and **3** were the most efficient catalysts for this transformation.[5] More recently, we have demonstrated the crucial choice of the nitrogen substituent of the imide in obtaining high levels of enantioselectivity in this transformation.[6] Herein, we would like to report the unprecedented use of B-substituted oxazaborolidines as catalysts for the kinetic resolution of racemic C-3 substituted pyrrolidine-2,5-diones.

Speckamp and co-workers showed that regioselectivity in the reduction of imide species is controlled by the size and electronic nature of the substituent at the C-3 position when nucleophilic hydride sources are employed as the reducing agent.[7] The major isomer formed in many cases was the hydroxylactam where reduction had occurred at the C-2 carbonyl, *i.e.* proximal to the bulky group. Since oxazaborolidine catalysts function by pre-complexation followed by intramolecular hydride delivery, it was initially unclear whether reduction would take place at the proximal or distal carbonyl group. In preliminary experiments, oxazaborolidine **3** was employed as the catalyst with BH_3·THF as the hydride source, followed by reduction of the initially formed hydroxylactam product to the corresponding γ-lactam for ease of analysis (Table 1). All imides were prepared by existing literature procedures.†

In all cases, full regiocontrol of the reaction was achieved, reducing only the carbonyl at the C-5 position (Table 1, entries 1–7). The absence of any of the C-2 reduced species was attributed to steric interactions between the catalyst and the substituent at the C-3 position, making binding between the C-2 carbonyl and the catalyst unfavourable. This selectivity raised two questions: first, would the interaction between the bound catalyst and substrate stereogenic centre be sufficient to allow a stereoselective process to occur, and second, since the steric environment around the C-5 carbonyl appeared to be relatively uncongested, would the catalyst turn-over too quickly with the usual loading of 10 mol%? The latter point was addressed by careful optimisation of the reaction conditions, using as little as 0.5 mol% of catalyst **2** or **3**, BH_3·THF as reductant, at 0 °C for 120 min using catalyst **2** and for 60 min with catalyst **3**.‡ Using these conditions, approximately 21–52% of the substrate was converted into product, depending upon the substituents present.

Applying these optimised conditions, the issue of enantioselectivity in the kinetic resolution of various C-3 substituted pyrrolidine-2,5-diones was assessed. Results showed that by increasing steric bulk at the C-3 position, the level of the selectivity in the reaction was greatly enhanced. When a methyl group was used selectivity was poor, giving selectivity or *s* factors of between 1 and 2 (Table 2, entries 1 and 2). When the substituent size was increased to phenyl or 3,5-dimethyl phenyl, the level of selectivity increased to between 3.7 and 4.1 (Table 2, entries 3–6). Further increases were observed when *o*-tolyl or 1-naphthyl substituents were employed, giving

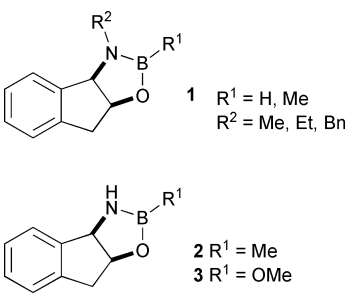

Fig. 1 *cis*-1-Amino-indan-2-ol oxazaborolidine catalysts.

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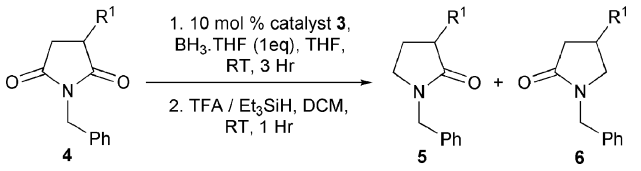
Table 1 Regioselective reduction of various C-3 substituted pyrrolidine-2,5-diones

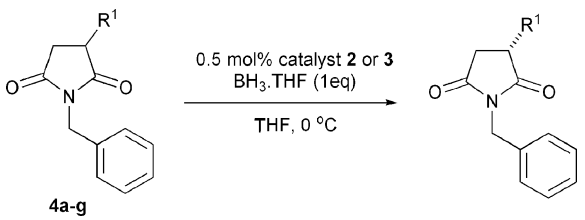


Entry	Imide	R^1	**5** : **6**[a]	Yield **5** (%)
1	**4a**	Me	100 : 0	17
2	**4b**	Ph	100 : 0	34
3	**4c**	3,5-$Me_2C_6H_3$	100 : 0	29
4	**4d**	*o*-Tolyl	100 : 0	45
5	**4e**	*t*-Bu	100 : 0	37
6	**4f**	1-Napthyl	100 : 0	48
7	**4g**	Mesityl	100 : 0	49

[a] Regioselectivity determined by ^{1}H NMR spectroscopy.

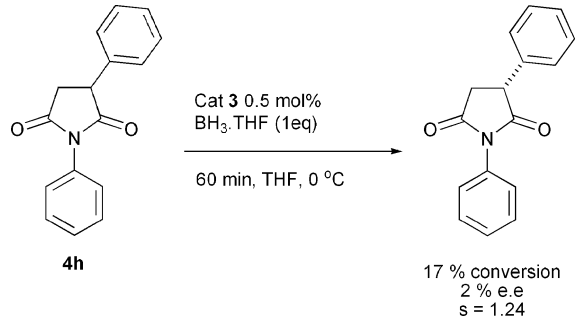
excellent *s* factors of 12 and 18, respectively (Table 2, entries 7–10). The most pleasing result was seen for the *t*-Bu derivative, giving quite remarkable *s* factors of 20–23 for this reaction (Table 2, entries 11 and 12). Surprisingly, the particularly large mesityl derivative gave very disappointing *s* factors of between 1.3 and 2.5 (Table 2, entries 13 and 14). This poor selectivity occurs since the methyl groups in the 2 and 6 positions of the phenyl ring restrict rotation around the

Table 2 Kinetic resolution of various C-3 substituted pyrrolidine-2,5-diones using oxazaborolidine catalysts **2** and **3**



Entry	R^1	Catalyst[a]	Conversion (%)[b]	ee (%)[c]	*s* factor
1	Me	**2**	46	16	1.8
2	Me	**3**	32	11	1.8
3	Ph	**2**	52	45	3.7
4	Ph	**3**	36	28	3.9
5	3,5-$Me_2C_6H_3$	**2**	48	41	3.8
6	3,5-$Me_2C_6H_3$	**3**	39	32	4.1
7	*o*-Tolyl	**2**	23	24	11.6
8	*o*-Tolyl	**3**	43	57	12.7
9	1-Naphthyl	**2**	21	23	17.3
10	1-Naphthyl	**3**	30	37	19.6
11	*t*-Bu	**2**	38	52	20.4
12	*t*-Bu	**3**	35	47	23.4
13	Mesityl	**2**	31[d]	16	2.5
14	Mesityl	**3**	34[d]	5	1.3

[a] 0.5 mol% catalyst was used in each case. Reactions performed with catalyst **2** were carried out for 120 min, while those with catalyst **3** for 60 min. [b] Conversion determined *via* ^{1}H NMR spectroscopy using maleimide as an external standard. [c] ee determined *via* chiral phase HPLC. [d] Conversion determined *via* ^{1}H NMR spectroscopy using *N*-benzotriazole as an external standard.



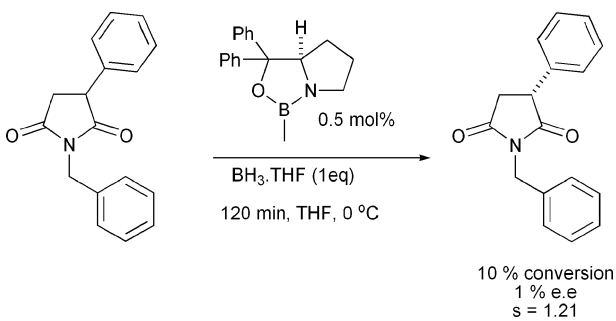
Scheme 1 Kinetic resolution of imide **4h** with oxazaborolidine **3**.

C–C bond, molecular modelling calculations predicting an energy of rotation around the C–Ph bond of 17 kcal mol^{-1}.[8] This is significantly large enough to be a barrier to rotation, effectively reducing the size of the mesityl group to that of a methyl resulting in the low selectivities seen.

The absolute stereochemistry in each case, except substrate **4e**, was determined by comparison with literature data. In all cases the (*R*) enantiomer was favoured, although in the case of imide **4a** the opposite sense of stereoselection was observed due to the assignment governed by the Cahn–Ingold–Prelog (CIP) rules.

A working model for the selectivity observed in this reaction has not yet been established, however, several key points crucial to obtaining high levels of enantioselectivity have been established. Firstly, the selectivity of the reaction increases with the size of the C-3 substituent. In previous studies on the desymmetrisation of *meso*-imides, a remarkable effect of the imide protecting group on the stereoselectivity of the reaction had been observed, with an *N*-phenyl group giving one enantiomer of product.[5] However, in the case of *N*-phenyl imide **4h**, the enantioselectivity dropped from an *s* factor of 4 to 1.2 (Scheme 1), clearly indicating that, unlike previous examples, *N*-benzyl is the preferred protecting group. The role of this group in determining the selectivity is unclear, however it could be functioning as a chiral relay,[9] controlling the reactive conformation of the substrate.

Additionally the original Corey–Bakshi–Shibata (CBS) catalyst was not as efficient in promoting this reaction. When used to resolve imide **4b**, the selectivity obtained was particularly poor, giving an *s* factor of 1.2 compared to 4 for the *cis*-amino-indanol derived catalysts (Scheme 2). Not only does this catalyst fail to give acceptable selectivity, but it also proceeds at a much slower rate, providing only 10%



Scheme 2 Kinetic resolution of imide **4b** using CBS oxazaborolidine.

conversion after 2 h compared to 52% for the *cis*-amino-indanol analogue.

In conclusion we have shown oxazaborolidine catalysts **2** and **3** to be extremely effective catalysts at extremely low loadings for the kinetic resolution of C-3 substituted pyrrolidine-2,5-dione species giving outstanding regio- and stereocontrol, complementing existing methods for the synthesis of related targets.[10] The origin of the enantioselectivity is still unclear but relies on the bulk of the C-3 substituent, the nature of the N-protecting group and the catalyst structure. Further work aimed at expanding the substrate scope and further elucidating the reaction mechanism is currently underway.

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Notes and references

‡ Procedure for experiments performed as in Table 2: (1*R*,2*S*)-*cis*-1-amino-indan-2-ol (149 mg, 1 mmol) was suspended in dry THF (5 cm^3) and treated with trimethylborate (88 μl, 1 mmol). After stirring at room temperature for 30 min, THF (15 cm^3) was added to give a known concentration of catalyst **3** which was used immediately. A solution of the imide **4a**–**4g** (1 mmol) in THF (8 cm^3) at 0 °C was added to the oxazaborolidine (0.1 cm^3, 0.5 mol%) and BH_3·THF (1M in THF, 1 mmol). The solution was allowed to stir at 0 °C for 60 min, then quenched by addition of MeOH (5 cm^3) and 1M HCl (5 cm^3). The product was then extracted with CH_2Cl_2 (1 × 10 cm^3, 3 × 5 cm^3) and the combined organic extracts dried over $MgSO_4$. The solvent was removed under vacuum to give a crude mixture. After analysis, the crude mixture was purified by column chromatography, eluting with 25% EtOAc–petroleum ether.

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