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Exploiting a novel size exclusion phenomenon for enantioselective acid/base cascade catalysis†

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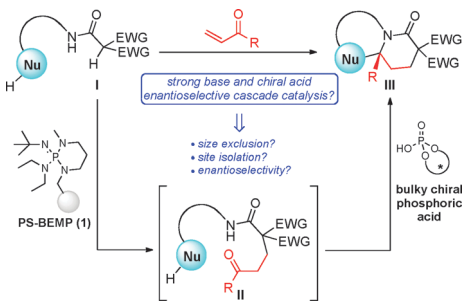
A novel size exclusion phenomenon between PS-BEMP and sterically bulky BPAs, has been discovered and exploited in a one-pot base-catalysed Michael addition/acid-catalysed enantioselective *N*-acyliminium cyclisation cascade, allowing the preparation of structurally complex *β*-carbolines with moderate to good enantiocontrol.

Strong chiral organic Brønsted acids such as the BINOL phosphoric acids (BPA) pioneered by Terada[1] and Akiyama[2] have found widespread use in asymmetric catalysis. As acid catalysts they have been successfully applied in asymmetric transformations ranging from the Mannich reaction[1–3] to complex multi-component reactions.[4] Their conjugate bases, as chiral counter anions, have also been exploited in asymmetric iminium ion catalysis[5] as well as in transition metal catalysis.[6] Together with other compatible catalytically active species they have also been shown to engage in dual catalysis.[7,8]

In a continuation of our work in the field of *tandem* base *and* acid catalysis[9] we were interested in developing reaction cascades involving the strong Schwesinger base 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine,[10,11] polymer supported (PS-BEMP **1**) and (*R*)-BPA **2** or bulky derivatives such as (*R*)-3,3′-bis(triphenylsilyl)-BPA [(*R*)-TPS-BPA **3**] and (*R*)-3,3′-bis(triphenylsilyl)-[H_8]BPA [(*R*)-TPS-H_8-BPA **4**] ($pK_a \sim 1$).[12] We believed a Michael addition/*N*-acyliminium ion cyclisation cascade would be an ideal platform since it is known to require distinct base-catalysed and acid-catalysed steps.[7,9] Not only would it showcase our concept but it would also allow the rapid construction of complex enantioenriched polycyclic products **III** from readily available starting materials **I** (Scheme 1).



Scheme 1 Concept of an acid/base catalysed enantioselective Michael addition, *N*-acyliminium cyclisation cascade.

However, to develop catalytic cascade reactions involving the simultaneous use of both strongly basic and strongly acidic reagents the problem of annihilation (catalyst quenching) had to be overcome. We and others have demonstrated that *site isolation* of acid and base functionalities by employment of separate insoluble polymeric analogues can effectively prevent annihilation and reaction products resulting from distinct base-catalysed and acid-catalysed steps can be readily obtained.[13–16] To date however, enantioselective cascade catalysis involving BPA derivatives *site-isolated* from what would otherwise be a mutually destructive catalyst (or reagent), such as a strong base, has not been reported despite the wealth of untapped synthetic opportunities that such a combination would create.

Initially, we considered the possibility of attaching the BPA to suitably functionalised polymeric supports or polymerising appropriate BPA monomers,[17,18] however the added step count and potentially detrimental effect of immobilisation on enantioselectivity relative to the soluble monomeric catalyst was unattractive. Accordingly, and as an exciting and practical alternative, *we considered whether size exclusion* (*molecular sieving*) *could be exploited to provide the necessary site isolation of mutually destructive acidic and basic functional groups*. Commercially available PS-BEMP **1** is a microporous 1–2% cross-linked polystyrene-based polymer[19] with pore sizes that vary significantly depending on the reaction solvent employed.[20] We hypothesised that in an appropriate solvent and with the appropriate 3,3′-substituents, BPAs could be made sufficiently large (Fig. 1) so as to prevent full penetration of the microporous lattice,[21] thus leaving unquenched both the internal basic residues *and* the BPA in solution.

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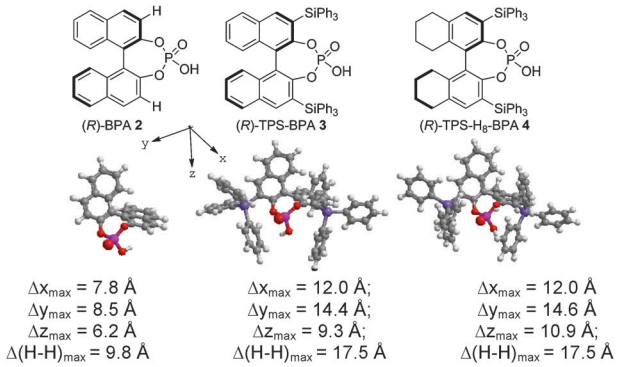


Fig. 1 3D models of (*R*)-BPA **2**, (*R*)-TPS-BPA **3** and (*R*)-TPS-H_8-BPA **4** and corresponding calculated dimensions.[22]

Provided that the smaller substrates/reagents could penetrate through to the internal catalytically active basic sites, this size exclusion phenomenon could allow both strong base and strong chiral acid catalysts to *co-exist and* function simultaneously in the same vessel. If viable, this strong base *and* strong acid site isolation concept would not only be general to numerous asymmetric reactions and cascades but would also be technically simple to carry out and negate the challenging and resource-consuming preparation of immobilised BPA derivatives. Herein we report our investigations leading to a new and potentially powerful discovery in the field of enantioselective BPA catalysis.

To probe whether a size exclusion phenomenon could exist at all, a series of ^{1}H NMR titration experiments were performed using PS-BEMP **1** as the insoluble base and either (*R*)-TPS-BPA **3** (a large BPA) or diphenyl phosphate **5** (DPP, a significantly smaller phosphoric acid) as the soluble acid. The amount of free acid remaining in solution was measured by ^{1}H NMR against an internal standard over time. The results shown in Fig. 2 strongly suggested that site isolation through size exclusion was in operation with (*R*)-TPS-BPA **3** *but was not with DPP*. For example, whereas DPP was quenched rapidly and fully by an equimolar quantity of PS-BEMP **1**, 24% TPS-BPA **3** remained in solution after ~4 days. Even with excess PS-BEMP **1**, (*R*)-TPS-BPA **3** was removed from solution only slowly. When the titration was performed with 50 mol% of PS-BEMP **1**, the amount of acid in solution stabilised at around 80% after 17 h. In other words, approximately 40% of the base was annihilated while 60% was still unquenched even after ~4 days.

With these data in hand, a series of quantitative control and optimisation studies on a base *then* acid catalysed

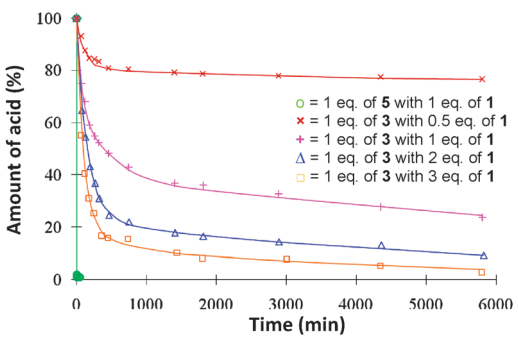
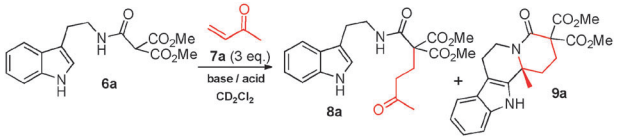


Fig. 2 Titration of DPP **5** and (*R*)-TPS-BPA **3** against various amounts of PS-BEMP **1** over time.

Table 1 Proof of principle and optimisation study



Entry	Base[a]	Acid[a]	Time	Result
1[b]	—	(*R*)-3	24 h	no conversion
2[b]	PS-BEMP	—	6 h	93% yield of **8a**
3[b]	BEMP	—	2 h	89% yield of **8a**
4[b]	BEMP	(*R*)-3	24 h	no conversion
5[b]	PS-BEMP	(*R*)-3	57 h	88% yield of **8a**
6[b]	PS-BEMP	DPP 5	24 h	no conversion
7[c]	PS-BEMP	(*R*)-2	24 h	no conversion
8[b]	PS-BEMP	(*R*)-3[d]	57 h	79.5% conv. of **6a**
9[e,f]	PS-BEMP	(*R*)-3[d]	16 h[g] + 36 h[h]	25% yield of **9a**–51% ee
10[f]	PS-BEMP	(*R*)-4[d]	24 h[g] + 24 h[h]	81% yield of **9a**–57% ee

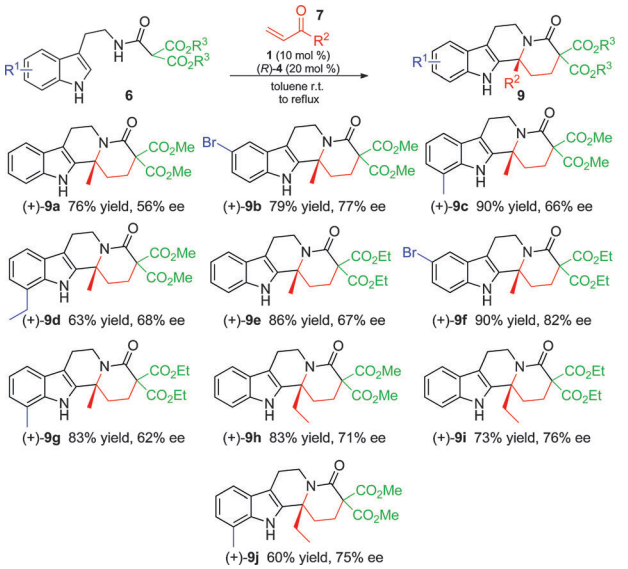
[a] 10 mol% unless otherwise stated; [b] performed in NMR tube at room temperature (r.t.) at 600 rpm; [c] performed in CH_2Cl_2 at r.t.; [d] 20 mol% of (*R*)-**3**; [e] 1.5 eq. of MVK; [f] toluene as solvent; [g] time at r.t.; [h] time at reflux.

Michael/*N*-acyliminium cyclisation cascade were then performed to assess the *catalytic competence* of both the PS-BEMP **1** and TPS-BPA **3** components when present in the same pot. We chose pro-nucleophile **6a** and methyl vinylketone (MVK **7a**) as our model system and the results are presented in Table 1.

At room temperature in CD_2Cl_2, (*R*)-TPS BPA **3** did not catalyse the Michael addition of **6a** with MVK (Table 1, entry 1). However, and as expected, good reactivity was observed when 10 mol% of soluble BEMP or PS-BEMP **1** were used as the sole catalyst (Table 1, entries 2–3).[23] Combining soluble BEMP (10 mol%) with (*R*)-TPS-BPA **3** (10 mol%) (not unexpectedly) rendered the BEMP catalytically incompetent (Table 1, entry 4). In contrast and very pleasingly, when both PS-BEMP **1** (10 mol%) and (*R*)-TPS-BPA **3** (10 mol%) were employed simultaneously, the Michael addition product **8a** was isolated in 88% yield, albeit after an extended reaction time (Table 1, entry 5). Significantly, no reactivity was observed when a combination of PS-BEMP and DPP or a combination of PS-BEMP and 3,3′-unsubstituted (*R*)-BPA **2** were evaluated (Table 1, entries 6–7). The use of excess acid (*R*)-**3** (two equivalents relative to PS-BEMP **1**) did not have a significant deleterious effect on the catalytic activity of PS-BEMP (Table 1, entry 8).

These findings, in addition to the results of the NMR titration experiments, clearly demonstrate that an effective site isolation phenomenon, attributable to size exclusion of the bulky 3,3′-disubstituted BPA from the internal catalytically active sites of PS-BEMP **1**, was occurring with (*R*)-TPS-BPA **3**. Exploiting this discovery, optimisation studies for the tandem reaction were performed† and revealed that (*R*)-TPS-H_8-BPA **4** gave the highest ee of product **9a** (57% ee) in good chemical yield (81%) when the Michael addition with MVK (3 eq) was performed at room temperature for 24 h and the enantioselective *N*-acyliminium cyclisation at reflux in toluene for 24 h (Table 1, entry 10).

In order to demonstrate that this cascade was general, a set of malonamate nucleophiles **6** was reacted with MVK **7a** and/or ethyl vinylketone (EVK **7b**) in the presence of our newly developed PS-BEMP **1** and (*R*)-**4** catalyst system (Scheme 2).



Scheme 2 Scope of the enantioselective base- and acid-catalysed cascade with MVK and EVK.

Malonamates **6** bearing various substituents at the 5, 6 and 7-position on the indole π-nucleophile successfully took part in the cascade. 5-Bromo substituted and 7-alkyl substituted indole-derived malonamates **6** showed higher selectivities in the *N*-acyliminium cyclisation compared to the unsubstituted counterpart. Methyl and ethyl malonamates could be used with identical reactivity and similar selectivity in the cascade. Although the EVK-derived Michael adducts cyclised slowly, the desired tetracycles were obtained in good yield and moderate to good enantioselectivities (57–82% ee). Substituted vinylketones (such as 3-methyl-3-buten-2-one) did not partake in the reaction and only degradation of the malonamate substrate was observed after prolonged heating. The absolute stereochemistry of all products was assigned by analogy with our previous studies.[7,24b]

To our knowledge, this is the first report of the steric properties of bulky 3,3′-disubstituted BPAs being exploited to gain site isolation. Taking advantage of a novel size exclusion phenomenon between PS-BEMP and sterically bulky BPAs, we have been able to develop a one-pot base-catalysed Michael addition followed by an acid-catalysed enantioselective *N*-acyliminium cyclisation cascade that has allowed the preparation of structurally complex *β*-carbolines with moderate to good enantiocontrol. We believe this approach is a viable and efficient alternative to the use of polymer supported BPAs in situations where site isolation is a necessity. Developments and further applications of this concept are currently under investigation in our laboratory and will be disclosed in due course.

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