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NH-Isoxazolo-bicycles; new molecular scaffolds for organocatalysis

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ABSTRACT

A new scaffold for organocatalysis of the Diels–Alder reaction is disclosed; an isoxazolidine ring forms the core of the catalyst and its activity is enhanced by judicious fusion of a second five-membered heterocycle to the *c*-edge. The catalyst performance is improved by the incorporation of an *endo*-cyclic electron withdrawing group adjacent to the fusion point. The organic core is effective only in the presence of an acid co-catalyst and whilst the two-component system shows potential as an enantioselective catalyst it is demonstrated that stereocontrol is a feature of the organic core and is fully independent of the choice of co-catalyst.

1. Introduction

Over the last decade organocatalysis has emerged as a vibrant research area and a wide repertoire of synthetic transformations has been demonstrated.[1–3] A range of catalyst architectures with varying modes of operation have been developed and whilst SOMO[4] and counter ion catalysis[5] are at early stages of development many applications of enamine,[6] iminium[7] and hydrogen bonding catalysis[8] have been reported. To-date the most successful catalysts are derivatives of the five-membered, secondary amine heterocycles proline[9] and imidazolidinone.[10] However, recent developments of iminium ion catalysis indicate significant enhancement of activity with catalysts bearing a second heteroatom α-to the secondary amine. Thus, conformationally rigid hydrazides, e.g. **1**,[11,12] cyclic and acyclic hydroxylamine or hydrazine derivatives, e.g. **2**, **3**,[13,14] are shown to be effective catalysts, Fig. 1.

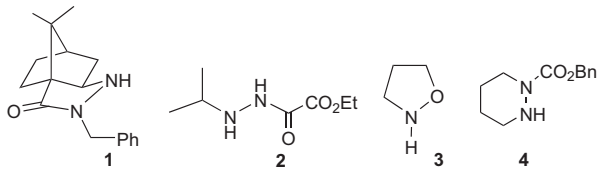

Fig. 1. α-Heteroatom secondary amine organocatalysts.

Significantly, a recent report finds isoxazolidines and pyrazolidines poor catalytic scaffolds, and concludes that catalysts designed with an α-heteroatom should be based on a six-membered ring and incorporate an *exo*-cyclic electron withdrawing group on the β-position, e.g. **4**.[15] In contrast, in this paper we describe significant organocatalytic activity of the 5,5-bicyclic isoxazolidines **5**–**7**, Fig. 2.

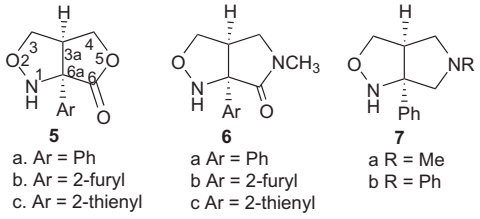

Fig. 2. Isoxazolo-fused bicyclic organocatalysts.

Featuring a five-membered ring, a secondary amine and an α-heteroatom *NH*-isoxazolidines bear the critical architectural elements of an organocatalyst designed to accelerate organic transformations through LUMO-lowering iminium catalysis. Conformational rigidity was built into the catalyst design and the first candidates were the bicyclic isoxazolidines **5** with an aryl substituent at the ring junction and an *endo*-cyclic electron attracting carbonyl group β′-to the nucleophilic nitrogen atom. The organic core of the catalyst was prepared as described elsewhere[16,17] and the Diels–Alder cycloaddition between cyclopentadiene and *trans*-cinnamaldehyde, Scheme 1, was selected as the model reaction for testing catalytic activity.

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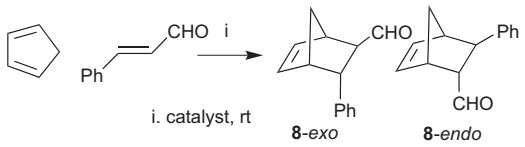

Scheme 1. Model reaction used in this study.

2. Results and discussions

Initial catalytic runs, analysed by ^{1}H NMR spectroscopy, employed **5a** together with a range of acid co-catalysts including HCl, TFA, H_2SO_4, $HClO_4$, tartaric acid and 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate **9**. No relationship was observed between catalytic activity and acid pK_a and whilst perchloric acid was almost as effective as (+)-10-camphor sulfonic acid (CSA), with a future view to counter ion and enantioselective organocatalysis, the latter was selected as co-catalyst of choice for further study (entries 1–8, Table 1). A time study revealed 71% conversion at 2 h rising to near quantitative results after 48 h (entries 9–12, Table 1). We identified 6 h reacting time as the most suitable for performance limitation studies. Further, it is noted that the simple mixing of equimolar amounts of the organic core with (+)-**10**-CSA furnished the same result as the preformed salt (entry 13, Table 1). Control runs indicated neither the bicycle nor CSA alone promoted the reaction (entries 14, 15 Table 1). A comparison of reactivity with 1, 5 and 10 mol % catalyst loadings determined the limitation of catalytic activity. With lower loadings after 6 h reaction time the extent of conversion to the products was poor to moderate. After 24 h a significant improvement in product yield was noted (entries 16–18, Table 1), however, the performance of the catalyst was deemed optimal at 10 mol % loading. The activity of **5a**·(+)-**10**-CSA was subsequently studied in a variety of solvents (6 h, rt). Considering both yield and diastereoselectivity MeOH/H_2O (86%, 38:63) and MeOH (88%, 39:61) were found to be superior to more bulky alcohols (^{i}PrOH, ^{t}BuOH), chlorinated solvents (CH_2Cl_2, $CHCl_3$), polar non-protic solvents (DMSO, dioxane) or hydrocarbon solvents (toluene). No cycloaddition products formed in pure H_2O [see Supplementary data]. In all cases diastereoselectivity was in favour of the *exo*-adduct (~2:1) as expected for catalysis by the iminium route.[14] Whilst no effort was made to *re*-isolate the catalyst at the end of the reaction ^{1}H NMR spectral analysis of the crude reaction products showed resonance signals attributable to the parent bicycle **5a** so confirming the stability of the catalyst to the reaction conditions.

Table 1
Diels–Alder reaction between cyclopentadiene and *trans*-cinnamaldehyde catalysed by **5a**·HX[a]

Entry	Co-catalyst HX	Time (h)	Loading	Conversion (%)[b]	Yield (%)[c]	*endo*/*exo*[b]	HX pK_a[18]
1	TFA	6	10 mol %	32	25	38:62	0.5
2	H_2SO_4	6	10 mol %	78	60	39:61	−3
3	HCl	6	10 mol %	66	52	38:62	−8
4	(±)-**9**[d]	6	10 mol %	65	53	38:62	1.14
5	L-(+)-Tartaric acid	6	10 mol %	0	0	—	2.98
6	D-(−)-Tartaric acid	6	10 mol %	0	0	—	2.98
7	$HClO_4$	6	10 mol %	88	82	40:60	−10
8	(+)-**10**-CSA	6	10 mol %	93	86	40:60	1.17
9	(+)-**10**-CSA	48	10 mol %	97	96	39:61	
10	(+)-**10**-CSA	24	10 mol %	94	85	40:60	
11	(+)-**10**-CSA	4	10 mol %	84	75	36:64	
12	(+)-**10**-CSA	2	10 mol %	71	61	36:64	
13	(+)-**10**-CSA[d]	6	10 mol %	93	86	38:62	
14	None[e]	48	10 mol %	1	—	—	
15	(+)-**10**-CSA[e]	48	10 mol %	7	—	—	
16	(+)-**10**-CSA	6	1 mol %	9	—	43:57	
17	(+)-**10**-CSA	6	5 mol %	65	51	39:61	
18	(+)-**10**-CSA	24	5 mol %	89	73	41:59	

[a] Conditions: 3 equiv of diene, 1 equiv of dienophile, **5a** (10 mol %), HX (10 mol %); MeOH/H_2O (19:1), 25 °C.
[b] Estimated from the ^{1}H NMR spectrum by relating the integrals of the aldehyde protons of the starting material and the Diels–Alder adducts.
[c] Combined isolated yield.
[d] Identical results were obtained in experiments conducted with pre-formation of the salt rather than the addition of the two components of the catalytic system in a 1:1 ratio.
[e] Control runs employing either the organic core or the co-catalyst alone.

There is little precedent for the existence of iminium ions of isoxazolidine frameworks; aside from sporadic mention as transient intermediates[19,20] to the best of our knowledge the benzisoxazolium trifluoroacetate **10**, Fig. 3, is the only claimed stable cation.[21] Thus, in support of an intermediary iminium species in the catalytic cycle, interaction between equimolar amounts of the isoxazolidinium salt, **5a**·(+)-**10**-CSA, and *trans*-cinnamaldehyde was followed by ^{1}H NMR spectroscopy. In CD_3OD/D_2O (19:1) formation of a single geometrical isomer of the iminium ion was visible within minutes. However, formation of the dimethyl acetal of cinnamaldehyde, **11**, indicated by minor signals at 6.65, 6.20 and 5.00 ppm, was competing with iminium formation. Major signals at 8.62 (d, 10.0 Hz) and 8.15 ppm (d, 15.5 Hz) are, with reference to reported structures,[22] deemed characteristic of H^1 and H^3 of the conjugated iminium ion **12**, Fig. 4. 2D-COSY experiments indicate the resonance of H^2 lies within a multiplet signal at ~7.6 ppm. To eliminate acetal formation, the experiment was repeated in CD_3CN, iminium ion formation, characterized by the appearance of doublet resonances at 8.26 and 8.01 ppm, was much slower and ~55% of the starting aldehyde remained after ~2 h. Iminium ion geometry is recognized as central to stereocontrol of catalysed reactions and thus it was disappointing that nuclear Overhauser difference spectroscopy experiments were inconclusive. Thus, Dreiding scale

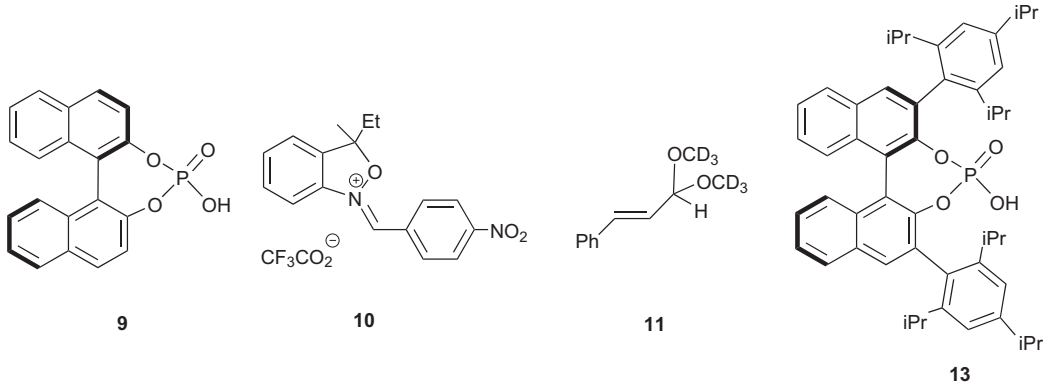

Fig. 3. Structures of phosphoric acids **9** and **13**, iminium ion **10**, and acetal **11**.

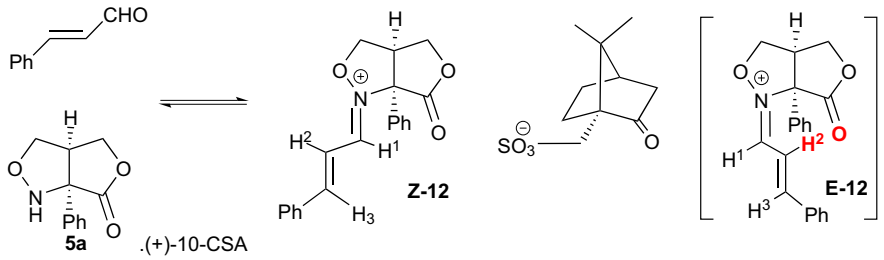

Fig. 4. Proposed iminium species from **5a** and (+)-**10**-CSA with *trans*-cinnamaldehyde.

models of *Z*- and *E*-**12** were examined and these suggest *E*-**12** suffers significant repulsive non-bonding interactions between the substrate olefin and the oxo-group; *Z*-**12** is thus most likely to represent the adopted geometry, Fig. 4.

To explore the scope of the reaction electron rich and electron poor dienophiles *o*-, and *p*-nitrocinnamaldehyde and *o*- and *p*-methoxycinnamaldehyde were selected as reaction partners with cyclopentadiene. As shown in entries 1–4, Table 2, product yields and selectivities varied significantly. It is known that the kinetics of iminium promoted reactions may depend both on iminium formation and the carbon–carbon bond forming event[10b] or simply on the latter.[23] Thus, steric effects are believed to account for the poor yield of Diels–Alder products from cycloaddition of cyclopentadiene to

Table 2
Effect of variation in substrate and catalyst structure on the Diels–Alder reaction between cyclopentadiene and α,β-unsaturated aldehydes[a]

Entry	Catalyst	Dienophile	Conversion (%)[b]		*endo*/*exo*[b]
			Yield (%)[c]		
1	**5a**·(+)-**10**-CSA	*o*-nitrocinnamaldehdye	61	52	55:45
2	**5a**·(+)-**10**-CSA	*p*-nitrocinnamaldehdye	88	86	40:60
3	**5a**·(+)-**10**-CSA	*o*-methoxycinnamaldehyde	96	83	40:60
4	**5a**·(+)-**10**-CSA	*p*-methoxycinnamaldehyde	26	16	38:62
5	**5a**·(+)-**10**-CSA	*trans*-cinnamaldehyde	93	86	38:62
6	**5b**·(+)-**10**-CSA	*trans*-cinnamaldehyde	40	35	43:57
7	**5c**·(+)-**10**-CSA	*trans*-cinnamaldehyde	62	60	43:57
8	**6a**·(+)-**10**-CSA[e]	*trans*-cinnamaldehyde	95	86	35:65
9	**6b**·(+)-**10**-CSA	*trans*-cinnamaldehyde	53	48	39:61
10	**6c**·(+)-**10**-CSA	*trans*-cinnamaldehyde	49	46	41:59
11	**7a**·(+)-**10**-CSA[e]	*trans*-cinnamaldehyde	1	—	—
12	**7a**·(+)-**10**-CSA[d,e]	*trans*-cinnamaldehyde	74	65	38:62
13	**7b**·(+)-**10**-CSA[e]	*trans*-cinnamaldehyde	70	64	38:62
14	**7b**·(+)-**10**-CSA[d,e]	*trans*-cinnamaldehyde	65	62	39:61

[a] Conditions: 3 equiv of diene, 1 equiv of dienophile, Organic core **5**–**7** (10 mol %), (+)-**10**-CSA (10 mol %), MeOH/H_2O (19:1), 25 °C, 6 h.
[b] Estimated from the ^{1}H NMR spectrum by relating the integrals of the aldehyde protons of the starting material and the Diels–Alder adducts.
[c] Combined isolated yield.
[d] **7a**/**b** (10 mol %), (+)-**10**-CSA (20 mol %).
[e] Identical results were obtained in experiments conducted with pre-formation of the salt rather than the addition of the two components of the catalytic system in a 1:1 ratio.

o- (52%) with respect to *p*-nitrocinnamaldehyde (86%). The reduced electrophilicity of the aldehyde and the H-bonding potential are likely responsible for the wide span in product yield from reaction of *p*-(16%) and *o*-methoxycinnamaldehyde (83%) with the diene. In the former case mesomeric donation may dominate causing the low yield. It is acknowledged that subtle interplays of H-bonding networks can determine the overall reaction profile of iminium ion formation[24] and we postulate, as shown in Fig. 5, that a H-bonding interaction involving the *o*-OMe substituent and the *NH*- of the catalytic system may assist iminium formation through anchorage of the relevant functional groups as well as reducing mesomeric donation to the aldehyde culminating in the high yield of Diels–Alder products from reaction of *o*-methoxycinnamaldehyde.

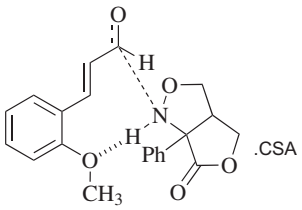

Fig. 5. Proposed interaction between **5a**·CSA and *trans*-*o*-methoxycinnamaldehyde.

In order to test the tolerance of the catalytic core to structural variation the bridgehead phenyl was replaced by furyl and thienyl rings. However, neither **5b**·CSA nor **5c**·CSA were as effective as **5a**·CSA in promoting the Diels–Alder reaction with cycloadducts furnished in just 35 and 60% yield, respectively. In each case, involvement of an intermediate iminium species is supported by a preference for the *exo*-adduct (~57:43), Table 2, entries 5–7. In rationalising the reduced reactivity of the heteroaryl analogues of **5a** we propose an intramolecular H-bond between the isoxazolidine *NH* and the pendant heterocycle may increase the activation energy of the iminium forming step. The particularly sluggish reactivity of **5b** may result from a furan-HX interaction involving both the π-electron system and the lone pair. The thiophene-HX interaction is expected to involve only the π-electron system[25] and this may account for its more minimal impact on catalytic activity. In a further probe of structure/activity relationships catalytic systems based on the lactam fused isoxazolidines **6a**–**c** were examined. Results for the Diels–Alder reaction in the presence of **6a**–**c**·(+)-**10**-CSA, summarised in Table 2, entries 8–10 suggest no significant change in reactivity followed from replacement of the electron withdrawing *endo*-cyclic *ester* of **5** with the *amide* in **6**.

To determine if the β′-electron withdrawing lactone and lactam groups of **5** and **6** were important for catalytic activity the pyrrolidine fused isoxazolidines **7** were designed and their CSA salts prepared. The catalytic performance of diamine-protic acid organocatalysts is known to be sensitive to the acid/amine ratio.[26–28] A comparison of the pK_{BH}^{+} values, obtained from ACD labs,[18] of the parent heterocycles suggest that the *N*-methyl pyrroloisoxazole **7a** should preferentially protonate at the tertiary amine and will require a second equivalent of CSA to form the isoxazolidinium salt. Indeed, under standard reaction conditions, **7a**·CSA was an ineffective catalyst, however, with 20 mol % (+)-**10**-CSA catalytic activity was observed and cycloadducts, obtained with *exo*-selectivity, were isolated in 65% yield (Table 2, entries 11, 12). The *N*-phenyl analogue, **7b** proved equally active with the employment of either 10 or 20 mol % (+)-**10**-CSA and cycloadducts were furnished in yields of ~63% (Table 2, entries 13, 14). The significant reduction in catalytic activity of the pyrrolidine fused bicycles, **7**·CSA, is suggestive of a role for the β′-*endo*-cyclic electron withdrawing groups of **5** and **6** in the catalytic cycle.

The potential of a β-electron withdrawing group to enhance the performance of α-heteroatom organocatalysts has previously been noted. Ogilvie believes this feature accelerates iminium hydrolysis[22] whilst Tomkinson, following from an observation that the synergistic effect of an α-heteroatom and a β-carbonyl group is more prominent in anhydrous than in aq MeOH,[14] believes the carbonyl moiety functions as a proton shuttle. To understand better the structure activity of relationships of the bicyclic isoxazolidine catalysts **5**–**7** the Diels–Alder reactions were repeated in anhydrous MeOH. The pyrrolidine fused catalysts **7a**,**b**·CSA performed more poorly in dry solvents with yields dropping by 13–30% (Table 3, entries 6–8) whilst increases in yields of similar magnitudes were observed for the lactone/lactam fused isoxazolidines **5**/**6a**–**c**·CSA (Table 3, entries 1–5). These results clearly highlight the involvement of the β′-carbonyl in the catalytic cycle, and we conclude that a carbonyl group located sufficiently intimately to the secondary amine can enhance catalytic performance in anhydrous solvents. The apparent acceptance of the location of this group either *endo*- or *exo*-cyclic, and either β- or β′-to the secondary amine broadens the possibilities for future catalyst design.

Tricyclic benzopyranoisoxazolidine derivatives have found success as chiral auxiliaries for asymmetric alkylation[29] and with a future goal to develop an enantioselective organocatalyst **5a** was resolved employing either (+)- or (−)-CSA as resolving agent. HPLC analysis confirmed (−)-**5a** was obtained optically pure whilst (+)-**5a** was furnished with ~90% ee. Prior to testing the enantiocontrol with catalytic systems based on the resolved bicycles we explored the possibility for counter ion directed organocatalysis.[5,30,31] Control experiments confirmed that *rac*-**5a**, in combination with either (+)- or (−)-CSA, furnished products with essentially with no enantioenrichment. Similarly, no enhancement was observed with (+)- or (−)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate **9** nor with the more sterically demanding (*R*)-TRIP **13** as co-catalyst with *rac*-**5a**; in the case of (*R*)-TRIP, limited solubility of the co-catalyst is reflected in the poor chemical yield, results are summarised in Table 4, entries 1–5. The failure to detect any enantioselection with the racemic bicycle rules out the possibility for counter ion directed catalysis with this system.

Gratifingly, catalytic systems based on (+)-**5a** furnished Diels–Alder products with a modest degree of enantioselectivity. For

Table 3
Effect of water in the reaction solvent on the model Diels–Alder reaction[a]

Entry	Catalyst[b]	Solvent[c]	Conversion (%)[d]		*endo*/*exo*[d]	Solvent	Conversion (%)[d]		*endo*/*exo*[d]
			Yield (%)[e]				Yield (%)[e]		
1	**5a**	aq MeOH	93	86	38:62	anh. MeOH	92	88	39:61
2	**5a**[f]	aq MeOH	84	75	36:64	anh. MeOH	91	82	36:64
3	**5b**	aq MeOH	40	35	43:57	anh. MeOH	52	47	45:55
4	**5c**	aq MeOH	62	60	43:57	anh. MeOH	91	86	41:59
5	**6a**	aq MeOH	95	86	35:63	anh. MeOH	96	85	34:66
6	**7a**[g]	aq MeOH	74	65	38:62	anh. MeOH	58	52	42:58
7	**7b**	aq MeOH	70	64	38:62	anh. MeOH	35	31	30:70
8	**7b**[g]	aq MeOH	65	62	39:61	anh. MeOH	46	43	44:56

[a] Conditions: 3 equiv of diene, 1 equiv of dienophile, 25 °C, 6 h.
[b] **5**–**7** (10 mol %), (+)-**10**-CSA (10 mol %).
[c] MeOH/H_2O (19:1).
[d] Estimated from the ^{1}H NMR spectrum by relating the integrals of the aldehyde protons of the starting material and the Diels–Alder adducts.
[e] Combined isolated yield.
[f] Reaction repeated over 4 h as after 6 h (entry 1) the extent of conversion was deemed too great to allow influence of solvent to be judged.
[g] **7a**/**b** (10 mol %), (+)-**10**-CSA (20 mol %).

Table 4
Investigation of the potential of the salts of (+)- and (−)-**5a**[a] to effect stereoselective catalysis of the model Diels–Alder reaction[b]

Entry	Catalyst	Temp (°C)	Time (h)	Conversion (%)[c]		*endo*/*exo*[d]	*endo* ee[e,f]	*exo* ee[e,f]
				Yield (%)[d]				
1	(±)-**5a**·(+)-**10**-CSA	25	6	93	86	38:62	0.3	2
2	(±)-**5a**·(−)-**10**-CSA	25	6	84	82	38:62	5	5
3	(±)-**5a**·(+)-**9**	25	6	62	57	35:65	0.4	1.3
4	(±)-**5a**·(−)-**9**	25	6	50	42	39:61	0.5	1.9
5	(±)-**5a**·(*R*)-TRIP	25	6	11	—	45:55	9	9
6	(+)-**5a**·(+)-**10**-CSA	25	6	92	84	37:63	41	58
7	(+)-**5a**·(−)-**10**-CSA	25	6	90	83	37:63	40	58
8	(−)-**5a**·(+)-**10**-CSA	25	6	82	74	38:62	37	42
9	(−)-**5a**·(−)-**10**-CSA	25	6	83	69	39:61	37	54
10	(+)-**5a**·(+)-**9**	25	6	66	52	38:62	45	59
11	(+)-**5a**·(−)-**9**	25	6	56	47	39:61	39	58
12	(−)-**5a**·(+)-**9**	25	6	31	27	39:61	37	54
13	(−)-**5a**·(−)-**9**	25	6	38	32	39:61	26	48
14	(+)-**5a**·(*R*)-TRIP	25	6	5	—	32:68	25	51
15	(−)-**5a**·(*R*)-TRIP	25	6	6	—	45:55	34	22
16	(+)-**5a**·$HClO_4$	25	6	93	91	38:62	32	51
17	(+)-**5a**·HCl	25	6	87	78	37:63	38	56
18	(+)-**5a**·(±)-**9**	25	6	65	42	39:61	35	56

[a] (−)-**5a** Homochiral; (+)-**5a** enantioenriched, ~90% ee.
[b] Conditions: 3 equiv of diene, 1 equiv of dienophile, MeOH/H_2O (19:1), **5a** (10 mol %) co-catalyst (10 mol %).
[c] Estimated from the ^{1}H NMR spectrum by relating the integrals of the aldehyde protons of the starting material and the Diels–Alder adducts.
[d] Combined isolated yield.
[e] Estimated by GLC.
[f] Those reactions catalysed by salts of (+)-**5a** provide products with the opposite sense of enrichment compared to those promoted by salts of (−)-**5a**.

example, the reaction promoted by (+)-**5a**(+)-CSA at 25 °C furnished the *exo*-adduct with 58% ee and the *endo*-adduct with 41% ee, similar diastereomeric and enantiomeric selectivity was observed with (−)-CSA as co-catalyst (Table 4, entries 6,7). In reactions catalysed by (−)-**5a** in combination with either (+)- or (−)-CSA yields and selectivities (opposite sense) were slightly lower (Table 4, entries 8,9). Whilst the rate of the Diels–Alder reactions were significantly compromised at reduced temperature there was only a marginal improvement in enantioselectivity at −20 °C [see Supplementary data]. The sense of asymmetric induction is consistent with selective formation of the *Z*-iminium ion and the shielding of one face of the catalyst framework by the bridgehead phenyl substituent as shown in Fig. 6.

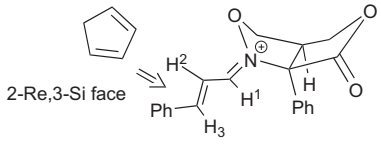

Fig. 6. Proposed alignment for the stereocontrolled Diels–Alder reaction.

Catalytic activity was lower with the phosphinic acid co-catalyst (+)- and (−)-**9**, however, in all cases the enantiocontrol paralleled that seen with corresponding CSA salts, chemical yields were too low with (*R*)-TRIP **13** as co-catalyst to permit comment on enantiocontrol (Table 4, entries 10–15). The results in Table 4 do not provide evidence for the operation of matched or mis-matched pairs with the two component catalytic systems based on (+)- or (−)-**5a** with either enantiomer of CSA or the phosphinic acid **9**. Thus, we hypothesised that enantiocontrol may rest entirely with the bicyclic nucleus. To demonstrate independence from the counter ion, catalytic systems based on (+)-**5a** with $HClO_4$, HCl and *rac*-**9** were examined. In all three cases, (Table 4, entries 16–18) the reaction products were formed with almost the same selectivity as observed with (+)-**5a**·(+)-CSA as catalyst.

In an effort to optimise enantiocontrol the model reaction was screened in a range of solvents. The results, summarised in Table 5 indicate, as previously observed for bipyrrolidine organocatalysts,[32] lower chemical yields and enantioselectivities in organic solvents in comparison to aq methanol. In particular, reactions in toluene and diethyl ether provided the *exo*-adducts in highest enantioselectivity whilst in dioxane the *endo*-adducts were formed more selectively.

3. Conclusion

We have discovered a new scaffold for organocatalysis of the Diels–Alder reaction. The active catalyst comprising an isoxazolidine ring with a second five-membered ring fused to the *c*-edge, is successfully used with camphor sulfonic acid as co-catalyst. The catalytic activity is influenced by the nature of the aryl group at the fusion point and is sensitive to reaction solvent. Those catalysts featuring a β′-*endo*-cyclic electron withdrawing group are most effective in anhydrous MeOH whilst those lacking this functionality perform better in wet MeOH. The conformational rigidity of the 5,5-bicycle together with the judiciously positioned *endo*-cyclic carbonyl group combine to provide a valuable catalytic framework in contrast to monocyclic five-membered α-heteroatom heterocycles, which are ineffective promoters of iminium ion mediated Diels–Alder reactions.[15] ^{1}H NMR studies confirm an intermediary iminium ion in the catalytic cycle and although initial results are modest, the potential for asymmetric induction, arising from the organic core of the catalytic system, and independent of the counter ion, has been demonstrated.

4. Experimental

4.1. General

Solvents were dried and purified in accordance with established procedures.[33] All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer at a probe temperature of 25 °C, operating at 300 MHz for the ^{1}H nucleus and 75.5 MHz for the ^{13}C nucleus. Infrared spectra were recorded on a Perkin–Elmer System 2000 FT spectrometer as thin films or as Nujol mulls. Melting points were measured on a Stuart Scientific (Bibby) Melting Point SMPI apparatus and are uncorrected. Microanalytical data were recorded on an Exeter Analytical CE-440 elemental analyser in Cork and Dublin. Flash column chromatography was performed using silica gel 60 (Merck, 0.040–0.063 mm) on a Buchi Automated Flash system. Analytical thin layer chromatography was carried out on aluminium sheets pre-coated with Merck TLC Silica gel 60 F_{254},

Table 5
Influence of solvent on enantioselectivity of the model Diels–Alder reaction[a]

Entry	Solvent	Catalyst[b]	Conversion (%)[c]		*endo*/*exo*[c]	*endo* ee[e]	*exo* ee[e]
			Yield (%)[d]				
1	MeOH/H_2O	(+)-**5a**·(+)-**10**-CSA[f]	92	84	37:63	41	58
	Toluene		16	14	45:55	11	21
	Dioxane		46	45	47:53	32	4
	Et_2O		28	25	46:54	8	30
2	MeOH/H_2O	(+)-**5a**·(−)-**10**-CSA[f]	90	83	37:63	40	58
	Toluene		28	19	46:54	3	31
	Dioxane		48	30	49:51	30	0.4
	Et_2O		41	36	47:53	4	35
3	MeOH/H_2O	(−)-**5a**·(+)-**10**-CSA[f]	82	74	38:62	37	42
	Toluene		29	25	48:52	0.8	19
	Dioxane		35	28	52:48	13	4
	Et_2O		36	32	43:57	9	21
4	MeOH/H_2O	(−)-**5a**·(−)-**10**-CSA[f]	83	69	39:61	37	54
	Toluene		18	12	43:57	8	16
	Dioxane		33	27	51:49	13	5
	Et_2O		34	29	41:59	12	18

[a] Conditions: 3 equiv of diene, 1 equiv of dienophile, MeOH/H_2O (19:1).
[b] **5a** (10 mol %) CSA (10 mol %).
[c] Estimated from the ^{1}H NMR spectrum by relating the integrals of the aldehyde protons of the starting material and the Diels–Alder adducts.
[d] Combined isolated yield.
[e] Estimated on the product aldehydes by chiral GLC.
[f] (−)-**5a** Homochiral; (+)-**5a** enantioenriched, ~90% ee.

developed sheets were visualised using a portable UVItec CV-006 lamp (λ=254). Analytical gas-phase chromatography (GC) was performed on a Perkin–Elmer Clarus 500 using a SUPLECO Beta Dex 110 fused silica capillary column (30 m×0.25 mm×0.25 μm; 160 °C then 2 °C/min to 200 °C). High Performance Liquid Chromatography (HPLC) was performed on a Perkin–Elmer Totalchrom v.6.2.0.0.1 or Gilson analytical HPLC using a CHIRALCEL OD analytical column in both cases (250×4.6 mm) [flow rate 1 mL/min, *iso*-propyl alcohol/hexane 1:1]. Optical rotations were measured on an Optical Activity AA 100 polarimeter in a 2 dm polarimeter tube. Reactions at 25 °C were carried out in a Grant W14 water bath without stirring. Low-temperature reactions were carried out in an ethanol bath and the temperature was controlled by a Julabo FT920 cooler.

4.2. Typical experimental procedure for catalytic runs

To a solution of the organic catalyst (0.076 mmol, 10 mol %) and acid co-catalyst (0.076 mmol, 10 mol %) in MeOH/H_2O 19:1 (0.78 mL) was added *trans*-cinnamaldehyde (100 mg, 0.76 mmol) and the resulting solution was stirred at rt for 5 min. To this solution was added freshly cracked cyclopentadiene (150 mg, 2.273 mmol, 3 equiv) in a single aliquot and the solution was maintained at 25 °C for a further 6 h. The reaction solvent was evaporated and hydrolysis followed by stirring a $CHCl_3$ (2 mL), TFA (1 mL) and H_2O (1 mL) solution of the residue for 3 h at rt. The solution was neutralised with satd aq $NaHCO_3$, the organic layer was extracted with DCM (2×10 mL), washed with H_2O (5 mL), dried ($MgSO_4$), filtered and evaporated to yield the crude product as a brown oil. Purification by flash column chromatography followed (SiO_2, Hex/EtOAc 98:2). ^{1}H NMR spectral analysis of the crude reaction mixtures was used to establish the extent of conversion of the starting material as well as the product *exo*/*endo* ratio through the integration of the signals representing the respective aldehyde protons. ^{1}H NMR data for the cycloaddition products agreed with previously reported literature values.[14]

The enantiomeric ratios were determined and diastereomeric ratios confirmed by GC analysis retention time; *exo* isomers: 10.31 and 10.52 min, *endo* isomers: 10.79 and 10.96 min.

*4.2.1. Preparation of the camphor sulfonic acid salt of racemic **5a**, **5a**·(+)-**10**-CSA 6-oxo-6a-phenyltetrahydro-1H,3H-furo[3,4-c][1,2]oxazol-1-ium (7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methane sulfonate.* Hot acetone (1 mL) was added to a flask containing *rac*-**5a** (100 mg, 0.49 mmol) and (+)-**10**-CSA (133 mg, 0.488 mmol). The resulting solution was allowed to stir at rt until the title salt precipitated as a white solid (228 mg, 98%); [found: C, 57.58; H, 6.22; N 3.23. $C_{21}H_{27}NSO_7$ requires C, 57.62; H, 6.21, N, 3.20%]; mp 153–158 °C; ν_{max} (KBr)/cm^{-1} 3451, 2952, 2530, 1781, 1734, 1451, 1386, 1231; δ_δ (300 MHz, DMSO) 7.56–7.52 (2H, m), 7.50–7.37 (3H, m) 4.66 (1H, dd *J*=9.7 and 7.2) 4.44 (1H, dd *J*=9.7 and 1.8) 4.21 (1H, dd *J*=8.7 and 2.2) 4.04 (1H, dd *J*=8.7 and 8.7) 3.66–3.59 (1H, m) 3.01 (1H, d *J*=14.8) 2.63–2.50 (2H, m) 2.31–2.23 (1H, m) 1.99–1.80 (3H, m) 1.40–1.25 (2H, m) 1.04 (3H, s) 0.76 (3H, s); δ_C (75.5, DMSO) 215.7, 176.1, 134.2, 128.7, 128.6, 126.7, 78.6, 75.3, 70.1, 58.0, 47.9, 47.0, 42.2, 42.1, 38.6, 26.3, 24.2, 19.9, 19.4.

*4.2.2. Preparation of the isoxazolidinium salt from (S)-(+)-1,1′-binaphthyl-2,2′-diylhydrogen phosphate with rac-**5a**, **5a**·(+)-**9** 6-oxo-6a-phenyltetrahydro-1H,3H-furo[3,4-c][1,2]oxazol-1-ium (+)-1,1′-binaphthyl-2,2′-diylhydrogen phosphate.* To a flask containing *rac*-**5a** (50 mg, 0.244 mmol) and (*S*)-(+)-1,1′-binaphthyl-2,2′-diylhydrogen phosphate (85 mg, 0.244 mmol) was added hot MeOH (8 mL). The resulting solution was stirred at rt for 15 h prior to evaporation to dryness to yield the product as a white solid (135 mg, 100%); [found: C, 66.45; H, 4.61; N 2.23. $C_{31}H_{24}NPO_7\cdot 1/2H_2O$ requires C, 66.19; H, 4.48, N, 2.49%]; mp 110–119 °C; ν_{max} (KBr)/cm^{-1} 3410, 1777, 1590, 1507, 1326, 1231; δ_δ (300 MHz, CD_3OD) 8.09 (2H, d *J*=8.9) 7.99 (2H, d *J*=8.2) 7.60–7.55 (4H, m) 7.49–7.29 (5H, m) 7.27–7.22 (4H, m) 4.68–4.61 (1H, m) 4.47–4.44 (1H, m) 4.43–4.19 (2H, m) 3.75–3.68 (1H, m); δ_C (75.5, CD_3OD) 176.2, 147.6, 147.5, 132.3, 132.2, 142.1, 131.6, 130.8, 129.3, 129.1, 128.9, 128.3, 126.5, 126.4, 125.3, 121.4, 120.5, 79.0, 75.6, 71.2, 48.0.

*4.2.3. Preparation of the camphor sulfonic acid salt of rac-**6a**, **6a**.(+)-**10**-CSA 5-methyl-6a-phenylhexahydro-1H-pyrrolo[3,4-c][1,2]oxazol-1-ium (7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methane sulfonate.* *rac*-**6a** (200 mg, 9.169 mmol) and (+)-**10**-CSA (213 mg, 9.169 mmol) were dissolved in hot acetone (1.6 mL) and the solution was allowed to cool to rt until precipitation of white solid had completed (384 mg, 93%); [found: C, 58.70; H, 6.71; N 6.11. $C_{22}H_{30}N_2SO_6$ requires C, 58.66; H, 6.72, N, 6.22%]; mp 180–186 °C; ν_{max} (KBr)/cm^{-1} 3455, 2929, 2645, 1741, 1711, 1590, 1504, 1451, 1267; δ_δ (300 MHz, DMSO) 7.48–7.39 (5H, m) 6.48 (2H, br s) 4.16–4.06 (2H, m) 3.80 (1H, dd *J*=10.5 and 7.5) 3.44–3.38 (2H, br m) 2.91 (1H, d *J*=9.8) 2.78 (3H, s) 2.67–2.43 (2H, m) 2.30–2.21 (1H, m) 1.97–1.78 (3H, m) 1.36–1.24 (2H, m) 1.04 (3H, s) 0.75 (3H, s); δ_C (75.5, DMSO) 216.0, 170.3, 136.0, 128.4, 128.2, 126.6, 78.7, 76.6, 58.1, 51.5, 47.1, 46.8, 42.2, 40.3, 39.8, 29.8, 26.3, 24.1, 20.0, 19.5.

*4.2.4. Preparation of the camphor sulfonic acid salt of rac-**7a**, **7a**.(+)-**10**-CSA 5-methyl-6a-phenylhexahydro-1H-pyrrolo[3,4-c][1,2]oxazol-5-ium (7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methane sulfonate.* *rac*-**7a** (250 mg, 1.230 mmol) and (+)-**10**-CSA (290 mg, 1.230 mmol) were dissolved in warm acetone (2 mL). The resulting solution was allowed to cool to rt and stirring continued at rt until precipitation of the title product as a white solid was complete (540 mg, 100%). [found: C, 60.55; H, 7.41; N 6.27. $C_{22}H_{32}N_2SO_5$ requires C, 60.49; H, 7.39, N, 6.42%]; mp 170–176 °C; ν_{max} (KBr)/cm^{-1} 3447, 3224, 2975, 2497, 1735, 1457, 1240; δ_δ (300 MHz, $CDCl_3$) 11.01 (1H, br m) 7.52–7.28 (5H, m) 4.44–3.32 (6H, br m) 3.14–2.92 (4H, d, br m) 2.75 (1H, d *J*=14.5) 2.57–2.47 (1H, br m) 2.29–2.17 (1H, m) 2.04–1.93 (2H, m) 1.80–1.66 (2H, m) 1.37–1.29 (1H, m) 1.02 (3H, s) 0.78 (3H, s); δ_C (75.5, $CDCl_3$) 216.1, 138.5, 136.7, 128.1, 127.7, 127.4, 125.2, 77.8, 77.2, 64.4, 63.7, 59.4, 57.4, 53.0, 50.8, 50.3, 46.9, 46.4, 41.9, 41.6, 40.2, 39.8, 28.7, 26.0, 23.5, 18.8, 18.8.

*4.2.5. Preparation of the bis-salt from camphor sulfonic acid and rac-**7a**, **7a**.**2**(+)-**10**-CSA 5-methyl-6a-phenylhexahydro-1H-pyrrolo[3,4-c][1,2]oxazol-1,5-diium (7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl) methane sulfonate. rac*-**7a** (201 mg, 0.985 mmol) and (+)-**10**-CSA (460 mg, 1.980 mmol) were added to warm acetone (1.6 mL). Upon cooling to rt the bis-salt precipitated as a yellow solid (660 mg, 100%); HRMS: M+Na$^+$ found 691.2689. $C_{32}H_{48}N_2S_2O_9$ +Na$^+$ requires 691.2693 (diff −0.65 ppm); mp 97–106 °C; ν_{max} (KBr)/cm^{-1} 3451, 2960, 2571, 1741, 1646, 1455, 1168, 1039; δ_δ (300 MHz, $CDCl_3$) 10.93–10.51 (3H, br) 7.61–7.41 (5H, m) 4.89–3.70 (7H, br m) 3.12–3.07 (5H, br m) 2.65 (2H, d *J*=14.7) 2.24–2.22 (4H, m′) 2.03–1.89 (4H, m) 1.77 (2H, m) 1.62–1.53 (2H, m) 1.36–1.26 (2H, m) 0.98 (6H, s) 0.76 (6H, s); δ_C (75.5, $CDCl_3$) 216.7, 207.0, 133.8, 133.5, 133.3, 129.7, 129.6, 129.5, 129.3, 127.3, 127.2, 79.5, 79.4, 78.8, 76.7, 75.9, 63.7, 63.3, 60.9, 59.7, 58.3, 50.7, 50.2, 48.0, 47.5, 42.7, 42.6, 41.7, 40.9, 40.6, 30.9, 26.9, 24.5, 19.8, 19.7.

*4.2.6. Preparation of the camphor sulfonic acid salt of rac-**7b**, **7b**.(+)-**10**-CSA 5,6a-diphenylhexahydro-1H-pyrrolo[3,4-c][1,2]oxazol-1-ium (7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonate. rac*-**7b** (202 mg, 0.759 m mol) and (+)-**10**-CSA (176 mg, 0.759 mmol) were dissolved in hot acetone (1.2 mL) following cooling to rt stirring was continued until precipitation was complete. The salt was filtered and dried to yield the title product as a brown solid (365 mg, 97%); [found: C, 64.69; H, 6.75; N 5.46. $C_{27}H_{34}N_2SO_5$ requires C, 65.01; H,

6.88, N, 5.62%]; mp 110–118 °C; ν_{max} (KBr)/cm^{-1} 3424, 2958, 2663, 1741, 1600, 1501, 1197, 1038, 756; δ_δ (300 MHz, $CDCl_3$) 8.85 (2H, br s) 7.61–7.56 (2H, m) 7.39–7.30 (3H, m) 7.27–7.22 (2H, m) 6.85–6.76 (3H, m) 4.84 (1H, dd J=8.3 and 8.3) 4.39 (1H, dd J=7.4 and 3.9) 4.25 (1H, dd J=8.3 and 4.0) 3.92–3.85 (1H, m) 3.73–3.62 (3H, m) 3.03 (1H, d J=14.8) 2.51 (1H, d J=14.8) 2.42–2.32 (1H, ddd J=14.9, 12.0 and 3.8) 2.29–2.20 (1H, m) 1.98–1.95 (1H, m) 1.93–1.81 (1H, m) 1.75 (1H, br d J=18.3) 1.54–1.45 (1H, ddd J=14.9, 9.3 and 4.7) 1.28–1.2 (1H, m) 0.93 (3H, s) 0.70 (3H, s); δ_C (75.5, $CDCl_3$) 216.7, 146.9, 146.8, 135.7, 135.6, 129.3, 129.3, 129.2, 129.2, 126.7, 126.7, 119.4, 119.2, 114.7, 114.6, 78.9, 78.8, 78.2, 59.0, 58.8, 58.3, 54.6, 54.4, 50.3, 47.9, 47.4, 42.8, 42.6, 26.9, 24.6, 19.8, 19.8.

*4.2.7. Preparation of the bis-salt from camphor sulfonic acid and rac-**7b**, **7b.2**(+)-**10**-CSA 5,6a-diphenylhexahydro-1H-pyrrolo[3,4-c][1,2] oxazole-1,5-diium (7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonate.* rac-**7b** (150 mg, 0.564 mmol) and (+)-**10**-CSA (262 mg, 1.127 mmol) were dissolved in hot acetone (1.8 mL) and following cooling to rt stirring continued until precipitation was complete. The salt was filtered and dried to yield the title product as a dark green solid (390 mg, 95%); mp 84–96 °C; ν_{max} (KBr)/cm^{-1} 3415, 2960, 1744, 1600, 1415, 1154, 1038; δ_δ (300 MHz, $CDCl_3$) 12.32 (3H, br) 7.63–6.91 (10H, m) 4.87 (1H, dd J=8.3 and 8.3) 4.74 (1H, dd J=12.0 and 2.5) 4.45 (1H, br dd J=8.3 and 2.6) 4.20–4.19 (1H, m) 3.97 (1H, d J=12.0) 3.94–3.74 (2H, m) 3.18 (2H, d J=14.8) 3.71 (2H, d J=14.8) 2.40–2.25 (4H, m) 2.02–1.87 (4H, m) 1.77 (2H, d J=18.4) 1.62–1.53 (2H, m) 1.33–1.25 (2H, m) 0.97 (6H, s) 0.76 (6H, s); δ_C (75.5, $CDCl_3$) 217.4, 207.8, 144.3, 144.0, 133.8, 133.6, 129.8, 129.7, 129.4, 127.2, 129.2, 117.1, 116.8, 79.4, 77.5, 60.0, 59.9, 58.4, 56.4, 56.2, 49.8, 48.2, 47.8, 42.8, 42.6, 30.9, 26.9, 25.0, 19.8, 19.7.

*4.2.8. Classical resolution of **5a** with (+)-**10**-CSA.* In a modification of a literature procedure[34] *rac*-**5a** (234 mg, 1.143 mmol) and (+)-**10**-CSA (266 mg, 1.143 mmol) were dissolved in warm acetone (13.5 mL). After cooling to rt stirring was continued for a further 26 h. A first crop of white crystals was collected (145 mg, 58%) $[\alpha]_D^{25}$ +76 (*c* 0.0023, MeOH). The mother liquor and washings were concentrated to ≃7 mL and allowed to stir at rt for 4 h after which a second crop was collected (10 mg, 4%) $[\alpha]_D^{25}$ +74 (*c* 0.0072, MeOH). The mother liquor and washings were concentrated to ≃3.5 mL and left to stir at rt for 26 h prior to collection of a third crop (11 mg, 5%) $[\alpha]_D^{25}$ +56 (*c* 0.0006, MeOH). Total yield of (+)-**5a**·(+)-**10**-CSA based on the first two crops was 62%.

*4.2.9. Classical resolution of **5a** with (−)-**10**-CSA.* *rac*-**5a** (1500 mg, 7.314 mmol) and (−)-**10**-CSA (3199 mg, 7.314 mmol) were dissolved in warm acetone (58 mL). After cooling to rt stirring was continued for a further 26 h after which a first crop of crystals was collected (321 mg, 20%) $[\alpha]_D^{25}$ −74 (*c* 0.002, MeOH). The mother liquor and washings were concentrated to ≃49 mL and stirred continued at rt for 69 h prior to collection of a second crop (144 mg, 9%) $[\alpha]_D^{25}$ −78 (*c* 0.0099, MeOH). The collection/concentration process was repeated affording the following crops: third (93 mg, 6%) $[\alpha]_D^{25}$ +21 (*c* 0.008, MeOH), fourth (240 mg, 15%) $[\alpha]_D^{25}$ −75 (*c* 0.0011, MeOH), fifth (276 mg, 17%) $[\alpha]_D^{25}$ +36 (*c* 0.0014, MeOH). Total yield of (−)-**5a**·(−)-**10**-CSA (crops 1,2 and 4, all white solids) was 44%.

*4.2.10. Determination of optical purity of resolved **5a**.* (+)-**5a** $[\alpha]_D^{25}$ +112 (*c* 0.0010, MeOH) and (−)-**5a** $[\alpha]_D^{25}$ −110 (*c* 0.0064, MeOH) were obtained quantitatively by treatment of the corresponding salts, (+)-**5a**·(+)-**10**-CSA and (−)-**5a**·(−)-**10**-CSA with 1 M NaOH. Following extraction with CH_2Cl_2 optical purity was measured by HPLC using a chiracel OD column, mobile phase Hexane/*iso*-propyl alcohol (1:1), flow rate 1 mL/min; (+)-**5a** 7.9 min; (−)-**5a** 9.1 min (+)-**5b** was found with 90% ee; (−)-**5a** was found enantiomerically pure.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.01.034. These data include MOL files and InChIKeys of the most important compounds described in this article.

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