Highly stereoselective synthesis of indanes with four stereogenic centers *via* sequential Michael reaction and [3 + 2] cycloaddition†

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A highly efficient organocatalytic sequential reaction involving Michael addition of bis(phenylsulfonyl)ethylene, *in situ* condensation and intramolecular nitrone [3 + 2] cycloaddition with a variety of aldehydes and hydroxyamines to afford a single diastereomer of indanes with four stereogenic centers in excellent yields and stereoselectivities was developed.

Indane ring structures are widely presented in a number of naturally occurring products such as Gnetuhainin E[1] and Mirabiloside C,[2] and indane derivatives have attracted much attention due to the broad scope of their biological activities.[3] Although several approaches for the synthesis of this skeleton have been explored, they usually require multi-steps and expensive reagents. Thus we were interested in developing a sequential approach that allows the rapid establishment of these polycyclic indanes in a single operation.

Organocatalytic sequential reactions have gained importance in recent years as they provide attractive approaches to synthesize molecules with complex architecture without the need to isolate or purify intermediates. Direct Michael addition of carbonyl donors *via* enamine activation features an appealing route to obtain versatile functionalized adducts in an atom-economical manner. Much investigations have been done on nitroalkenes as Michael acceptors, but the use of vinyl sulfones in Michael reactions was left largely unexplored until Alexakis reported the first organocatalyzed asymmetric Michael addition of aldehydes to vinyl sulfones in 2005.[4] Since then, there has been some reports on the use of vinyl sulfones as Michael acceptors for reactions with various aldehydes,[5] ketones[6] and nitroalkanes.[7] However, to the best of our knowledge, there have been no reports on the application of vinyl sulfones in sequential reactions.

Besides the Michael reaction, the intramolecular nitrone/alkene cycloaddition is also another useful methodology that has attracted much attention in the synthesis of interesting frameworks found in numerous biologically active compounds.[8] Such reactions often provide products with high levels of regio- and stereocontrol. Our group has recently demonstrated the combination of these two useful reactions to furnish optically pure bicyclic isoxazolidines[9] and tetrahydronaphthalenes.[10] We reasoned that if we change the Michael acceptor to vinyl sulfones, we can provide a different dipolarophile to direct the stereochemistry of the cycloaddition products so as to obtain the indane skeleton with a very high level of stereocontrol. Herein, we present a highly stereocontrolled synthesis of indanes with four stereogenic centers *via* a sequential reaction involving Michael addition of bis(phenylsulfonyl)ethylene, *in situ* condensation and intramolecular nitrone [3 + 2] cycloaddition. This protocol may be useful in the synthesis of biologically interesting compounds due to the versatility of the multi-substituents on the tricyclic heterocycles, simple operating procedures and excellent stereocontrol.

To assess the viability of this sequential approach, we first synthesized our rationally designed substrate **1a** through a series of simple transformations (for details, see the ESI†). We started our investigation by conducting the Michael reaction with aldehyde **1a**, 1,1-bis(phenylsulfonyl)-ethylene **2** and catalyst **I** in dichloromethane at −20 °C. Upon completion of reaction, hydroxyamine **3a** was then added to the reaction mixture and stirred at 22 °C for 3 h. To our delight, the desired product **4a** was isolated as a single diastereomer in 92% yield and 94% enantiomeric excess (ee) (Table 1, entry 1). Changing the catalyst did not give any significant improvements to the results (Table 1, entries 2–4). Though catalyst **IV**[11] gave slightly higher ee, its yield was significantly lower than that with catalyst **I**. Thus, catalyst **I** was chosen for further optimization of the reaction conditions. Out of curiosity, we explored the effects of increasing the equivalents of aldehyde **1a** to 3 equivalents (Table 1, entry 5). As expected, there were slight improvements in both the yield and enantioselectivity, but it seems unjustifiable to use large excess of substrate for such minor improvements. A brief solvent screening revealed that toluene is the best solvent as it gave the highest yield and enantioselectivity (Table 1, entries 6–9). Next, we investigated the effects of catalyst loading (Table 1, entries 10 and 11). Decreasing the catalyst loading to 5 mol% of catalyst **I** appeared to be the most suitable as a further decrease in the catalyst loading led to a loss of enantioselectivity. We also looked into the influence of temperature on the reaction (Table 1, entry 12). Lower yield and enantioselectivity were observed for the reaction that was conducted at 4 °C for the first step. In view of the above optimizations, the most suitable reaction conditions for the sequential reaction was determined to be aldehyde **1a** (1.5 equiv.), catalyst **I** (5 mol%) and 1,1-bis(phenylsulfonyl)-ethylene **2** (0.05 mmol) in toluene (0.3 mL) at −20 °C, followed by addition of hydroxyamine **3a** (1.5 equiv.) at 22 °C for 3 h upon completion of the first step.

With the optimized reaction conditions in hand, we explored the generality of the sequential Michael/[3 + 2] cycloaddition reaction. For all the substrates investigated, we only observed

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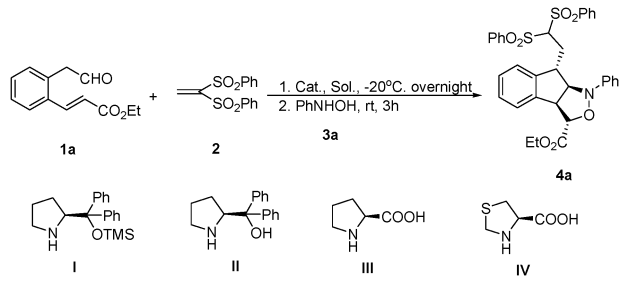
Table 1 Optimization of reaction conditions[a]



Entry	Solvent	Catalyst	Yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	**I**	92	94
2	CH_2Cl_2	**II**	59	39
3	CH_2Cl_2	**III**	75	60
4	CH_2Cl_2	**IV**	76	98
5[d]	CH_2Cl_2	**I**	96	95
6	$CHCl_3$	**I**	81	97
7	THF	**I**	65	81
8	EA	**I**	65	85
9[e]	Toluene	**I**	89	97
10[e,f]	**Toluene**	**I**	**98**	**98**
11[e,g]	Toluene	**I**	91	95
12[e,f,h]	Toluene	**I**	82	76

[a] Conditions: aldehyde **1a** (1.5 equiv.) was added to catalyst (10 mol%), 1,1-bis(phenylsulfonyl)-ethylene **2** (0.05 mmol) and solvent (0.1 mL) at −20 °C and upon completion of reaction, hydroxyamine **3a** (1.5 equiv.) was then added to the reaction mixture and stirred at 22 °C for 3 h, unless otherwise stated. [b] Isolated yields. [c] Determined by chiral phase HPLC. [d] 3 equiv. of **1a** used. [e] 0.3 mL of toluene. [f] 5 mol% catalyst loading. [g] 2 mol% catalyst loading. [h] Reaction conducted at 4 °C for the first step.

a single diastereomer for the sequential reactions and the products were obtained in excellent yields and ee with a variety of aldehydes **1** and hydroxyamines **3** (Table 2). First of all, we investigated the effects of using different hydroxyamines (Table 2, entries 1–7). Although the position and electronic properties of the substituents on the aromatic rings of hydroxyamines do not significantly affect the yield and enantioselectivity of the sequential reaction (Table 2, entries 2–6), we noticed that *ortho*- and *meta*-substituted hydroxyamines require harsher reaction conditions for the cycloaddition reaction (Table 2, entries 3 and 5). Not only were aryl hydroxyamines **3a–3f** able to give good results for the reaction, alkyl hydroxyamine **3g** was also able to afford comparable results (Table 2, entry 7). The yields and enantioselectivities were not significantly affected by changing the ester group (Table 2, entry 8) or the substituents of aldehyde **1** (Table 2, entries 9 and 10).

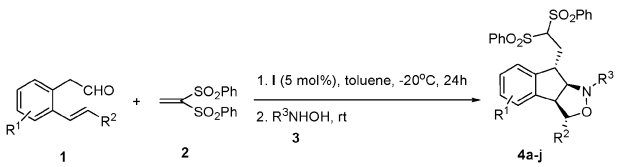
With the success of employing the above reaction protocol for *ortho*-substituted phenylacetaldehydes, we decided to try linear aldehydes. The reaction proceeded smoothly in the presence of (*E*)-methyl 7-oxohept-2-enoate (**1e**) to afford the bicyclic compound **4k** in 94% yield and 94% ee (Scheme 1). This demonstrated that the reaction protocol is not only restricted to *ortho*-substituted phenylacetaldehyde and is applicable to linear aldehydes of suitable chain length.

To determine whether the enantioselectivity of this tandem reaction is dependent on the initial Michael reaction, we isolated the Michael product **A** with 97% ee (Scheme 2). This demonstrated that this stereocenter controls the formation of the other stereogenic centers.

Based on X-ray structural analysis of product **4d**, the stereochemistry of **4d** was assigned (CCDC 778385†) and this was in accordance with our prediction. In addition, we subjected indane **4a** to the cleavage of the N–O bond to afford α-hydroxy-γ-amino acid derivative **5** in almost quantitative yield and with no significant loss of enantioselectivity (Scheme 3).

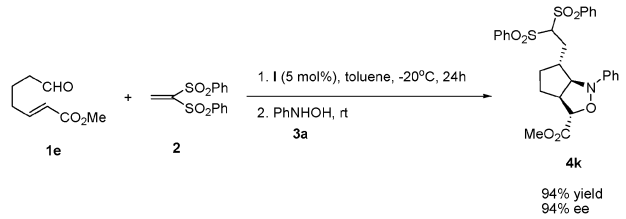
Furthermore, we also treated indane **4j** with magnesium for desulfonylation. To our surprise, in addition to successful desulfonylation, the cleavage of the N–O bond afforded α-hydroxy-γ-lactam derivative **6** in moderate yield with 94% ee (Scheme 4). Both derivatives **5** and **6** may have potential applications in synthetic organic chemistry and the pharmaceutical industry.

Table 2 Generality of the sequential Michael reaction–[3 + 2] cycloaddition[a]

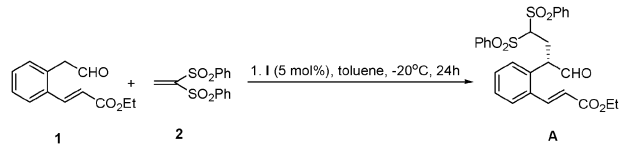


Entry	R^1	R^2	R^3	Product	Yield (%)[b]	ee (%)[c]
1	H	CO_2Et	Ph	**4a**	98	98
2	H	CO_2Et	4-BrC_6H_4	**4b**	92	96
3[d]	H	CO_2Et	3-ClC_6H_4	**4c**	97	98
4[e]	H	CO_2Et	4-ClC_6H_4	**4d**	92	98
5[d]	H	CO_2Et	2-$CH_3C_6H_4$	**4e**	97	95
6	H	CO_2Et	4-$CH_3C_6H_4$	**4f**	96	98
7	H	CO_2Et	CH_2Ph	**4g**	91	98
8	H	CO_2Me	Ph	**4h**	90	98
9[e,f]	3-OMe	CO_2Et	Ph	**4i**	98	92
10	3,4-OCH_2O	CO_2Et	Ph	**4j**	97	99

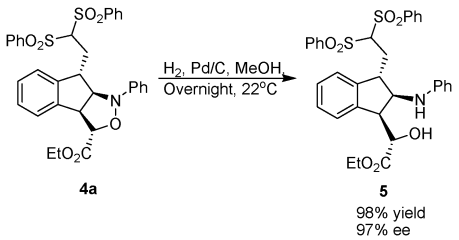
[a] Conditions: corresponding aldehyde **1** (1.5 equiv.) was added to catalyst **I** (5 mol%), 1,1-bis(phenylsulfonyl)ethylene **2** (0.1 mmol) and toluene (0.6 mL) at −20 °C and upon completion of reaction, respective hydroxyamine **3** (1.5 equiv.) was then added to the reaction mixture and stirred at 22 °C for 3 h, unless otherwise stated. [b] Isolated yields. [c] Determined by chiral phase HPLC. [d] Reaction conducted at 50 °C for the second step. [e] Reaction was conducted for 4 h for the second step. [f] Reaction was conducted for 48 h for the first step.



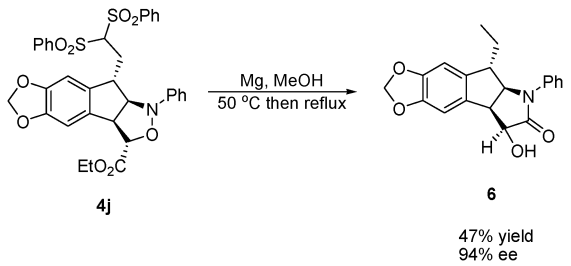
Scheme 1 Synthesis of bicyclic compound **4k**.



Scheme 2 Isolated Michael product **A**.



Scheme 3 Synthesis of α-hydroxy-γ-amino acid **5**.



Scheme 4 Synthesis of α-hydroxy-γ-lactam **6**.

In conclusion, we have developed an organocatalytic sequential approach involving Michael addition of bis(phenylsulfonyl)ethylene, *in situ* condensation and intramolecular nitrone [3 + 2] cycloaddition with a variety of aldehydes and hydroxyamines to afford a single diastereomer of indanes with four stereogenic centers with excellent yields and stereoselectivities. The advantages of this reaction protocol lie in the versatility of the multi-substituents on the indane core structure, simple operating procedures and excellent stereocontrol.

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