The First Organocatalytic Hetero-Domino Knoevenagel–Diels–Alder-Epimerization Reactions: Diastereoselective Synthesis of Highly Substituted Spiro[cyclohexane-1,2′-indan]-1′,3′,4-triones

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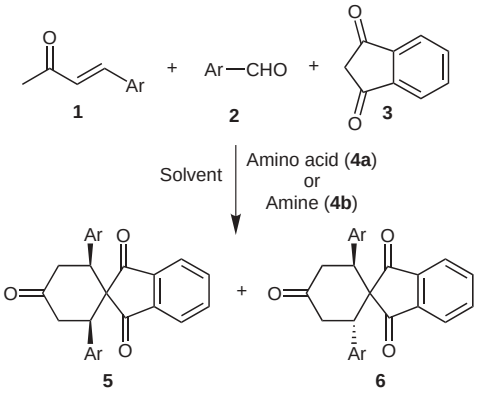
Abstract: L-Proline and pyrrolidine catalyzed the three component hetero-domino Knoevenagel–Diels–Alder–Epimerization reactions of readily available precursors enones **1a**–**i**, arylaldehydes **2a**–**i** and 1,3-indandione **3** to furnish highly substituted prochiral spiro[cyclohexane-1,2′-indan]-1′,3′,4-triones **5a**–**i** in a highly diastereoselective fashion with excellent yields. We demonstrate the first L-proline and pyrrolidine catalyzed epimerization reactions of *trans*-spiranes **6a**–**i** to *cis*-spiranes **5a**–**i**. Prochiral spiranes **5a**–**i** are excellent starting materials for the synthesis of benzoannelated centropolyquinanes.

Key words: 2-amino-1,3-butadiene, Diels–Alder reaction, domino reactions, organocatalysis, organic Lewis acid

One of the ultimate goals in organic chemistry is the catalytic asymmetric assembly of simple and readily available precursor molecules into stereochemically complex products. In this regard, the development of domino and other multicomponent reaction methodologies can provide expedient access to complex products from simple starting materials.[1] Key to many interesting variants of these reactions is the incorporation of a Diels–Alder reaction sequence.[2] Recently organocatalysis has emerged as a promising synthetic tool for constructing C–C and C–N bonds in aldol,[3] Michael,[4] Mannich,[5] Diels–Alder[6] and related reactions[7] with high diastereoselectivity and enantioselectivity. In these recently described reactions, structurally simple and stable chiral organoamines facilitate iminium- and enamine-based transformations with carbonyl compounds and may be used as catalysts in operationally simple and in some cases environmentally friendly experimental protocols. Extending our studies of organoamine-catalyzed aldol,[3a–d] Michael,[4a,b] Mannich[5a–c] and related reactions[7c,g] founded on enamine catalysis, we reported the first direct asymmetric Diels–Alder reactions of α,β-unsaturated ketones with nitro olefins using in situ generated 2-amino-1,3-butadienes as diene.[6a]

As part of our program to develop novel organocatalytic assembly or multicomponent reactions,[3c,d,4a,5c,7g] herein we report the first highly diastereoselective organocatalytic direct hetero-domino Knoevenagel–Diels–Alder-Epimerization (K–DA-E) reactions that provide highly substituted prochiral spiro[cyclohexane-1,2′-indan]-1′,3′,4-triones **5** from commercially available 4-substituted-3-buten-2-ones **1a**–**i**, aldehydes **2a**–**i** and 1,3-indandione **3** (Scheme 1). Spirocyclic ketones **5** are attractive intermediates in the synthesis of natural products and in materials chemistry and are the excellent starting materials for the synthesis of fenestranes, which could serve as unusual motifs for liquid crystal engineering and dendrimer chemistry, and for the construction of graphite cuttings bearing a saddle-like, three-dimensionally distorted core.[8]



Scheme 1 Organocatalytic hetero-domino K–DA-E reaction of arylidene acetones **1**, arylaldehydes **2** and 1,3-indandione **3**

In our reaction we envisioned that L-proline (**4a**) and pyrrolidine (**4b**) would catalyze the domino Knoevenagel condensation of aldehyde **2** with 1,3-indandione **3** to provide arylidene indandione **8**, which would then undergo a concerted [4+2] cycloaddition with a 2-amino-1,3-butadiene generated in situ from enone **1** and proline or pyrrolidine to form substituted spiro[cyclohexane-1,2′-indan]-1′,3′,4-triones **5** and **6** in a diastereoselective manner. Epimerization of the minor diastereomer *trans*-spirane **6** to the more stable *cis*-spirane **5** could occur under the same reaction conditions as shown in Scheme 2. The domino Knoevenagel–Diels–Alder reaction would then generate a quaternary center with formation of three new carbon–carbon σ-bonds via organocatalysis. This proposal was reflective of the pioneering studies of Tietze[1a,b] and our recent disclosure of the first direct asymmetric Knoevenagel–Michael reactions with ketones, aldehydes and malonates involving alkylidene

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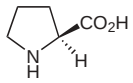
Table 1 Catalyst and Solvent Effect on Organocatalytic Hetero-Domino K–DA-E Reaction of *trans*-4-Phenyl-3-buten-2-one (**1a**), Benzaldehyde (**2a**) and 1,3-Indandione (**3**)[a]



4a

4b

Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Products	Yield (%)[b]	Dr[c] **5aa**:**6aa**
1	**4a**	CH_3OH	24	24	**5aa**, **6aa**	87	66:33
2	**4a**	CH_3OH	24	96	**5aa**	96	>100:1
3	**4a**	CH_3OH	70	2	**5aa**	96	>100:1
4	**4a**	[bmim]BF_4	24	24	**5aa**, **6aa**	53	33:66
5	**4a**	[bmim]PF_6	24	96	**5aa**, **6aa**	55	33:66
6	**4b**	CH_3OH	24	8	**5aa**	90	>100:1
7	**4b**	CH_3OH	70	0.75	**5aa**	90	>100:1
8	**4b**	THF	24	7	**5aa**	85	>100:1
9	**4b**	$CHCl_3$	24	7	**5aa**	70	>100:1
10	**4b**	DMSO	24	70	**5aa**	75	>100:1
11	**4b**	DMF	24	24	**5aa**	80	>100:1
12[d]	**4b**	CH_3OH	70	1	**5aa**	95	>100:1

[a] Experimental conditions: L-Proline (0.1 mmol) or pyrrolidine (0.15 mmol), benzaldehyde **2a** (0.5 mmol) and 1,3-indandione **3** (0.5 mmol) in the solvent (1 mL) was stirred at ambient temperature for 30 min then enone **1a** (1 mmol) was added (see experimental section).
[b] Yield refers to the purified product obtained by column chromatography.
[c] Ratio based on NMR analysis of unpurified products.
[d] Enone **1a**, benzaldehyde **2a** and 1,3-indandione (**3**) were all used on a 0.5 mmol scale.

malonates generated under organocatalysis that subsequently react as electrophiles with ketone derived enamines also generated under organocatalysis.[4a]

We were pleased to find that the three-component reaction of *trans*-4-phenyl-3-buten-2-one (**1a**), benzaldehyde **2a** and 1,3-indandione (**3**) with a catalytic amount of L-proline in methanol at ambient temperature for 24 hours furnished Diels–Alder products **5aa** and **6aa** in 87% yield with prochiral spirane **5aa** as the major isomer (Table 1, entry 1). The same reaction albeit with an extended reaction time furnished *cis*-spirane **5aa** as a single diastereomer in 96% yield (Table 1, entry 2). The minor diastereomer, *trans*-spirane **6aa** was effectively epimerized to the thermodynamically stable *cis*-spirane **5aa** under prolonged reaction times via proline catalysis. Significantly, pyrrolidine also catalyzed the hetero-domino K–DA-E reaction at ambient temperature to furnish *cis*-spirane **5aa** as a single diastereomer in 90% yield (Table 1, entry 6). The stereochemistry of products **5aa** and **6aa** was established by NMR analysis.[9]

In the three-component hetero-domino K–DA-E reaction of enone **1a**, benzaldehyde **2a** and 1,3-indandione (**3**) catalyzed directly by L-proline or pyrrolidine, we found that the solvent (dielectric constant) and temperature had a significant effect on reaction rates, yields and drs (Table 1). Our studies revealed that the hetero-domino K–DA-E reaction catalyzed by L-proline produces products **5aa** and **6aa**[10] in low yields and poor selectivity in aprotic nonpolar solvents (results not shown) and with excellent yields and selectivity in protic/polar solvents (Table 1, entries 1–3). The same reaction in the ionic liquids [bmim]BF_4 and [bmim]PF_6 catalyzed by L-proline provided the kinetic product *trans*-spirane **6aa** as the major diastereomer in moderate yield (Table 1, entry 4 and 5).[10] Under pyrrolidine catalysis, the hetero-domino K–DA-E reaction worked well in various solvents and the optimal conditions involved mixing equimolar amounts of enone **1a**, aldehyde **2a** and dione **3** in methanol with heating to 70 °C for one hour to furnish *cis*-spirane **5aa** as a single diastereomer in 95% yield.

Diastereospecific synthesis of *cis*-spirane **5aa** in the reaction of enone **1a**, benzaldehyde **2a** and 1,3-indandione (**3**) can be explained as illustrated in Scheme 2. Amine-catalyzed Knoevenagel condensation[11] of aldehyde **2a** with 1,3-indandione (**3**) provides the benzylidene-indandione (**8a**) via imine cation **7a**, which is an excellent organic Lewis acid[12] that undergoes a Diels–Alder or a double Michael reaction with the soft nucleo-

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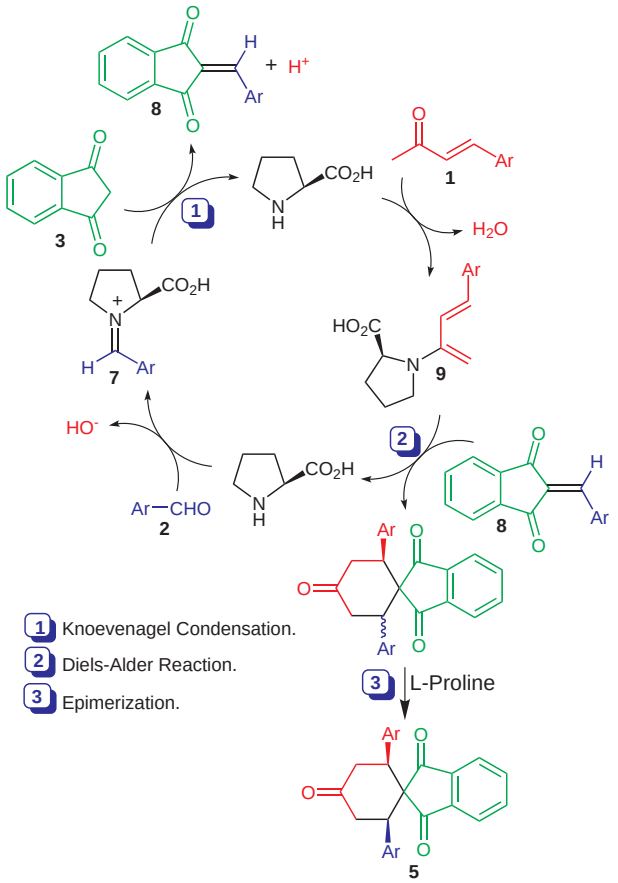
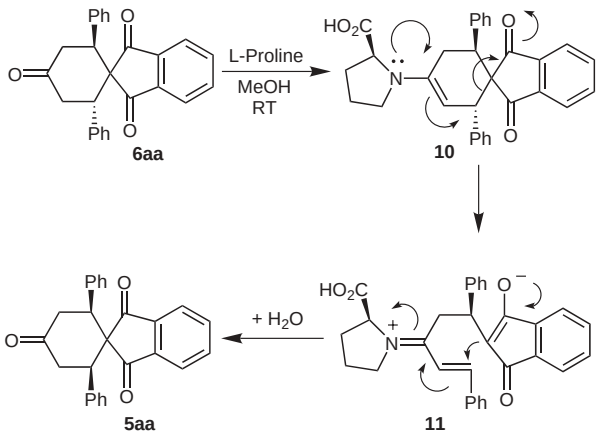


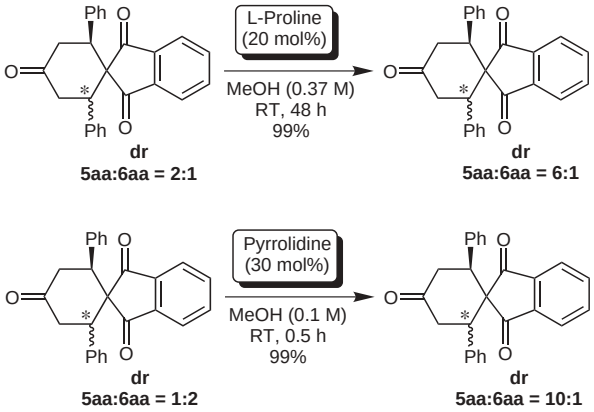
Scheme 2 Proposed catalytic cycle for the L-proline (or pyrrolidine) catalyzed hetero-domino K–DA–E reactions

phile 2-amino-1,3-butadiene (**9a**) generated in situ from enone **1a** and the amine catalyst to produce products **5aa** and **6aa**. The minor *trans*-spirane isomer **6aa** was epimerized to the thermodynamically stable *cis*-spirane **5aa** via deprotonation/reprotonation or retro-Michael/Michael reactions catalyzed by L-proline and pyrrolidine. We favor the later mechanism, see Scheme 3.



Scheme 3 Proposed mechanism for the L-proline catalyzed epimerization of *trans*-spirane **6aa**

Epimerization of *trans*-spirane **6aa** to *cis*-spirane **5aa** was confirmed by the L-proline and pyrrolidine catalyzed reaction in methanol at ambient temperature (Scheme 4). The epimerization reaction catalyzed by pyrrolidine was significantly faster than proline catalysis in methanol. No epimerization was observed in the absence of catalyst.



Scheme 4 Organocatalytic epimerization of *trans*-spirane **6aa** to *cis*-spirane **5aa**

We further explored the scope of the pyrrolidine catalyzed hetero-domino K–DA-E reaction with various arylaldehydes **2b–i** and 4-substituted-3-buten-2-ones **1b–i**. Each of the targeted prochiral spirotriones **5** were obtained as single diastereomers in excellent yields. Prochiral spiranes **5bb–ii** were generated in very good yields with aromatics bearing either electron withdrawing or electron donating groups in the *para* position as shown in Table 2. The prochiral hetero aromatic *cis*-spirane **5ii** was also synthesized in good yield under the same reaction conditions (Table 2, entry 9).

Prochiral *cis*-spirane **5aa** is an excellent starting material for the synthesis of tetrabenzo[5.5.5.5]fenestrane (fenestrindane)[8a,h] as shown in Scheme 5 and spiranes **5bb–hh** could serve as suitable synthons for the synthesis of fenestrindanes with fourfold peripheral functionalization. These functionalized fenestrindanes should provide materials with a range of physical characteristics.

In summary, we have developed the first amino acid and amine catalyzed direct hetero-domino K–DA-E reactions. This astonishingly simple and atom-economic approach can be used to construct highly substituted prochiral spiro[cyclohexane-1,2′-indan]-1′,3′,4-triones **5** in a diastereospecific fashion. A full account detailing asymmetric variants of this reaction will be forthcoming. Selective multi-step reactions of this type inspire analogies with biosynthetic pathways and compliment traditional multicomponent synthetic methodologies. As we have suggested previously, the synthesis of polyfunctionalized molecules under organocatalysis provides a unique and under explored perspective on prebiotic synthesis. A complete understanding of the scope of organocatalysis should not only empower the synthetic chemist but also

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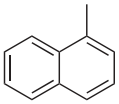
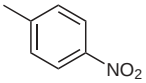
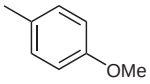
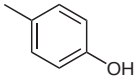
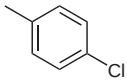
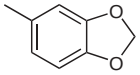
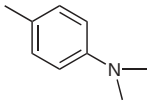
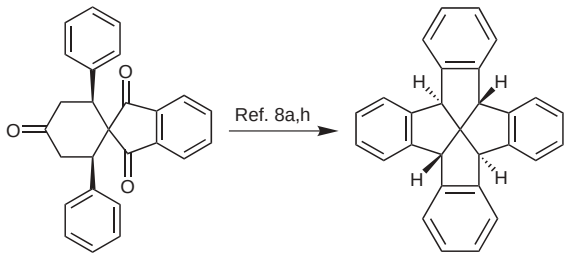
Table 2 Pyrrolidine Catalyzed Hetero-Domino K–DA-E Reactions of Various *trans*-4-Aryl-3-buten-2-ones **1a–i**, Arylaldehydes **2a–i** and 1,3-Indandione (**3**) in Methanol[a]

Entry	Ar	Products	Yield (%)[b]	Dr[c] **5**:**6**
1		**5aa**	93	>100:1
2		**5bb**	95	>100:1
3		**5cc**	98	>100:1
4		**5dd**	95	>100:1
5		**5ee**	95	>100:1
6		**5ff**	98	>100:1
7		**5gg**	98	>100:1
8		**5hh**	90	>100:1
9		**5ii**	93	>100:1

[a] Experimental conditions: Pyrrolidine (0.15 mmol), arylaldehydes **2a–i** (0.5 mmol) and 1,3-indandione (**3**) (0.5 mmol) in MeOH (1 mL) was stirred at ambient temperature for 30 min then arylidene acetones **1a–i** (0.5 mmol) was added and heated to 70 °C for 1–2 h (see experimental section).

[b] Yield refers to the purified product obtained by column chromatography.

[c] Ratio based on NMR analysis of unpurified products.



5aa **12**
all-cis-[5.5.5.5]fenestrane

Scheme 5 Application of *cis*-spirane **5aa** in the synthesis of benzo-annelated centropolyquinanes

provide a new perspective on the origin of complex molecular systems.

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References

(1) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) Tietze, L. F.; Evers, T. H.; Topken, E. *Angew. Chem. Int. Ed.* **2001**, *40*, 903. (d) Oikawa, Y.; Hirasawa, H.; Yonemitsu, O. *Tetrahedron Lett.* **1978**, 1759. (e) Oikawa, Y.; Hirasawa, H.; Yonemitsu, O. *Chem. Pharm. Bull.* **1982**, *30*, 3092.

(2) (a) Evans, D. A.; Johnson, J. S. *Comprehensive Asymmetric Catalysis*, Vol. 3; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: New York, **1999**, 1177. (b) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (c) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. (d) Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662. (e) Corey, E. J.; Perez, A. G. *Angew. Chem. Int. Ed.* **1998**, *37*, 388; *Angew. Chem.* **1998**, *110*, 402.

(3) (a) List, B.; Lerner, R. A.; Barbas, C. F. III *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. III *J. Am. Chem. Soc.* **2001**, *123*, 5260. (c) Cordova, A.; Notz, W.; Barbas, C. F. III *J. Org. Chem.* **2002**, *67*, 301. (d) Chowdari, N. S.; Ramachary, D. B.; Cordova, A.; Barbas, C. F. III *Tetrahedron Lett.* **2002**, *43*, 9591. (e) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (f) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Jorgensen, K. A. *Chem. Commun.* **2002**, 620. (g) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167.

(4) (a) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F. III *Tetrahedron Lett.* **2001**, *42*, 4441. (b) Betancort, J. M.; Barbas, C. F. III *Org. Lett.* **2001**, *3*, 3737. (c) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894. (d) Enders, D.; Seki, A. *Synlett* **2002**, 26. (e) Halland, N.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331. (f) List, B.; Castello, C. *Synlett* **2001**, *11*, 1687. (g) Halland, N.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331.

(5) (a) Notz, W.; Sakthivel, K.; Bui, T.; Barbas, C. F. III *Tetrahedron Lett.* **2001**, *42*, 199. (b) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F. III *J. Am. Chem. Soc.* **2002**, *124*, 1842. (c) Cordova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F. III *J. Am. Chem. Soc.* **2002**, *124*, 1866. (d) Watanabe, S.; Cordova, A.; Tanaka, F.; Barbas, C. F. III *Org. Lett.* **2002**, *4*, 4519. (e) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.

(6) (a) Thayumanavan, R.; Ramachary, D. B.; Sakthivel, K.; Tanaka, F.; Barbas, C. F. III *Tetrahedron Lett.* **2002**, *43*, 3817. (b) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F. III *Tetrahedron Lett.* **2002**, *43*, 6743. (c) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. (d) Nakamura, H.; Yamamoto, H. *Chem. Commun.* **2002**, 1648. (e) Asato, A. E.; Watanabe, C.; Li, X.-Y.; Liu, R. S. H. *Tetrahedron Lett.* **1992**, *33*, 3105.

(7) (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (c) Bui, T.; Barbas, C. F. III *Tetrahedron Lett.* **2000**, *41*, 6951. (d) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jorgensen, K. A.

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Angew. Chem. Int. Ed. **2002**, *41*, 1790. (e) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (f) Rajagopal, D.; Moni, M. S.; Subramanian, S.; Swaminathan, S. *Tetrahedron: Asymmetry* **1999**, *10*, 1631. (g) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F. III *Org. Lett.* **2003**, *5*, 1685.

(8) (a) Bredenkotter, B.; Florke, U.; Kuck, D. *Chem.–Eur. J.* **2001**, *7*, 3387. (b) Tellenbroker, J.; Kuck, D. *Eur. J. Org. Chem.* **2001**, 1483. (c) Bredenkotter, B.; Barth, D.; Kuck, D. *Chem. Commun.* **1999**, 847. (d) Thommen, M.; Keese, R. *Synlett* **1997**, 231. (e) Seifert, M.; Kuck, D. *Tetrahedron* **1996**, *52*, 13167. (f) Kuck, D. *Chem. Ber.* **1994**, *127*, 409. (g) Kuck, D.; Schuster, A.; Krause, R. A. *J. Org. Chem.* **1991**, *56*, 3472. (h) Kuck, D.; Bogge, H. *J. Am. Chem. Soc.* **1986**, *108*, 8107. (i) Hoeve, W. T.; Wynberg, H. *J. Org. Chem.* **1980**, *45*, 2925. (j) Hoeve, W. T.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 1508.

(9) **General Experimental Procedure for the Preparation of Prochiral Spiro[cyclohexane-1,2′-indan]-1′,3′,4-triones by Using L-Proline and Pyrrolidine Catalyzed Hetero-Domino Knoevenagel–Diels–Alder–Epimerization Reaction: Method A.** In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of the aldehyde and 0.5 mmol of 1,3-indandione was added 1.0 mL of solvent, and then the catalyst L-proline (0.1 mmol) or pyrrolidine (0.15 mmol) was added and the reaction mixture was stirred at ambient temperature for 15–30 min. When the reaction mixture solidified, more solvent was added, 0.5 mL. Then 0.5 mmol of the enone was added and the reaction stirred at 70 °C for 1–2 h (Table 2). The crude reaction mixture was treated with saturated aq NH_4Cl solution, the layers were separated, and the organic layer was extracted three to four times with CH_2Cl_2 (10 mL), dried with anhyd Na_2SO_4, and evaporated. The pure Domino products were obtained by flash column chromatography (silica gel, mixture of hexane/EtOAc). **Method B.** In an ordinary glass vial equipped with a magnetic stirring bar, to 0.5 mmol of aldehyde, 0.5 mmol of enone, 0.5 mmol of 1,3-indandione was added 1.0 mL of solvent, and then the catalyst L-proline (0.1 mmol) or pyrrolidine (0.15 mmol) was added and the reaction mixture was heated slowly to 70 °C with stirring for 1–h. the Domino products were isolated as in Method A. Both methods gave identical results. **(2β,6β)-2,6-Diphenylspiro[cyclohexane-1,2′-indan]-1′,3′,4-trione(5aa).** Plane of symmetry with chair conformation. ^{1}H NMR (399 MHz, $CDCl_3$): δ = 7.64 (1 H, td, *J* = 7.6 and 1.2 Hz), 7.48 (1 H, m), 7.41 (2 H, m), 7.08–6.90 (10 H, m, 2 × Ph-*H*), 3.81 (4 H, m), 2.66 (2 H, ABq, *J* = 17.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.4 (C, C=O), 203.4 (C, C=O), 201.8 (C, C=O), 142.7 (C, C-8′), 141.9 (C, C-9′), 137.3 (2 × C), 135.2 (2 × CH), 128.3 (4 × CH), 128.0 (4 × CH), 127.6 (2 × CH), 122.4 (CH), 122.0 (CH), 62.0 (C, C-1 or C-2′), 48.7 (2 × CH), 43.4 (2 × CH_2). HRMS (MALDI-FTMS): *m/z* = 381.1492 [M + H^+], calcd for $C_{26}H_{20}O_3H^+$ 381.1485. **(2β,6α)-2,6-Diphenylspiro[cyclohexane-1,2′-indan]-1′,3′,4-trione(6aa).** C_2-Symmetry with twist conformation. ^{1}H NMR (399 MHz, $CDCl_3$): δ = 7.57 (2 H, m), 7.52 (2 H, m), 7.08–6.90 (10 H, m, 2 × Ph-*H*), 3.99 (2 H, dd, *J* = 13.5 and 3.2 Hz, H-2 and 6), 3.62 (2 H, dd, *J* = 16.3 and 13.5 Hz, H-3β and 5β), 2.78 (2 H, dd, *J* = 16.7 and 3.2 Hz, H-3α and 5α). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.0 (C, C=O), 202.8 (2 × C, C=O), 142.0 (2 × C, C-8′ and 9′), 137.2 (2 × C), 135.3 (2 × CH, C-7′ and 4′), 128.3 (4 × CH), 128.1 (4 × CH), 127.3 (2 × CH), 122.4 (2 × CH, C-5′ and 6′), 61.5 (C, C-1 or 2′), 43.4 (2 × CH, C-6 and 2), 41.5 (2 × CH_2, C-3 and 5). HRMS (MALDI-FTMS): *m/z* = 403.1300 [M + Na^+], calcd for $C_{26}H_{20}O_3Na^+$ 403.1305.

(10) Formation of the kinetic product, *trans*-spirane **6aa** as the major isomer in ionic liquids, as opposed to the *cis*-spirane **5aa** through the *endo*-transition state in the classical Diels–Alder route is likely explained by unique solvation in the ionic liquid of the 2-amino-1,3-butadiene **9a** and dienophile **8a** in the transition states shown below. Asymmetric solvation in the ionic liquids may produce a steric hindrance with the phenyl group on the dienophile, in the endo-transition state, thereby disfavoring it (Figure 1).

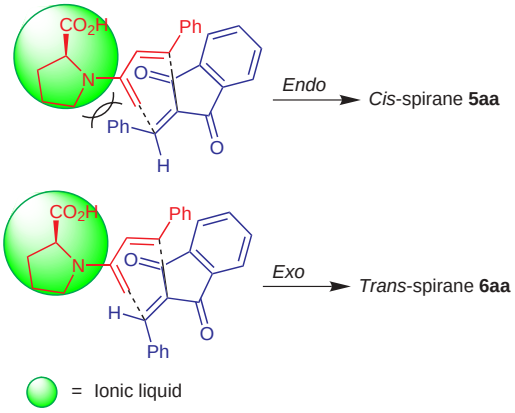

Figure 1

(11) (a) Tanikaga, R.; Konya, N.; Hamamura, K.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3211. (b) Tietze, L. F.; Beifuss, U. *The Knoevenagel Reaction,* In *Comprehensive Organic Synthesis*, Vol. 2; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, Chap. 1.11, 341–392.

(12) (a) Haslinger, E.; Wolschann, P. *Bull. Soc. Chim. Belg.* **1977**, *86*, 907. (b) Margaretha, P. *Tetrahedron* **1972**, *28*, 83.

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