JOC Articles

Direct Organocatalytic Asymmetric Heterodomino Reactions: The Knoevenagel/Diels−Alder/Epimerization Sequence for the Highly Diastereoselective Synthesis of Symmetrical and Nonsymmetrical Synthons of Benzoannelated Centropolyquinanes

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Amino acids and amines have been used to catalyze three component hetero-domino Knoevenagel/Diels−Alder/epimerization reactions of readily available various precursor enones (**1a**−**l**), aldehydes (**2a**−**p**), and 1,3-indandione (**3**). The reaction provided excellent yields of highly substituted, symmetrical and nonsymmetrical spiro[cyclohexane-1,2′-indan]-1′,3′,4-triones (**5**) in a highly diastereoselective fashion with low to moderate enantioselectivity. The Knoevenagel condensation of arylaldehydes (**2a**−**p**) and 1,3-indandione (**3**) under organocatalysis provided arylidene-1,3-indandiones (**17**) in very good yields. We demonstrate for the first time amino acid- and amine-catalyzed epimerization reactions of *trans*-spiranes (**6**) to *cis*-spiranes (**5**). The mechanism of conversion of *trans*-spiranes (**6**) to *cis*-spiranes **5** was shown to proceed through a retro-Michael/Michael reaction rather than deprotonation/reprotonation by isolation of the morpholine enamine intermediate of *cis*-spirane (**22**). Prochiral *cis*-spiranes (**5ab**) and *trans*-spiranes (**6ab**) are excellent starting materials for the synthesis of benzoannelated centropolyquinanes. Under amino acid and amine catalysis, the topologically interesting dispirane **24** was prepared in moderate yields. Organocatalysis with pyrrolidine catalyzed a series of four reactions, namely the Michael/retro-Michael/Diels−Alder/epimerization reaction sequence to furnish *cis*-spirane **5ab** in moderate yield from enone **1a** and 1,3-indandione **3**.

Introduction

Critical objectives in modern synthetic organic chemistry include the improvement of reaction efficiency, the avoidance of toxic reagents, the reduction of waste, and the responsible utilization of our resources. Domino or tandem reactions, which consist of several bond-forming reactions, address many of these objectives. Domino reactions involve two or more bond-forming transformations that take place under the same reaction conditions. Combinations of reactions involving the same mechanism are classified as homodomino reactions, whereas a sequence of reactions with different mechanisms are classified as heterodomino reactions.[1] One of the ultimate goals in organic synthesis is the catalytic asymmetric assembly of simple and readily available precursor molecules into stereochemically complex products, a process that ultimately mimics biological synthesis. In this regard, the development of domino and other multicomponent reaction methodologies can provide expedient access to complex products from simple starting materials.[2] Domino reactions have gained wide acceptance because they increase synthetic efficiency by decreasing the number of laboratory operations required and the quantities of chemicals and solvents used. Thus, these reactions can facilitate ecologically and economically favorable syntheses.

Recently organocatalysis has emerged as a promising synthetic tool for constructing C−C, C−N, and C−O bonds in aldol,[3] Michael,[4] Mannich,[5] Diels−Alder,[6] and related reactions[7] in highly diastereo- and enantioselective processes. In these recently described reactions, structurally simple and stable chiral organoamines facilitate iminium- and enamine-based transformations with carbonyl compounds. Often, the organocatalysts can be used in operationally simple and environmentally friendly experimental protocols. Because these reactions

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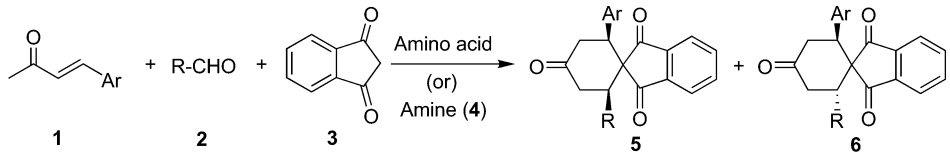
SCHEME 1. Organocatalytic Heterodomino K-DA-E Reaction of 4-Substituted 3-Buten-2-ones 1a−l, Aldehydes 2a−p, and 1,3-Indandione 3



1a: Ar = C_6H_5
1b: Ar = 1-Napthalenyl
1c: Ar = 4-$MeOC_6H_4$
1d: Ar = 3,4-$(OCH_2O)C_6H_3$
1e: Ar = 4-$NMe_2C_6H_4$
1f: Ar = 4-OHC_6H_4
1g: Ar = 4-ClC_6H_4
1h: Ar = 4-$NO_2C_6H_4$
1i: Ar = 4-CNC_6H_4
1j: Ar = 4-$CO_2MeC_6H_4$
1k: Ar = 2-Thiophenyl
1l: Ar = 2-Furanyl

2a: R = 4-$NO_2C_6H_4$
2b: R = C_6H_5
2c: R = 4-$MeOC_6H_4$
2d: R = 3,4-$(OCH_2O)C_6H_3$
2e: R = 4-$NMe_2C_6H_4$
2f: R = 4-OHC_6H_4
2g: R = 4-ClC_6H_4
2h: R = 2-$NO_2C_6H_4$
2i: R = 4-CNC_6H_4
2j: R = 4-$CO_2MeC_6H_4$
2k: R = 1-Napthalenyl
2l: R = 2-Furanyl
2m: R = 2-Thiophenyl
2n: R = 2-Pyrrolyl
2o: R = *trans*-C_6H_5CH=CH-
2p: R = 4-$CHOC_6H_4$

share common mechanistic features they may be linked to create one-pot and domino reaction schemes (assembly reactions). To date, we have described asymmetric assembly reactions involving aldol−aldol,[3c,d] Michael−aldol,[7d] Mannich−cyanation,[5d] Mannich−allylation,[5f] amination−aldol,[7g] and Knoevenagel−Michael[4a] reactions. Recently, we reported two interesting domino reactions founded on Knoevenagel/Diels−Alder reaction sequences. The first was the direct organocatalytic asymmetric domino Knoevenagel/Diels−Alder reaction sequence to accomplish the diastereo- and enantioselective construction of highly substituted spiro[5.5]undecane-1,5,9-triones.[6a] The second was the direct organocatalytic, hetero-domino, Knoevenagel/Diels−Alder/epimerization sequence to prepare symmetric prochiral and highly substituted spiro[cyclohexane-1,2′-indan]-1′,3′,4-triones (**5**) in diastereospecific fashion from commercially available 4-substituted 3-buten-2-ones (**1**), aldehydes (**2**), and 1,3-indandione.[6b] Herein, we report the first direct organocatalytic asymmetric hetero-domino Knoevenagel/Diels−Alder/epimerization (K-DA-E) reaction sequence to generate highly substituted spiro[cyclohexane-1,2′-indan]-1′,3′,4-triones (**5**) in a highly diastereoselective and modestly enantioselective process from commercially available 4-substituted-3-buten-2-ones (**1a**−**l**), aldehydes (**2a**−**p**), and 1,3-indandione (**3**) as shown in Scheme 1. Spirocyclic ketones (**5**) are attractive intermediates in the

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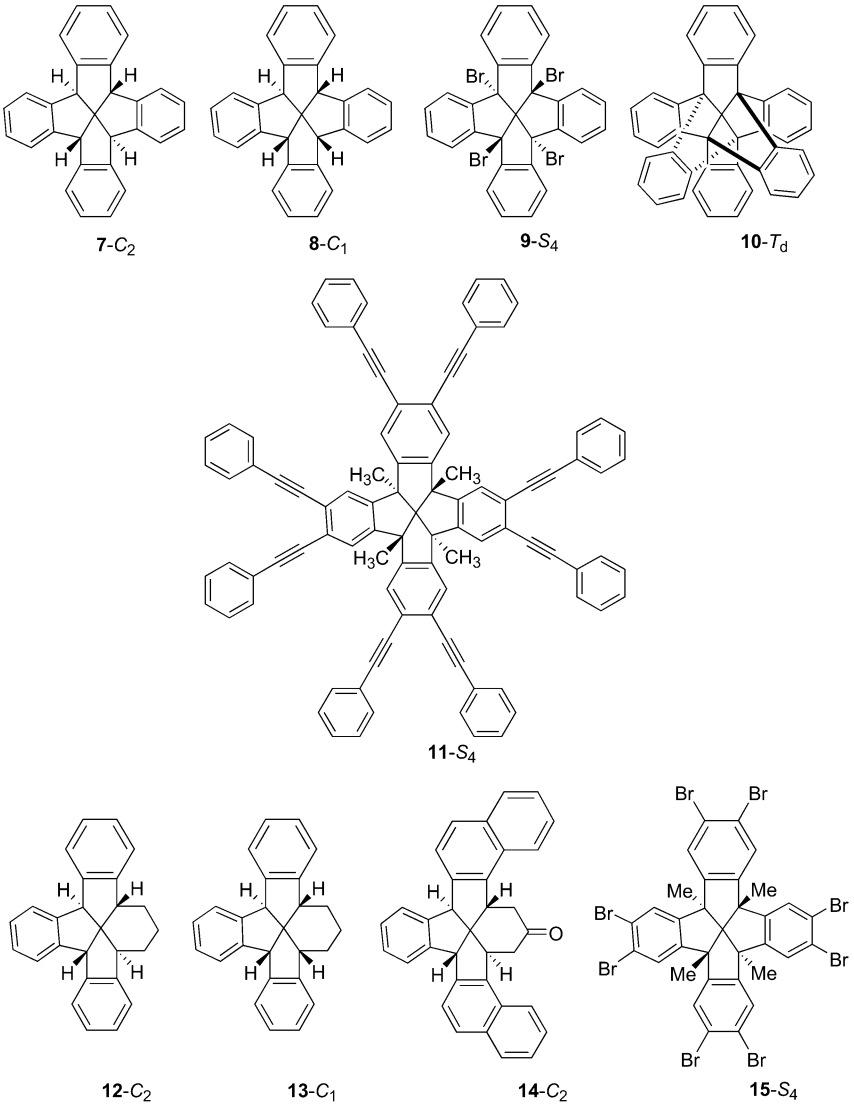
CHART 1. Benzoannelated Centropolyquinanes



synthesis of natural products and in material chemistry and are the excellent starting materials for the synthesis of fenestranes[8] (centrotriindane and centrotetraindanes), topologically nonplanar hydrocarbon centrohexaindane, and other frameworks bearing the [5.5.5.5]fenestrane core as shown in Chart 1. Fenestrindanes with 8-fold peripheral functionalization 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]

Results and Discussion

We envisioned that amino acids **4a**−**e** and simple amines **4f**−**j** (Chart 2) would act as organocatalysts of the Knoevenagel condensation of aldehydes **2a**−**p** with 1,3-indandione **3** to provide arylidene indandiones **17a**−**p**. There is ample precedence for amine-catalyzed Knoevenagel reactions.[9] 2-Arylideneindan-1,3-diones (**17**) are attractive compounds in medicinal and material chemistry. For example, substituted 2-arylideneindan-1,3-

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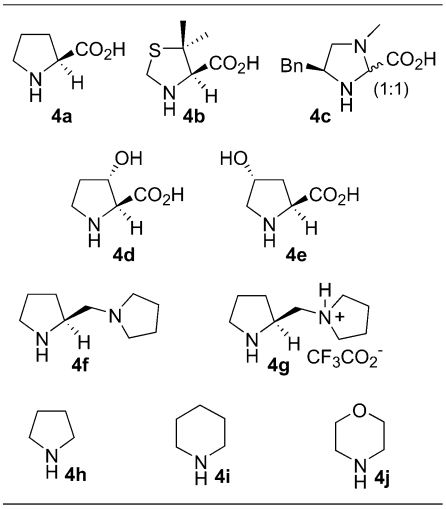
CHART 2. Screened Organocatalysts for the K-DA-E Reaction



diones **17** derivatives show antibacterial activites,[10] nonlinear optical properties,[11] electroluminescent devices,[12] and are useful as eye lens clarification agents.[13] The arylidene indandiones are very good organic Lewis acids[14] (OLA) with low energy LUMO configurations and are useful as heterodienes and Michael acceptors in cycloaddition reactions.[15] Here, we have utilized arylidene indandiones **17** as dienophiles in Diels−Alder chemistry. As dienophiles, **17a**−**p** undergo [4 + 2] cycloaddition reactions with 2-amino-1,3-butadienes **18a**−**l** generated in situ from enones **1a**−**l** and amino acids or amines to generate substituted spiro[cyclohexane-1,2′-indan]-1′,3′,4-triones **5** and **6** in a diastereoselective manner (Figure 1). Epimerization of the minor diastereomer *trans*-spirane **6** to the more stable *cis*-spirane **5** occurred under the same reaction conditions. This domino Knoevenagel/Diels−Alder reaction generates a quaternary carbon center with formation of three new carbon−carbon σ bonds via organocatalysis.

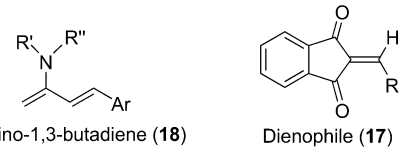
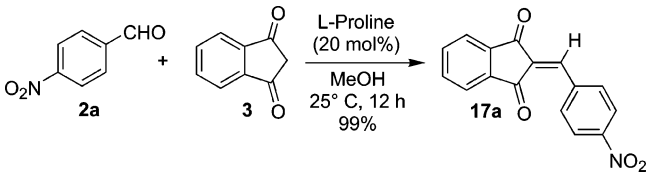


FIGURE 1. Dienes and dienophiles generated under organocatalysis.

SCHEME 2. Organocatalytic Knoevenagel Condensation



In these three component organocatalytic K-DA-E reactions, the Knoevenagel condensation generates reactive dienophiles that can be readily isolated from the reaction mixture. For example, reaction of 4-nitrobenzaldehyde **2a** and 1,3-indandione **3** in methanol at ambient temperature under L-proline or pyrrolidine catalysis furnished the expected 2-(4-nitro-benzylidene)-indan-1,3-dione **17a** in almost quantitative yield as shown in Scheme 2. Under similar reaction conditions with different aromatic aldehydes, a wide variety of 2-arylideneindan-1,3-dione dienophiles (**17**) were synthesized in very good yields.

Amino Acid-Catalyzed Direct Asymmetric Hetero-Domino K-DA-E Reactions. We found that the three-component reaction of *trans*-4-phenyl-3-buten-2-one **1a**, 4-nitrobenzaldehyde **2a**, and 1,3-indandione **3** with a catalytic amount of L-proline (20 mol %) in methanol at ambient temperature for 24 h furnished the expected nonsymmetrical Diels−Alder products **5aa** and **6aa**$^{\Psi}$ in 86% yield with thermodynamically stable *cis*-spirane **5aa** as the major isomer, dr 24:1 (Table 1, entry 1) ($^{\Psi}$In all compounds denoted **5xy** and **6xy**, **x** is incorporated from reactant enones **1** and **y** is incorporated from the reactant aldehydes **2**.) Unfortunately, the enantiomeric excess (ee) of the major *cis*-spirane **5aa** was only 5%. Interestingly, the same reaction with an extended reaction time furnished *cis*-spirane **5aa** as a single diastereomer in 96% yield, however with 3% ee (Table 1, entry 2). The minor diastereomer, *trans*-spirane **6aa**, was effectively epimerized to the thermodynamically stable *cis*-spirane **5aa** under prolonged reaction time via proline catalysis. The stereochemistry of products **5aa** and **6aa** was established by NMR analysis.[16]

In the three-component hetero-domino K-DA-E reaction of enone **1a**, 4-nitrobenzaldehyde **2a**, and 1,3-indandione **3** catalyzed directly by L-proline, we found that the solvent (dielectric constant) and temperature had a significant effects on reaction rates, yields, dr's, and ee's (Table 1). The hetero-domino K-DA-E reaction catalyzed by L-proline at ambient temperature in aprotic/nonpolar solvents produced products **5aa** and **6aa** in low

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(16) Stereochemistries of the *cis*- and *trans*-spiranes were established using COSY experiments and were also based on MOPAC calculations of the thermodynamic equilibration between the two isomers (see the Supporting Information).

TABLE 1. Effect of Solvent and Amino Acid on the Direct Amino Acid Catalyzed Asymmetric Heterodomino K-DA-E Reaction of 1a, 2a, or 2b and 3[a]

entry	catalyst (20 mol %)	aldehyde	solvent (0.5 M)	*T* (°C)	time (h)	products	yield[b] (%)	dr[c] (cis/trans)	ee[d] (cis/trans)
1	**4a**	**2a**	MeOH	25	24	**5aa**, **6aa**	86	24:1	5/−
2	**4a**	**2a**	MeOH	25	96	**5aa**	98	≥99:1	3/−
3	**4a**	**2a**	DMSO	25	96	**5aa**, **6aa**	95	30:1	1/−
4	**4a**	**2a**	THF	25	120	**5aa**, **6aa**	54	2.8:1	18/15
5	**4a**	**2a**	$CHCl_3$	25	120	**5aa**, **6aa**	63	1:1	13/6
6	**4a**	**2a**	C_6H_6	25	120	**5aa**, **6aa**	≤5		
7	**4a**	**2a**	[bmim]BF_4	25	96	**5aa**, **6aa**	80	34:1	1/−
8	**4a**	**2a**	[bmim]PF_6	25	96	**5aa**, **6aa**	45	1.5:1	6/7
9	**4b**	**2a**	MeOH	25	72	**5aa**, **6aa**	62	8.5:1	17/−
10[e]	**4b**	**2a**	MeOH	4	96	**5aa**, **6aa**	18	1.3:1	30/3
11[e]	**4b**	**2a**	THF	25	96	**5aa**, **6aa**	≤10	1:1.4	42/6
12[e]	**4b**	**2a**	THF	4	96	**5aa**, **6aa**	≤5		
13	**4c**	**2a**	MeOH	25	96	**5aa**	68	≥99:1	9/−
14[e]	**4c**	**2a**	MeOH	4	96	**5aa**, **6aa**	40	1.6:1	17/4
15	**4d**	**2a**	MeOH	25	36	**5aa**	92	≥99:1	2/−
16[e]	**4e**	**2a**	MeOH	25	46	**5aa**, **6aa**	19	1:1	14/13
17	**4a**	**2b**	MeOH	25	24	**5ab**, **6ab**	87	2:1	
18	**4a**	**2b**	MeOH	25	98	**5ab**	96	≥99:1	
19	**4a**	**2b**	MeOH	70	2	**5ab**	96	≥99:1	
20	**4a**	**2b**	[bmim]BF_4	25	24	**5ab**, **6ab**	53	1:2	
21	**4a**	**2b**	[bmim]PF_6	25	96	**5ab**, **6ab**	55	1:2	

[a] Experimental conditions: amino acid (0.1 mmol), 4-nitrobenzaldehyde **2a** or benzaldehyde **2b** (0.5 mmol), and 1,3-indandione **3** (0.5 mmol) in solvent (1 mL) were stirred at ambient temperature for 30 min then benzylidene acetone **1a** (1 mmol) was added (see the Experimental Section). [b] Yield refers to the purified product obtained by column chromatography. [c] Ratio based on isolated products (^1H and ^{13}C NMR analysis). [d] Enantiomeric excesses determined by using chiral-phase HPLC. [e] 60−80% of unreacted Knoevenagel product **17a** was isolated.

to moderate yields with poor diastereoselectivity (Table 1, entries 4−6, 11, and 12). Enantioselectivity improved in aprotic/nonpolar solvents (Table 1, entries 4−6, 11, and 12). Excellent yields, good diastereoselectivity, and poor enantioselectivity were observed in protic/polar solvents (Table 1, entries 1−3). For example, the K-DA-E reaction in THF furnished spiranes **5aa** and **6aa** in 54% yield with dr of 2.8:1 and with ee of 18% for the major *cis*-spirane **5aa** and an *ee* of 15% for the minor *trans*-spirane **6aa** (Table 1, entry 4). The same reaction using ionic liquid [bmim]BF_4, a "green solvent", catalyzed by L-proline at 25 °C furnished the thermodynamically stable product *cis*-spirane **5aa** as the major diastereomer in 80% yield with dr of 34:1, albeit with a low ee value of 1% (Table 1, entry 7). Interestingly, the same reaction under proline catalysis in ionic liquid [bmim]PF_6 at 25 °C furnished the spiranes **5aa** and **6aa** in 45% yield with dr of 1.5:1 and with ee of 6% (*cis*-spirane) and 7% (*trans*-spirane) (Table 1, entry 8). In the hetero-domino K-DA-E reaction under L-proline catalysis, diastereoselectivity was directly affected by the nature of the solvent (dielectric constant) as reflected in the epimerization reaction and exo/endo selectivity. Rates of organocatalytic reactions catalyzed by amino acids were faster in protic/polar solvents than in nonprotic/nonpolar solvents presumably due to enhanced stabilization of charged intermediates and more facile proton-transfer reactions. This is especially true for the epimerization reaction where the dr's of the produces obtained using protic/polar solvents were very high.

Next we probed the structure and reactivity relationships among a family of amino acids and pyrrolidine-based catalysts by monitoring the reaction yields, dr's, and ee values of the hetero-domino K-DA-E reaction and compared them to the results of the organocatalytic asymmetric three-component Diels−Alder (ATCDA) reaction of **1a**, **2a**, and Meldrum's acid.[6a] Among the catalysts screened in the ATCDA reaction, the 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC) proved to be the most efficient catalyst with respect to yield and ee. When DMTC was tested in the K-DA-E reaction of **1a**, **2a**, and **3** in methanol at 25 °C for 72 h, the domino products **5aa** and **6aa** were obtained in 62% yield with dr of 8.5:1 and ee of the major *cis*-spirane **5aa** of 17% (Table 1, entry 9). The same reaction under DMTC catalysis at reduced temperature (4 °C) in methanol for 96 h furnished products **5aa** and **6aa** in 18% yield with a dr of 1.3:1. Under these conditions, the ee of the major *cis*-spirane **5aa** was 30% and ee for the minor *trans*-spirane **6aa** was 3% (Table 1, entry 10). With DMTC catalysis in THF as solvent at 25 °C, products **5aa** and **6aa** were obtained in poor yields (≤10%) with dr of 1:1.4 and ee for the minor *cis*-spirane of 42%, while the ee for the major *trans*-spirane of 6% (Table 1, entry 11). DMTC-catalyzed K-DA-E reaction in THF at 4 °C for 96 h furnished the domino products in very poor yields (Table 1, entry 12). An imidazoline-type catalyst, 4-benzyl-1-methylimidazolidine-2-carboxylic acid **4c**, also catalyzed the K-DA-E reaction with moderate yield, very good dr, and low ee at 25 °C and moderate to low yield, and poor dr with improved ee at 4 °C (Table 1, entries 13 and 14). *trans*-3-Hydroxy-L-proline **4d** catalyzed the domino K-DA-E reaction of **1a**, **2a**, and **3** with very good yield and excellent diastereoselectivity, but the ee was poor (Table 1, entry 15). *trans*-4-Hydroxy-L-proline **4e** also catalyzed the domino K-DA-E reaction of **1a**, **2a**, and **3** but reaction yield (19%), dr (1:1), and ee (14 and 13) were poor (Table 1, entry 16). While the Knoevenagel product **17a** was formed and consumed in most of the amino acid-catalyzed heterodomino K-DA-E reactions, in some reactions (Table

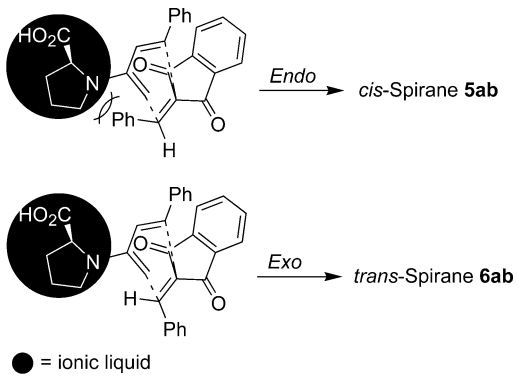

FIGURE 2. Asymmetric solvation in the ionic liquids.

1, entries 10, 11, 12, 14, and 16) unreacted **17a** was isolated in 60−80% yield. Unreacted **17a** was the result of a very slow rate of the formation of the key intermediate 2-amino-1,3-butadiene and subsequent Diels−Alder reaction under these conditions.

The L-proline-catalyzed three-component hetero-domino K-DA-E reaction of *trans*-4-phenyl-3-buten-2-one **1a** and 1,3-indandione **3** with a different aldehyde, benzaldehyde **2b**, furnished products **5ab** and **6ab** in 87% yield with dr of 2:1 (Table 1, entry 17). The same reaction, albeit with an extended reaction time, furnished prochiral *cis*-spirane **5ab** as a single diastereomer in 96% yield (Table 1, entry 18). The stereochemistry of products **5ab** and **6ab** was established by NMR analysis. The minor diastereomer, *trans*-spirane **6ab** was effectively epimerized to the thermodynamically stable *cis*-spirane **5ab** under prolonged reaction time via proline catalysis. Increasing the reaction temperature to 70 °C facilitated the epimerization reaction and furnished the expected domino product **5ab** as a single diastereomer in 96% yield within 2 h. Interestingly the same reaction in the ionic liquids, [bmim]BF_4 and [bmim]PF_6, catalyzed by L-proline at ambient temperature provided the kinetic product *trans*-spirane **6ab** as the major diastereomer in moderate yield (Table 1, entries 20 and 21). In these reactions, enantioselectivity for the minor kinetic product **6ab** was poor. *cis*-Spirane **5ab** has been used as a synthon for the synthesis of variety of benzoannelated centropolyquinanes as shown in Chart 1.[8]

cis-Spirane **5ab** is obtained via an *endo*-transition state in the classical Diels−Alder route. In ionic liquids, however, the kinetic product, *trans*-spirane **6ab**, was the major isomer formed. This is likely due to a unique organization of the ionic liquid solvent with the 2-amino-1,3-butadiene **18a** and dienophile **17b** in the transition states as shown in Figure 2. Asymmetric solvation in the ionic liquids then produces a steric hindrance with the phenyl group on the dienophile in the *endo*-transition state, thereby disfavoring it. In the case of dienophile **17a**, the high epimerization rate of *trans*-spirane **6aa** provides *cis*-spirane **5aa** as the major isomer (Table 1, entries 7 and 8). Ratio of exo/endo products in ionic liquids or other solvents mainly depend on four factors, which are (i) substrate effect (electronic factor), (ii) protic solvent effect (polarization factor), (iii) steric hindrance induced by ionic solvation, and (iv) basic nature of organo catalyst.

Amine-Catalyzed Direct Heterodomino K-DA-E Reactions. Amines **4f**−**j** can also catalyze the heterodomino K-DA-E reaction under different solvent and temperature conditions. The three-component heterodomino K-DA-E reaction of *trans*-4-phenyl-3-buten-2-one **1a**, 4-nitrobenzaldehyde **2a**, and 1,3-indandione **3** with a catalytic amount of chiral diamine, (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine **4f**, in methanol at ambient temperature for 24 h furnished the domino product **5aa** as a single diastereomer in 79% yield but with very poor ee (Table 2, entry 1). The bifunctional acid/base catalyst[17] **4g**, the trifluoroacetic acid salt of diamine **4f**, also catalyzed the heterodomino K-DA-E reaction of **1a**, **2a**, and **3** in DMSO at ambient temperature to furnish the expected domino products **5aa** and **6aa** in 71% yield with dr of 13.5:1, but with poor ee (Table 2, entry 2). Since enantioselection in these reactions was typically unsatisfactory, we studied the simple achiral amine pyrrolidine **4h** and found that it furnished *cis*-spirane **5ab** as a single diastereomer in 90% yield (Table 2, entry 3). Further we found that pyrrolidine catalysis was not dramatically affected with respect to reaction rates, yields, or dr's by solvent and temperature modification (Table 2). Under pyrrolidine catalysis, the heterodomino K-DA-E reaction worked well in a variety of solvents and the optimal conditions involved mixing equimolar amounts of enone **1a**, aldehyde **2b**, and 1,3-diketone **3** in methanol with heating to 70 °C for 1 h to furnish *cis*-spirane **5ab** as a single diastereomer in 95% yield (Table 2, entry 9). Interestingly, the six-membered cyclic amines piperidine (**4i**) and morpholine (**4j**) also catalyzed the heterodomino K-DA-E reaction. Typically, pyrrolidine-based catalysts are much more effective than six-membered cyclic amines as organocatalysts and six-membered cyclic amines are extremely poor catalysts of aldol reactions.[3b] The reaction of enone **1a**, aldehyde **2b**, and 1,3-diketone **3** under piperidine **4i** catalysis in methanol at 70 °C for 4 h furnished the expected domino products **5ab** and **6ab** in 71% yield with dr of 43:1 (Table 2, entry 10). Under the same conditions, morpholine **4j** catalyzed formation of **5ab** and **6ab** in 46% yield with dr of 18.6:1 (Table 2, entry 11). The pyrrolidine-catalyzed heterodomino K-DA-E reaction was, however, faster.

Organocatalytic Epimerization of *trans*-Spirane 6 to *cis*-Spirane 5. Epimerization of *trans*-spirane **6** or the diastereospecific synthesis of *cis*-spirane **5** in the heterodomino K-DA-E reaction of enone **1**, aldehyde **2**, and 1,3-indandione **3** can be explained as illustrated in Scheme 3. Amino acid or amine-catalyzed Knoevenagel condensation[9] of aldehyde **2** with 1,3-indandione **3** provides the arylidene-indandione **17** via the in situ generated reactive cationic imine **16**. Arylideneindandione **17** then undergoes a concerted [4 + 2] cycloaddition or a double-Michael reaction with the soft nucleophile, 2-amino-1,3-butadiene **18** generated in situ from enone **1** and the amino acid or amine catalyst, to produce products **5** and **6**. The energy difference (ΔH) between the two isomers

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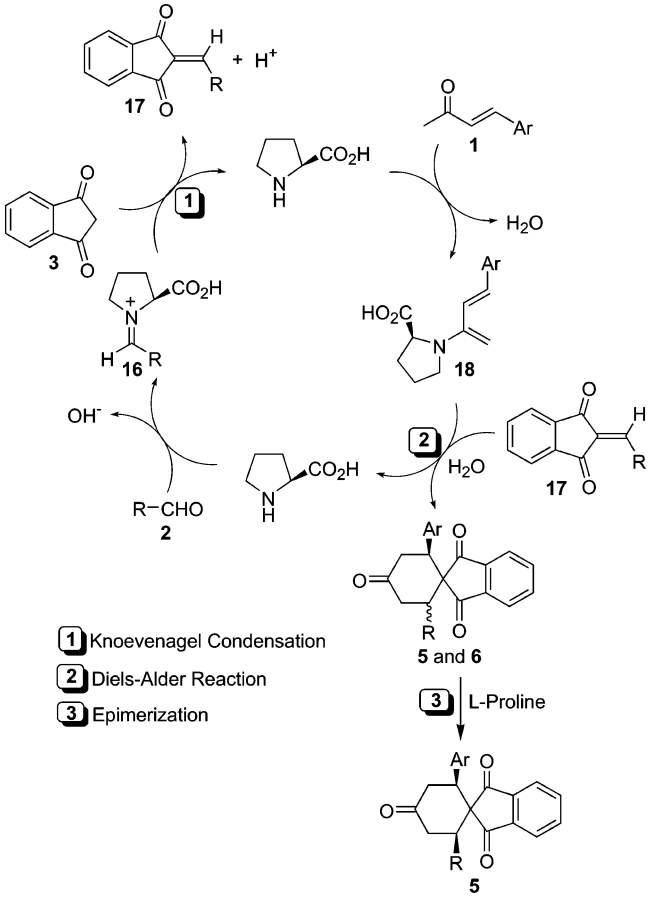
TABLE 2. Effect of Solvent and Amine on the Direct Amine-Catalyzed Asymmetric Heterodomino K-DA-E Reaction of 1a, 2a or 2b, and 3[a]

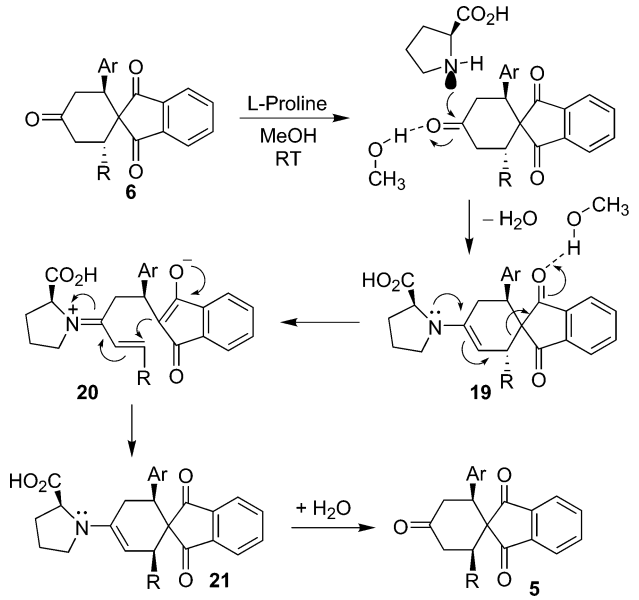
entry	catalyst (20 mol %)	aldehyde	solvent (0.5 M)	*T* (°C)	time (h)	products	yield[b] (%)	dr[c] (cis/trans)	ee[d] (cis/trans)
1	**4f**	**2a**	MeOH	25	24	**5aa**	79	≥99:1	1
2	**4g**	**2a**	DMSO	25	39	**5aa**, **6aa**	71	13.5:1	3
3	**4h**	**2b**	MeOH	25	8	**5ab**	90	>99:1	
4	**4h**	**2b**	MeOH	70	0.75	**5ab**	90	>99:1	
5	**4h**	**2b**	THF	25	7	**5ab**	85	>99:1	
6	**4h**	**2b**	$CHCl_3$	25	7	**5ab**	70	>99:1	
7	**4h**	**2b**	DMSO	24	70	**5ab**	75	>99:1	
8	**4h**	**2b**	DMF	25	24	**5ab**	80	>99:1	
9[e]	**4h**	**2b**	**MeOH**	**70**	**1**	**5ab**	**95**	**>99:1**	
10	**4i**	**2b**	MeOH	70	4	**5ab**, **6ab**	71	43:1	
11	**4j**	**2b**	MeOH	70	4	**5ab**, **6ab**	46	18.6:1	

[a] Experimental conditions: amines **4f**,**g** (0.1 mmol), **4h**−**j** (0.15 mmol), 4-nitrobenzaldehyde **2a** or benzaldehyde **2b** (0.5 mmol), and 1,3-inandione **3** (0.5 mmol) in solvent (1 mL) were stirred at ambient temperatures for 30 min, then benzyl acetone **1a** (1 mmol) was added (see the Experimental Section). [b] Yield refers to the purified product otabined by column chromatography. [c] Ratio based on isolated products (^{1}H and ^{13}C NMR analysis). [d] Enantiomeric excesses determined by using chiral-phase HPLC. [e] Enone **1a**, benzealdehyde **2b** and 1,3-indandione **3** were used in 0.5 mmol scale.

SCHEME 3. Proposed Catalytic Cycle for the L-Proline (or Amino Acid or Amine) Catalyzed Heterodomino K-DA-E Reactions



SCHEME 4. Proposed Mechanism for the L-Proline (Amino Acid or Amine) Catalyzed Epimerization of *trans*-Spirane 6 to *cis*-Spirane 5



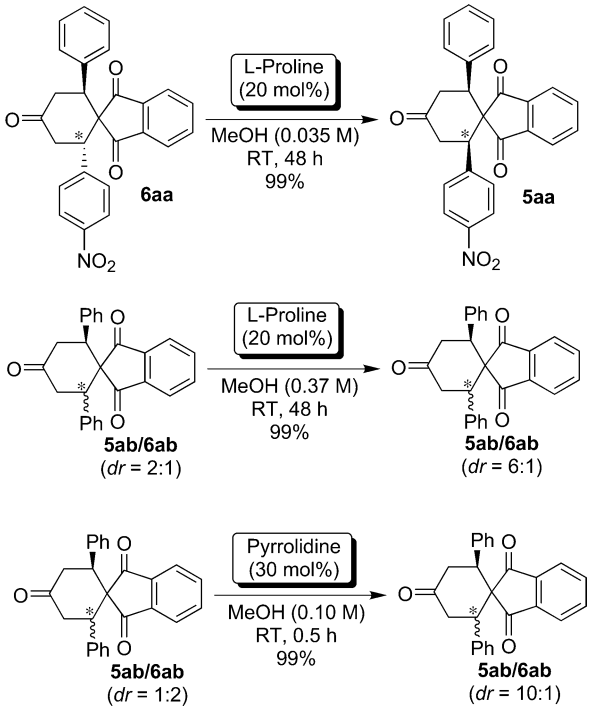
5aa and **6aa** is 5.626 kcal/mol based on AM1 and 4.114 kcal/mol based on PM3 calculations. The energy difference (ΔH) between the two isomers of **5ab** and **6ab** is 6.158 kcal/mol based on AM1 and 5.680 kcal/mol based on PM3 calculations. Minimized structures of **5aa**, **6aa**, **5ab**, and **6ab** are depicted in the Supporting Information. Since the differences in ΔH's between the two isomers of **5aa**/**6aa** and **5ab**/**6ab** are greater than 5 kcal/mol, the minor kinetic isomers **6aa** and **6ab** are epimerized to the thermodynamically more stable *cis*-isomers **5aa** and **5ab**, respectively, at room temperature under mild organocatalysis. Epimerization of *trans*-spiranes **6** to *cis*-spiranes **5** was favored not only by thermodynamic considerations but also electronic effects.[18] The minor kinetic isomer *trans*-spirane **6** was epimerized to the thermodynamically stable *cis*-spirane **5** via deprotonation/reprotonation or retro-Michael/Michael reactions catalyzed by amino acid or amine. This is in agreement with the previously proposed retro-Michael/Michael reaction mechanism[19] at the epimerization step as shown in Scheme 4.

The rate of the epimerization was also related to the nucleophilic strength of the amino acid or amine catalyst,

(18) Zalukaev, L. P.; Anokhina, I. K.; Aver'yanova, I. A. *Dokl. Akad. Nauk SSSR* **1968**, *181*, 103.

(19) (a) Shternberg, I. Y.; Freimanis, Ya. F. *Zh. Org. Khim.* **1970**, *6*, 48. (b) Rowland, A. T.; Filla, S. A.; Coutlangus, M. L.; Winemiller, M. D.; Chamberlin, M. J.; Czulada, G.; Johnson, S. D. *J. Org. Chem.* **1998**, *63*, 4359.

SCHEME 5. Organocatalytic Epimerization of *trans*-Spirane 6 to *cis*-Spirane 5



reaction temperature, and nature of the solvent. Epimerization rate of *trans*-spirane **6** to *cis*-spirane **5** in protic/polar solvents under amino acid catalysis was faster than that in aprotic/nonpolar solvents (Table 1). But under amine catalysis, the nature of the solvent did not have much effect on the epimerization rate. In protic/polar solvents, stabilization of the highly reactive ionic species generated in the reaction media by hydrogen bonding or dipolar−dipolar interactions enhanced the reaction rate. As shown in Scheme 4, the amino acid or amine reacts with cyclohexanone **6** to generate the enamine **19**. The retro-Michael reaction to form the ring-opened imine/enolate **20** should be accelerated by hydrogen bonding with protic/polar solvents. Imine/enolate **20** then undergoes Michael reaction to form the enamine of the thermodynamically stable *cis*-spirane **21**, which undergoes hydrolysis in situ to furnish *cis*-spirane **5**.

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

To further probe the epimerization mechanism we sought to study the intermediate enamine of *cis*-spirane **22**. A mixture of *cis*- and *trans*-spiranes **5aa** and **6aa** (1.5:1) was treated with morpholine in the presence of catalytic amount of *p*-TSA under reflux in toluene for 30 min to furnish the enamine of the epimerized *cis*-spirane **22**. NMR analysis of the unpurified mixture showed features of the enamine (Scheme 6). We studied the morpholine derived enamine because morpholine enamine hydrolysis is slower than that of pyrrolidine or L-proline enamines.[19] Attempted purification of the enamine **22** by flash column chromatography on silica gel resulted in the formation of the hydrolysis product, *cis*-spirane **5aa**, in quantitative yield.

Synthesis of Nonsymmetrical *cis*-Spiranes. We further explored the scope of the L-proline and pyrrolidine catalyzed hetero-domino K-DA-E reactions with various arylaldehydes (**2a**−**p**) and 4-substituted-3-buten-2-ones (**1a**−**l**). Each of the targeted spirotriones **5** was obtained as single diastereomers in excellent yields. In this case, even though the enantioselectivities are poor, L-proline was used as catalyst as it is available at reasonable cost. The L-proline-catalyzed heterodomino K-DA-E reactions of *trans*-4-phenyl-3-butene-2-one **1a**, various arylaldehydes (**2a**−**p**) and 1,3-indandione **3** in methanol at 25 °C for 96 h furnished the expected *cis*-spiranes in good yields with high diastereoselectivity as shown in Table 3. None of these nonsymmetrical *cis*-spiranes were known in the literature. Various arylaldehydes with different electron-donating or -withdrawing groups, as well as heteroaromatic aldehydes furnished the spiranes without the loss of diastereoselectivity. Interestingly, the heterodomino K-DA-E reaction of enone **1a**, 4-methoxybenzaldehyde **2c**, and 1,3-indandione **3** furnished the expected *cis*-spirane in 6:1 diastereomeric ratio. In this case, the epimerization rate of *trans*-spirane **6ac** to *cis*-spirane **5ac** was slower than with other substrates and so the diastereoselectivity was poor. Reaction of an arylaldehyde bearing an electron-donating *p*-hydroxy substitute furnished *cis*-spirane **5af** in very good yield and a surprisingly high dr (Table 3, entry 3). Likewise, arylaldehydes with electron withdrawing substituents such as *o*-nitro, *p*-chloro, *p*-cyano, and *p*-methoxycarbonyl also furnished the *cis*-spiranes **5ah**, **5ag**, **5ai**, and **5aj** with high diastereoselectivities. The heterodomino K-DA-E reaction of heteroaromatic aldehydes, 2-furanaldehyde, and 2-thiophenaldehyde furnished spiranes **5al** and **5am** with

SCHEME 6

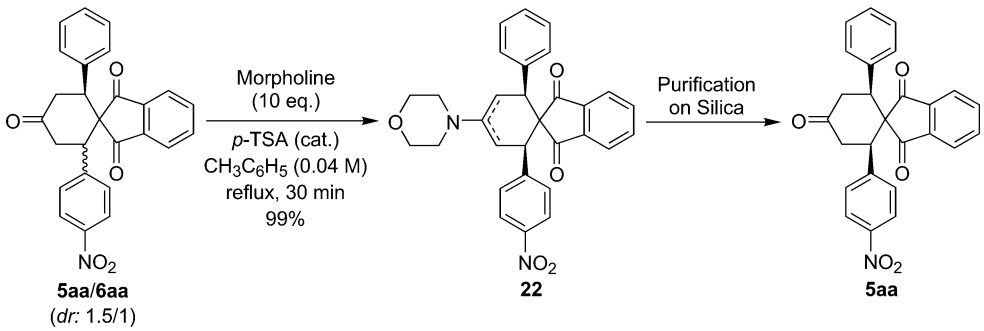
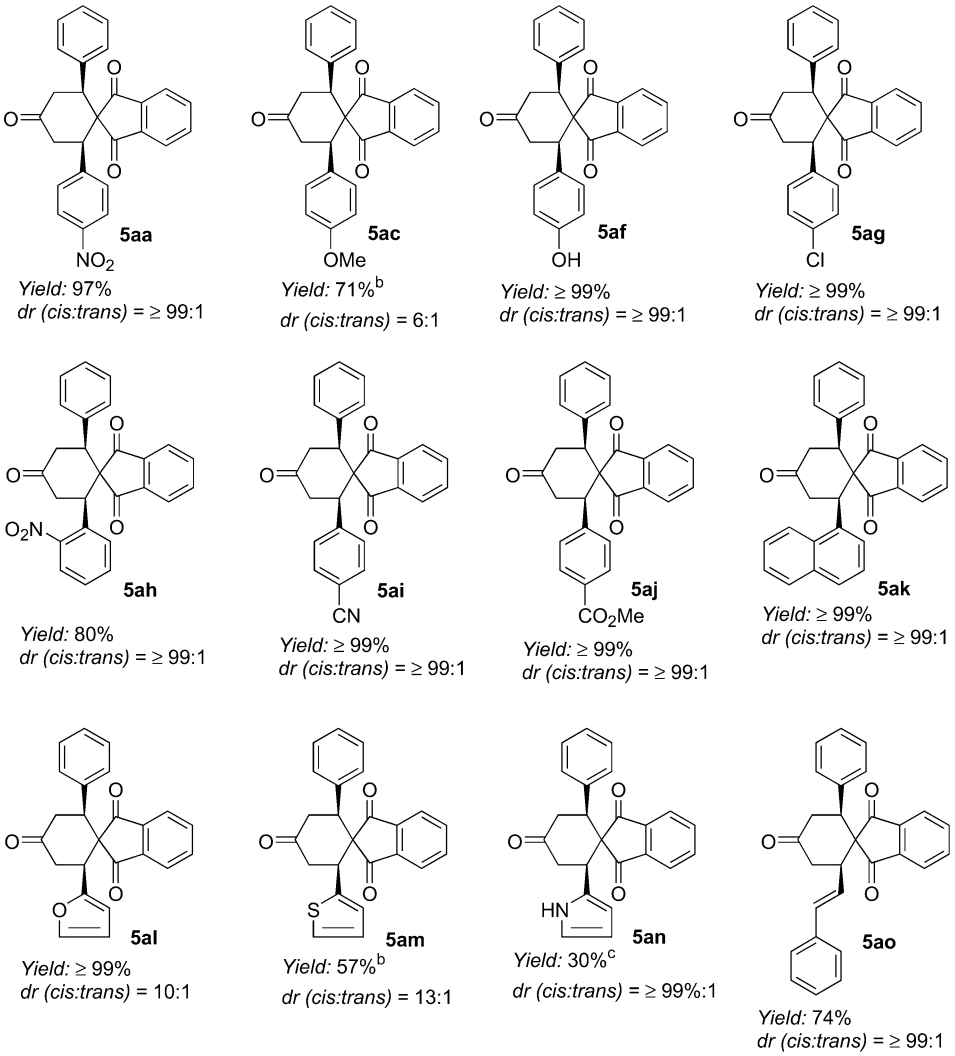


TABLE 3. L-Proline-Catalyzed Heterodomino K-DA-E Reactions of *trans*-4-Phenyl-3-buten-2-one 1a, Various Aldehydes 2a−o, and 1,3-Indandione 3 in Methanol at 25 °C for 96 h[a]



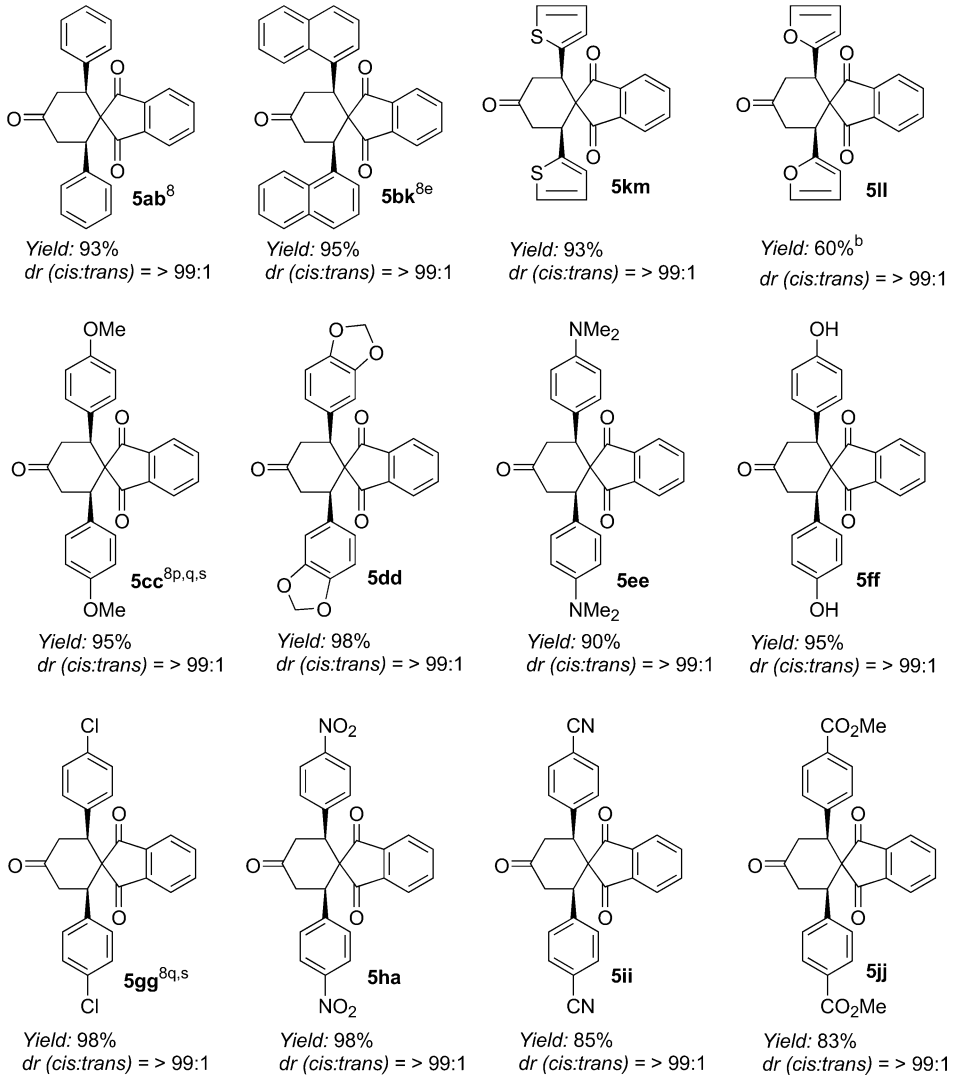
[a] Experimental conditions: L-proline (0.1 mmol), aldehyde **2a**−**o** (0.5 mmol), and 1,3-indandione **3** (0.5 mmol) in methanol (1 mL) was stirred at ambient temperature for 30 min, and then benzylidine acetone **1a** (1.0 mmol) was added (see the Experimental Section). [b] 20% of unreacted dienophiles are isolated. [c] Reaction was performed under pyrrolidine catalysis at 60 °C for 2 h. This product was accompanied by unexpected product *cis*-sprirane **5ab** (16%) and Knoevenagel product **17n** (25%) (see the Experimental Section).

good to moderate yields but with moderate diastereoselectivities due to slow epimerization rates. Reaction of 1*H*-pyrrole-2-carboxyaldehyde **2n** with **1a** and **3** under L-proline catalysis did not furnish the expected domino product, but under pyrrolidine catalysis at 60 °C for 2 h furnished the domino product **5an** in 30% yield with high dr. This domino product **5an** was accompanied by an unexpected product, *cis*-spirane **5ab**, in 16% yield and unreacted Knoevenagel product **17n** in 25% yield. Formation of unexpected product **5ab** in above reaction will be considered in the next section. Reaction of α,β-unsaturated aldehyde, *trans*-C_6H_4−CH=CH−CHO **2p** with **1a** and **3** under L-proline catalysis also furnished the expected domino product **5ao** in good yields with high dr.

Synthesis of Prochiral Symmetrical *cis*-Spiranes. Pyrrolidine catalyzed, hetero-domino K-DA-E reactions of *trans*-4-aryl-3-butene-2-ones (**1a**−**l**), arylaldehydes (**2a**−**p**), and 1,3-indandione **3** in methanol at 70 °C for 1−2 h furnished the expected *cis*-spiranes **5** diastereospecifically in very good yields as shown in Table 4. Various *trans*-4-aryl-3-buten-2-ones and aryl aldehydes with different substituents on the aromatic ring (ranging from the electron-donating groups such as *p*-methoxy, *m*,*p*-methylenedioxy, *p*-dimethylamino, and *p*-hydroxy and electron-withdrawing groups such as *p*-chloro, *p*-nitro, *p*-cyano, and *p*-methoxycarbonyl) and also the heteroaromatic counterparts furnished the expected *cis*-spiranes (**5**) in good yields with high diastereospecificity. The chloro-, cyano-, and methoxycarbonyl-substituted *cis*-spiranes **5gg**, **5ii**, and **5jj** are potentially interesting intermediates for materials chemistry as they can be readily manipulated. Thus, numerous arylaldehydes and various enones are readily reacted under either L-proline or pyrrolidine catalysis to generate a library of highly functionalized *cis*-spiranes (**5**) (Tables 3 and 4).

Synthesis of Highly Substituted *cis*-Spiranes. To prepare highly substituted dispiranes, we used an aryldialdehyde instead of a simple arylaldehyde. Thus, the heterodomino K-DA-E reaction of terephthalaldehyde **2p**,

TABLE 4. Pyrrolidine-Catalyzed Heterodomino K-DA-E Reactions of Various *trans*-4-Aryl-3-buten-2-ones 1a−l, Arylaldehydes 2a−o, and 1,3-Inandione 3 in Methanol at 70 °C for 1−2 h[a]

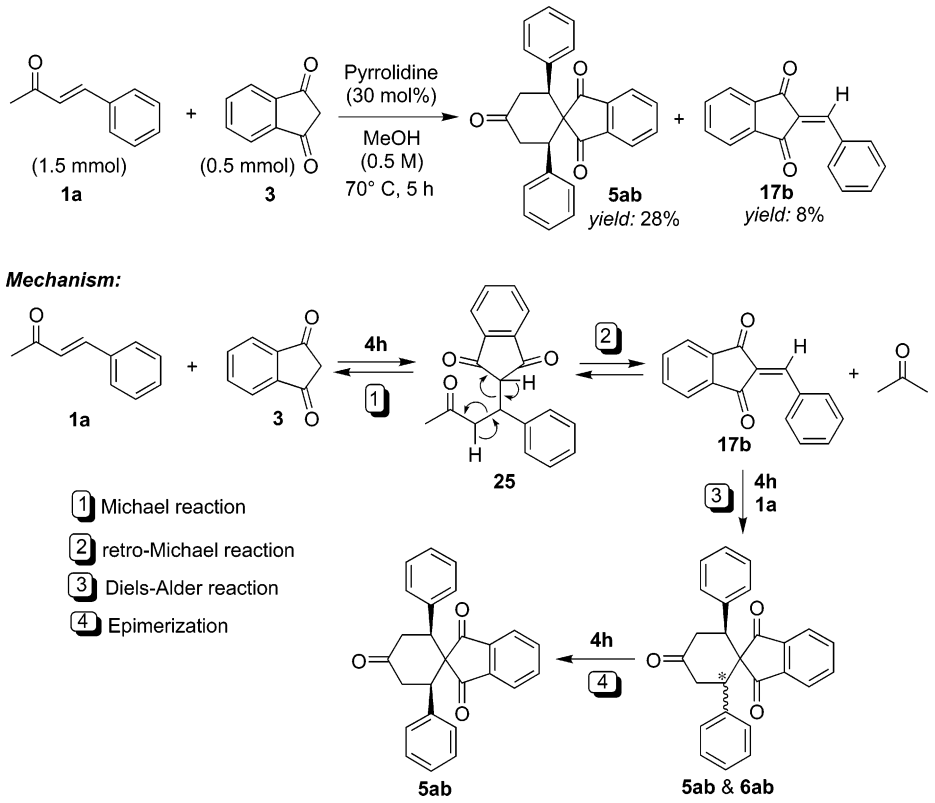


[a] Experimental conditions: pyrrolidine (0.15 mmol), aldehyde **2a**−**o** (0.5 mmol), and 1,3-inandione **3** (0.5 mmol) in methanol (1 mL) was stirred at ambient temperature for 30 min, and then arylidene acetone **1a**−**l** (0.5 mmol) was added (see the Experimental Section). [b] Reaction conversion is 50% only.

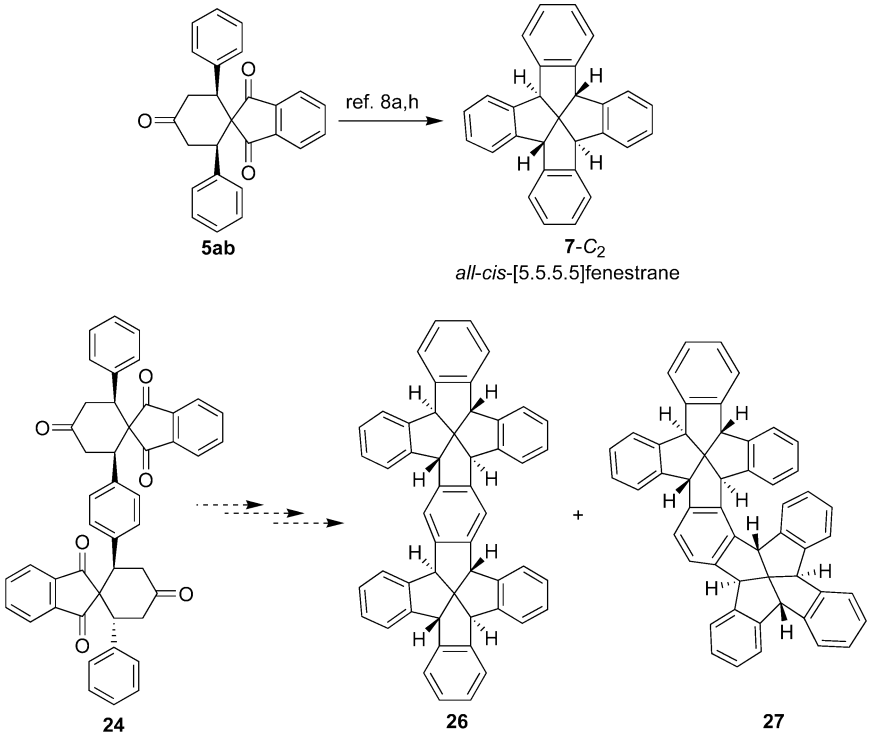
a dialdehyde, with *trans*-4-phenyl-3-butene-2-one **1a** and indandione **3** catalyzed by L-proline or pyrrolidine furnished the *cis*-spiranealdehyde **23** and the dispirane **24** as well as the unexpected product **5ab** as shown in Table 5. When L-proline was used as a catalyst, incubation of the reaction at 25° C for 96 h furnished products **23** and **24** in 16% and 18% yield, respectively (Table 5, entry 1), while the same reaction performed at 25 °C for 24 h and 40 °C for 48 h resulted in the formation of **23** and **24** in 60% and 18% yield, respectively (Table 5, entry 2). Under L-proline catalysis, the unexpected product **5ab** did not form. The reaction catalyzed by pyrrolidine at 70 °C for 2 h furnished the dispirane **24** and the unexpected product **5ab** in 15% and 45% yield, respectively (Table 5, entry 3). The identity of dispirane **24** was confirmed by proton, ^{13}C NMR, and mass analysis. We had previously observed that the domino product **5ab** was also formed unexpectedly in the hetero-domino K-DA-E reaction of enone **1a**, aldehyde **2n** and 1,3-indandione **3** under pyrrolidine catalysis with 16% yield (Table 3, entry 11).

To investigate the formation of the unexpected product **5ab**, the reaction was carried out without the aldehyde. Pyrrolidine catalyzed the reaction of *trans*-4-phenyl-3-buten-2-one **1a** with 1,3-indandione **3** in methanol at 70 °C for 5 h to furnish the *cis*-spirane **5ab** and the Knoevenagel product **17b** in 28% and 8% yield, respectively, as shown in Scheme 7. The mechanism of formation of the unexpected product *cis*-spirane can be explained as shown in Scheme 7. First, the Michael addition of indandione **3** to *trans*-4-phenyl-3-buten-2-one **1a** takes place to generate the adduct **25**, which can then undergo a retro-Michael reaction in one of two ways. The retro-Michael reaction can either regenerate the starting materials **3** and **1a** or generate acetone and the Knoevenagel product **17b**. Compound **17b** undergoes a Diels−Alder reaction with *trans*-4-phenyl-3-buten-2-one **1a** to furnish the mixture of *cis*- and *trans*-spiranes **5ab** and **6ab** as described earlier. Finally, epimerization of the *trans*-spirane **6ab** takes place to furnish the *cis*-spirane **5ab**. Thus the mechanism of formation of the unexpected

SCHEME 7. Pyrrolidine-Catalyzed Direct Michael/Retro-Michael/Diels−Alder/Epimerization Reaction of Enone 1a and 1,3-Indandione 3 in Methanol at 70 °C



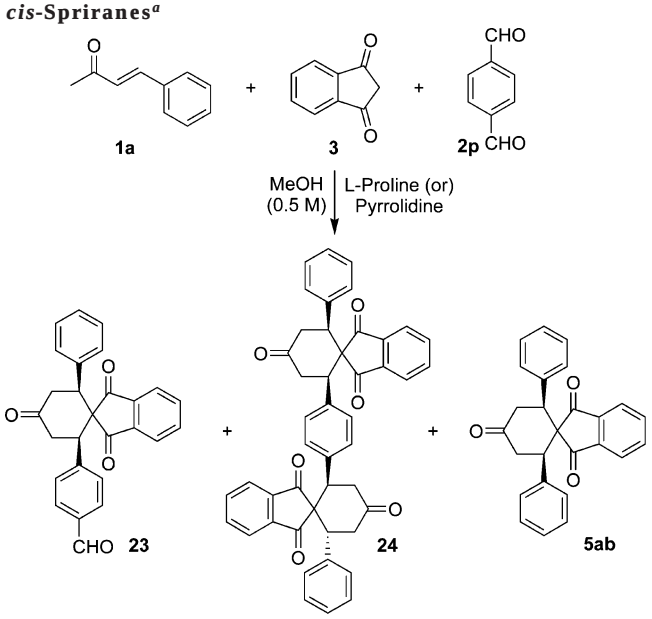
SCHEME 8. Application of *cis*-Spiranes 5 in the Synthesis of Benzoannelated Centropolyquinanes



product **5ab** involves four steps: a Michael reaction, a retro-Michael reaction, a Diels−Alder reaction, and finally an epimerization reaction.

Application of *cis*-Spiranes 5. Prochiral *cis*-spiranes **5** are very useful starting materials in the synthesis of benzoannelated centropolyquinanes. Prochiral *cis*-spirane **5ab** and *trans*-spirane **6ab** have served as useful synthons in the synthesis of fenestranes.[8] Kuck and coworkers have reported the synthesis of a highly strained centrotetracyclic framework of fenestranes starting from *cis*- and *trans*-spiranes **5ab** and **6ab**. In their study, the *cis*-spirane **5ab** was converted to *all-cis*-[5.5.5.5]feneS-

TABLE 5. Synthesis of Highly Substituted *cis*-Spriranes[a]



entry	catalyst (30 mol %)	*T* (°C)	time (h)	yield[b] (%) 23	24	5ab
1	**4a**	25	96	16	18	
2	**4a**	25 → 40	24 → 48	60	18	
3	**4h**	70	2		15	45

[a] Experimental conditions: L-proline **4a** or pyrrolidine **4h** (0.15 mmol), terephthalaldehyde **2p** (0.5 mmol), and 1,3 indandione **3** (1.0 mmol) in methanol (1 mL) were stirred at ambient temperature for 30 min, and then benzylidine acetone **1a** (1.0 mmol) was added (see the Experimental Section). [b] Yield refers to the purified product obtained by column chromatography.

trane **7** in nine synthetic steps as depicted in Scheme 8. The dispirane **24** could serve as a suitable synthon for the synthesis of topologically interesting difenestranes **26** and **27**. Fenestranes containing reactive functional groups such as chloro, cyano, and methoxycarbonyl should allow for the development of a rich chemistry by extension of the peripheral functional groups. Thus, dendrimers, liquid crystals and poly-condensed ring systems with saddle-like molecular structures may be synthesized using the synthons described here.

Conclusions

The results presented here demonstrate amino acid or an amine-based organocatalysis of three different reactions in a single pot. This astonishingly simple and atom-economic approach can be used to construct highly functionalized symmetric and nonsymmetric spiro[cyclohexane-1,2′-indan]-1′,3′,4-triones (**5**) in a diastereospecific fashion. Selective multistep reactions of this type inspire analogies to biosynthetic pathways and compliment traditional multicomponent synthetic methodologies. Further improvements with respect to the enantioselectivity of these reactions might be accessible through the screening or design of novel catalysts. 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 provide a new perspective on the origin of complex molecular systems.

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Supporting Information Available: Characterization data (^{1}H NMR, ^{13}C NMR, and mass) for all new compounds and details of experimental procedures. Copies of ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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