

# Organocatalytic Enantioselective Cascade Michael–Michael–Wittig Reactions of Phosphorus Ylides: One-Pot Synthesis of the *all-cis* Trisubstituted Cyclohexenecarboxylates via the [1 + 2 + 3] Annulation

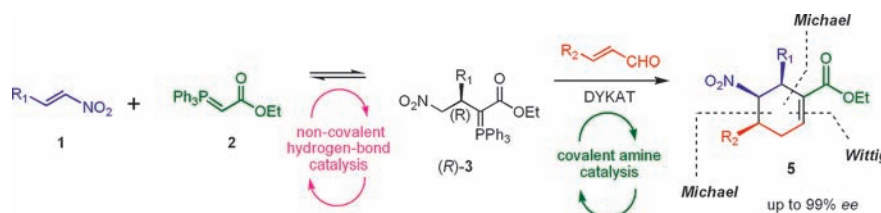
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## ABSTRACT



The stereoselective synthesis of *all-cis* 5-nitro-4,6-diphenylcyclohex-1-enecarboxylic ester has been achieved by an organocatalytic asymmetric Michael–Michael–Wittig cascade reaction of phosphorus ylides, nitroolefins, and  $\alpha,\beta$ -unsaturated aldehydes with excellent enantioselectivities (up to >99% ee).

Nitroalkenes, known as chemical chameleons for the ease of their functional group transformation, have received extensive attention in organic chemistry.<sup>1</sup> Of these transformations, asymmetric conjugate addition reactions of carbon nucleophiles (especially aldehydes and ketones) to nitrostyrenes are of great interest.<sup>2,3</sup> Apart from carbon nucleophiles, enantioselective Michael additions of phosphorus nucleophiles, such as diphenylphosphine oxide, dialkyl phosphite, and benzylphosphonate, to nitroalkenes have only of late been successful.<sup>4,5</sup> Recently, a cascade organocatalytic conjugate addition of sulfur ylides to nitroolefins for the synthesis of oxazolidin-2-ones was accomplished.<sup>6</sup> However, the efficient organo-

catalytic and enantioselective conjugate addition of phosphorus ylides to nitroalkenes remains elusive.<sup>7</sup> Moreover, conjugate additions of nitroalkanes to electron-poor alkenes (Michael acceptors) giving the corresponding 1,4-adducts with high stereoselectivity are of great interest to synthetic chemists.<sup>8</sup> Despite many examples of organocatalytic conjugate addition of nitroalkanes to  $\alpha,\beta$ -unsaturated ketones<sup>9</sup> and esters,<sup>10</sup> reactions with  $\alpha,\beta$ -unsaturated aldehydes have been far less successful, mainly because the 1,2-addition toward the enal could interfere with the desired 1,4-addition

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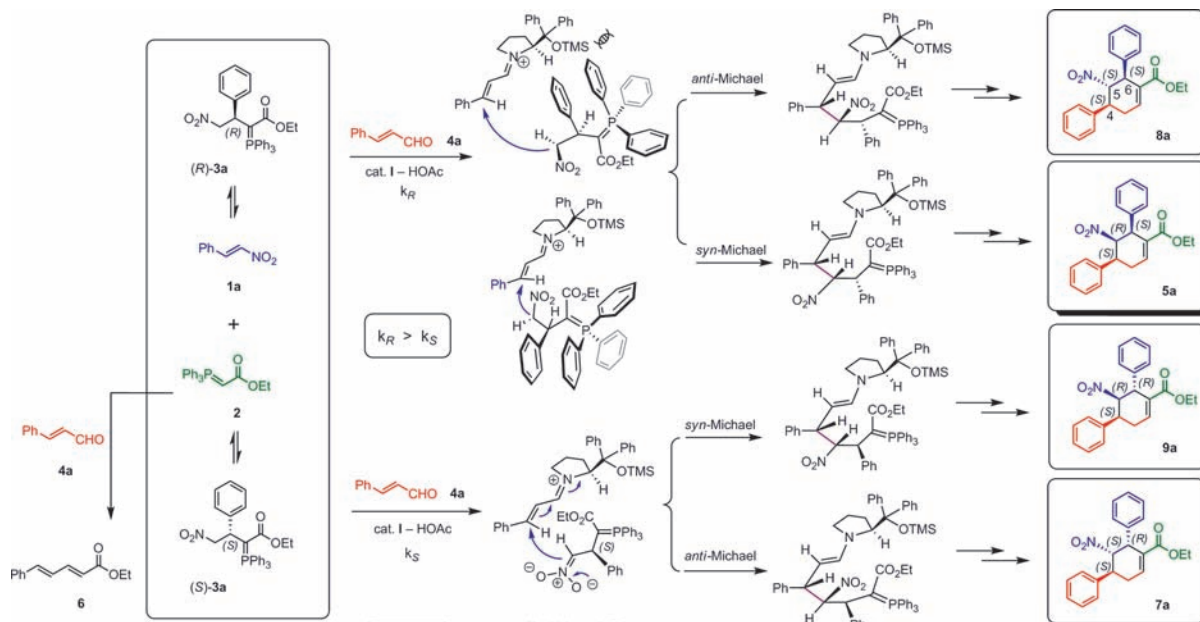
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Scheme 1



process.<sup>11</sup> A few examples of the catalytic asymmetric addition of nitroalkanes to  $\alpha,\beta$ -unsaturated aldehydes have been recently reported, but those protocols usually gave low selectivity (*syn/anti* ratios) and provided mixtures of *trans*- and *cis*-adducts, sometimes in nearly 1:1 ratios.<sup>12</sup> In the few reported cases of intramolecular conjugate addition of nitroalkanes to  $\alpha,\beta$ -unsaturated aldehydes, the *anti*-Michael addition predominated and furnished the *trans*-adducts.<sup>13</sup> Consequently, the highly enantioselective *syn*-Michael addition of nitroalkanes to  $\alpha,\beta$ -unsaturated aldehydes, yielding the three *all-cis* consecutive stereocenters in the cyclohexene

derivatives, is rare, because synthesis of contiguous *cis* stereocenters is a persistent challenge in organic synthesis due to steric hindrance. Taking into account the above observations and considering domino reactions<sup>14</sup> for developing organocatalytic annulation, especially for multicomponent reactions,<sup>15</sup> we envisioned that a suitable substrate, such as a stabilized Wittig reagent, may permit the objective of organocatalytic dynamic kinetic asymmetric transformation (DYKAT)<sup>16,17</sup> as illustrated in Scheme 1. Conjugate addition of stabilized Wittig reagent **2** to nitrostyrene **1a** would generate racemic **3a** (another stabilized Wittig reagent), which could decompose back to **1a** and **2**,<sup>18</sup> and provide a vehicle for their interconversion. Consequently, if the racemization process is fast relative to the subsequent nitro-Michael and Wittig reactions, an effective DYKAT results, followed by organocatalytic enantioselective conjugate addition of the in situ generated nitroalkane to the  $\alpha,\beta$ -unsaturated aldehyde, with the subsequent Wittig reaction, giving the [1 + 2 + 3] annulation adducts. Although general

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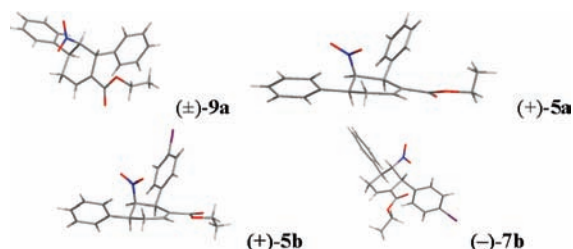
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studies of the facile racemization of  $\alpha$ -branched carbonyl compounds have been reported, the nitro phosphonium ylide has never been applied in an organocatalytic DYKAT. In this paper, we explore the feasibility of such an idea and demonstrate herein an unusual stereoselective synthesis of *all-cis* substituted cyclohexene derivatives.

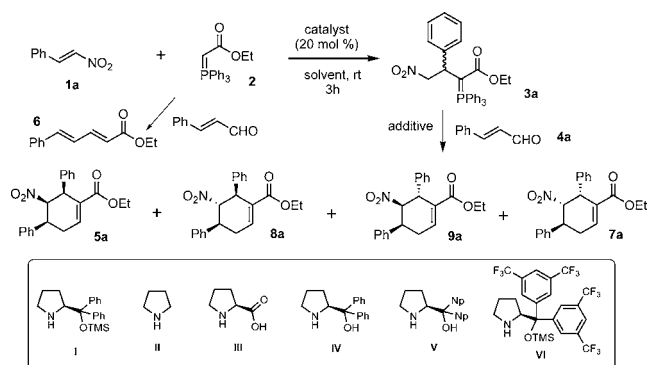


**Figure 1.** Stereoplots for X-ray crystal structures of (±)-**9a**, (+)-**5a**, (+)-**5b**, and (–)-**7b**: C gray, N blue, O red, and Br purple

To assess the feasibility of this strategy, a solution of nitrostyrene (**1a**), (carboxymethylene)triphenylphosphorane (**2**), and catalyst **I** (20 mol %) in  $\text{CHCl}_3$  (0.4 M) was stirred at ambient temperature for 3 h, affording **3a**. Following the addition of HOAc (20 mol %) and cinnamaldehyde (**4a**), the solution was stirred at room temperature for 3 days until completion of the reaction, monitored by TLC and  $^1\text{H}$  NMR,<sup>20</sup> and afforded an 82% yield of **5a**, **9a**, and **7a** in a ratio of 8:1:3 (Table 1, entry 1). Notably, **5a** is the *all-cis* trisubstituted cyclohexenecarboxylate, and **8a** was not observed in the reaction mixtures, probably due to the steric hindrance of the *anti*-Michael approach of (*R*)-**3a** to cinnamaldehyde (**4a**), Scheme 1. The relative structures of **5a** and **9a** were assigned unambiguously by single-crystal X-ray analysis (Figure 1). We note that no epimerization occurred during purification. The diastereomeric ratio determined by  $^1\text{H}$  NMR spectroscopic analysis of the crude reaction mixture was maintained after isolation of the single isomers, and high enantioselectivities were observed (95% ee for **5a** and >99% ee after a single recrystallization). The absolute configurations of the stereoisomers were assigned by single-crystal X-ray analysis of (+)-**5b** and (–)-**7b**,<sup>21</sup> prepared from 4-bromo- $\beta$ -nitrostyrene, vide infra. The structures indicate that the conjugate addition of nitroalkane (**3b**) to the enal takes place from the *Si* face through the control of the catalyst **I**.

We evaluated a series of solvents for this reaction. In  $\text{CH}_2\text{Cl}_2$ , **5a** was the major product, but with somewhat more **6**, the parasitic dead end product of the cascade reaction (entry 2, Table 1). Conducting the same reaction in other solvents (e.g.,  $\text{CH}_3\text{CN}$ , DMF, toluene, and THF) afforded lower yields and lower stereoselectivity (entries 3–6, Table 1). The solubility of **3a** in pure MeOH was very low, but addition of a small amount of

**Table 1.** Screening of Catalysts and Conditions for the Reaction of **1a**, **2**, and Cinnamaldehyde (**4a**)<sup>a</sup>



entry	cat.	solvent	additive (20 mol %)	yield (%) <sup>b</sup>	dr <sup>c</sup> <b>5:8:9:7:6</b>
1	<b>I</b>	$\text{CHCl}_3$	HOAc	82	8:0:1.3:1: <sup>d,e</sup>
2	<b>I</b>	$\text{CH}_2\text{Cl}_2$	HOAc	78	20:0:1:5:7
3	<b>I</b>	$\text{CH}_3\text{CN}$	HOAc	61	7:1:1:2:3
4	<b>I</b>	DMF	HOAc	33	3:0:1:2:5
5	<b>I</b>	toluene	HOAc	45	8:0:1:4:2
6	<b>I</b>	THF	HOAc	35	4:0:1:1:2
7	<b>I</b>	$\text{CH}_2\text{Cl}_2$ -MeOH <sup>g</sup>	HOAc	87	28:1:5:11:0 <sup>f</sup>
8	<b>II</b>	$\text{CHCl}_3$	HOAc	34	3:1:1:1:2
9	<b>III</b>	$\text{CHCl}_3$	HOAc	9	1:0:0:0:10
10	<b>IV</b>	$\text{CHCl}_3$	HOAc	11	1:0:0:0:6
11	<b>V</b>	$\text{CHCl}_3$	HOAc	5	1:0:0:0:9
12	<b>VI</b>	$\text{CHCl}_3$	HOAc	9	1:0:0:0:8
13	<b>I</b>	$\text{CHCl}_3$	$\text{PhCO}_2\text{H}$	81	7:0:1:3:2
14	<b>I</b>	$\text{CHCl}_3$	PNBA	79	7:0:1:4:3
15	<b>I</b>	$\text{CHCl}_3$	DNBA	82	5:0:1:4:2
16	<b>I</b>	$\text{CHCl}_3$	DABCO	82	0:6:1:2:1 <sup>h</sup>
17	<b>I</b>	$\text{CHCl}_3$	DBU	80	1:3:1:2:1

<sup>a</sup> Unless otherwise noted, the reactions were performed in 0.4 M **2** with a ratio 1.2/1/1.2 of **1a/2/4a** at 25 °C for 60–72 h. <sup>b</sup> Isolated yields of the adducts (**5a–9a**), not including **6**. <sup>c</sup> Determined by  $^1\text{H}$  NMR analysis of the crude reaction mixture. <sup>d</sup> Determined by HPLC with a chiral column (Chiracel OD-H). <sup>e</sup> Ee: 95% for **5a**; 90% for **7a**. <sup>f</sup> 85% for **5a**. <sup>g</sup> 0.1 mL of MeOH was added before the addition of cinnamaldehyde. <sup>h</sup> Ee: 92% for **8a**. PNBA: *p*-nitrobenzoic acid. DNBA: 3,5-dinitrobenzoic acid.

MeOH in  $\text{CH}_2\text{Cl}_2$  (1:10) slightly increased the yields with no observable **6**, although **5a** was obtained with lower ee, 85% vs. 95%, (entry 7, Table 1). Catalyst **I** was found to be the most promising candidate for the transformation among a series of potential organocatalysts (entries 8–12, Table 1). Reaction with pyrrolidine (**II**)-HOAc afforded lower overall yields along with substantial quantities of **6** and other diastereomers. Nevertheless, this racemic product was a suitable standard for HPLC analysis in determining the ee of **5a** in Table 1. The reactions with other catalysts (**III–VI**) predominately gave **6**, and were not suitable for this process. Replacement of HOAc by other acids under the same reaction conditions gave similar yields and selectivities (entries 13–15, Table 1). Replacement of the acid additive by a base (e.g., DABCO, DBU) favored formation of the adduct **8a** (entries 16 and 17, Table 1).<sup>22</sup> Notably, when **8a** was observed as the major product, **5a** was not obtained in the reaction with the additive DABCO. Presumably, **8a** was produced from the isomerization of the initially formed **5a** under basic conditions. This assumption was confirmed by the treatment of **5a** (99% ee) with DABCO in

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(20) The reaction at 0.1 M of **2** took nearly 30 days for completion.

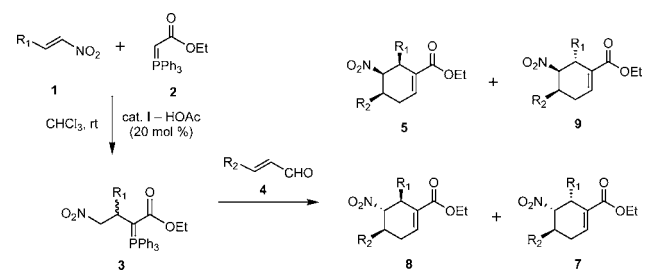
(21) 99% ee for **5b**, and 96% for **7b**.

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CHCl<sub>3</sub> to give **8a** predominately with a similar enantioselectivity (>99% ee). Having established the optimal reaction conditions, we studied the use of different nitroolefins as well as different  $\alpha,\beta$ -unsaturated aldehydes to synthesize a variety of trisubstituted cyclohexene derivatives. The major isomers (**5b–j**) were, in all cases, isolated in good yields and with high enantioselectivities (entries 2–10, Table 2). For the trinitro derivative, however, **5h** and **8h** were observed in a ratio of 2:1. The isomerization of **5h** to **8h** during the regular reaction and workup conditions may be attributed to the highly acidic nature of the CHNO<sub>2</sub> group in the polysubstituted nitro derivative.

**Table 2.** Scope of the Organocatalytic [1 + 2 + 3] Annulations



entry	R <sup>1</sup>	R <sup>2</sup>	yield (%) <sup>a</sup>	dr <sup>b</sup> 5:9:7:8	ee (%) <sup>c</sup>
1	Ph	Ph	<b>5a</b> : 55 (83)	6:1:2:0 <sup>d</sup>	95 <sup>e</sup>
2	4-BrC <sub>6</sub> H <sub>4</sub>	Ph	<b>5b</b> : 41 (82)	4:1:3:0	99 <sup>f</sup>
3	4-OMeC <sub>6</sub> H <sub>4</sub>	Ph	<b>5c</b> : 50 (90)	5:1:3:0	99
4	4-FC <sub>6</sub> H <sub>4</sub>	Ph	<b>5d</b> : 52 (91)	4:1:2:0	96
5	3,4-OCH <sub>2</sub> OC <sub>6</sub> H <sub>3</sub>	Ph	<b>5e</b> : 39 (71)	5:1:3:0	99
6	Ph	4-OMeC <sub>6</sub> H <sub>4</sub>	<b>5f</b> : 47 (73)	9:2:3:0	95
7	Ph	4-BrC <sub>6</sub> H <sub>4</sub>	<b>5g</b> : 59 (82)	5:1:1:0	97
8	Ph	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>5h</b> : 34 (85)	4:1:3:2	99
9	Ph	4-MeC <sub>6</sub> H <sub>4</sub>	<b>5i</b> : 48 (76)	5:1:2:0	92
10	Ph	4-ClC <sub>6</sub> H <sub>4</sub>	<b>5j</b> : 51 (77)	8:1:3:0	95

<sup>a</sup> Isolated yields of the major diastereomers (**5a–j**), combined isolated yields of the isomers in parentheses. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>c</sup> Ee of the major stereoisomer (**5a–j**), determined by HPLC with a chiral column (Chiracel OD-H). <sup>d</sup> **5:9:7:8** = 6:0:1:0 from 51% ee of (*R*)-**3a**, prepared in situ from **1a** and **2** with the thiourea catalyst **VII**. <sup>e</sup> >99% ee, following a single recrystallization. <sup>f</sup> 96% for **7b**.

The successful transformation that gave 55% isolated yields of **5a** (83% for all isomers) with high enantioselectivity suggested that the process may follow a novel dynamic kinetic resolution (DKR)-mediated reaction, as we proposed. The initially formed intermediate **3a** would undergo a DKR process in the presence of base (the secondary amine catalyst), whereby deprotonation of the highly acidic nitroalkane proton of **3a** would lead to a reversible process and the subsequent Michael–Wittig reaction would favor the reaction of (*R*)-**3a** to give the diastereoselectivity, even though the *k<sub>R</sub>/k<sub>S</sub>* is ~2. Compound **3a** recovered from the reaction during 50% conversion showed 0% ee. This outcome would result from the rapid racemization or because no enantioselective addition of **2** to **1a** occurred in the presence of catalyst **I**. To shed light on the

equilibrium between **2** and **3a** as well as to obtain improved diastereoselectivity of **5a**, an enantiomerically enriched **3a** was needed. Unfortunately, unlike the previous examples of phosphorus and enolizable carbon nucleophiles, vide infra, enantioselective addition of **2** to the nitroalkene (**1a**) remained elusive. While many examples of organocatalysis rely on covalent attachment of the catalyst (e.g., proline catalysis via enamine/iminium intermediates), noncovalent organocatalysis (e.g., thiourea derivatives and cinchonidine acting as general acids and general bases) provides alternative catalytic strategies.<sup>23</sup> Taking this concept into account, we screened a series of thiourea catalysts for the enantioselective formation of **3a**. After numerous attempts at the enantioselective addition of the naked nucleophile (nonenolizable) **2** to **1a**, the successful reaction with catalyst **VII** afforded 51% ee of (*R*)-**3a**.<sup>24</sup> Treatment of (*R*)-**3a** (51% ee) under standard reaction conditions (catalyst **I**-HOAc) with **4a** provided **5a** with the same 4*S*,5*R*,6*S* configuration and with much better dr (**5:9:7:8** = 6:0:1:0). In addition, the same reaction conditions conducted in the absence of **4a** afforded the racemization of **3a**, further demonstrating the occurrence of DYKAT in the process. On the other hand, addition of **4a** to the reaction mixture of **3a** and thiourea catalyst **VII** in the absence of catalyst **I** gave no reaction for 4 days. Therefore, the two-step reaction (with noncovalent and covalent catalyst) was able to function independently and proceeded in a one-pot manner.

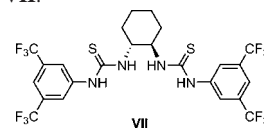
In conclusion, we have discovered an unprecedented organocatalytic enantioselective cascade nitro-Michael–Michael–Wittig reaction with certain evidence of dynamic kinetic asymmetric transformation. It is remarkable that this annulation provides a simple and direct protocol for the stereoselective construction of trisubstituted cyclohexenecarboxylates in a multicomponent one-pot operation; the presence of three contiguous chiral centers, with *all-cis* stereochemistry in the product and with high enantioselectivity, is especially noteworthy. An increase in diastereoselectivity was achieved by the first organocatalytic asymmetric conjugate addition of phosphonium ylide to nitrostyrenes with the noncovalent thiourea catalyst. Further work is underway to gain more insight into this annulation as well as the exploration of its synthetic applications.<sup>25</sup>

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**Supporting Information Available:** Experimental procedures and characterization data for the new compounds and X-ray crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(24) Structure of **VII**:



(25) The reaction with  $\beta$ -alkyl-substituted enals was stopped at the second-step conjugate addition. Attempts at activating the reaction are underway. The reaction of  $\beta$ -alkyl-substituted nitroolefins with compound **2** is feasible and actively being investigated.

(23) For reviews, see: (a) Connon, S. J. *Synlett* **2009**, 354. (b) Connon, S. J. *Chem. Commun.* **2008**, 2499. (c) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, 38, 1187.