Corrections

**BIOCHEMISTRY**


The authors note that Fig. 6 appeared incorrectly. There was an error in the alignment of the molecular mass markers, and minor adjustments have been made to the assignment of caspase-12 bands. The authors also note that the source of the anti-caspase-12 antibody for Fig. 6 was Sigma (clone 14F7). This error does not affect the conclusions of the article. The corrected figure and its corresponding legend appear below.

![Fig. 6](https://www.pnas.org/cgi/doi/10.1073/pnas.1302753110)

**CHEMISTRY**


The authors note that they incorrectly assigned the structure of the reaction product reported in Scheme 4. The published structure represents the γ-aminated adduct 8, when it should instead be the α-analogue arising from an α-site selective pathway. As a result of this, Scheme 4 and its related comments should be removed from the article.

On page 20642, left column, within the Abstract, lines 16–18, “Finally, we describe the extension of the dienamine catalysis-induced vinylogous nucleophilicity to the asymmetric γ-amination of cyclohexene carbaldehyde” should be removed from the article.

On page 20645, right column, third full paragraph, lines 1–8, to page 20646, left column, first paragraph, lines 1–2, “Finally, to explore the potential of the chiral primary amine-induced vinylogous nucleophilicity, we wondered whether this unique reactivity concept may be translated to an aldehyde derivative adorned with a six-membered ring scaffold, reminiscent of the β-substituted cyclohexanone framework. Although the vinylogous Michael addition of 1-cyclohexene-1-carboxaldehyde 7 to nitrostyrene 2a did not proceed at all, the combination with tert-butyldiazodicarboxylate under the catalysis of A furnished the γ-amination product 8 with perfect regio- and enantioselectivity (Scheme 4)” should be removed from the article.

These errors do not affect the conclusions of the article of the vinylogous Michael addition of cyclic enones to nitroalkenes. The ability of primary amine catalysis to address the synthetic issue connected with the enantioselective carbon–carbon bond formation gamma to a carbonyl group, promoting vinylogous nucleophilicity upon selective activation of unmodified cyclic unsaturated ketones, is fully supported by the separated results presented in Tables 1, 2, and 3, and Schemes 2 and 3.

www.pnas.org/cgi/doi/10.1073/pnas.1302980110
MICROBIOLOGY

The authors note the following: “The mating frequencies reported in Table 1 of this paper did not follow a multinomial distribution, making the statistical analysis inapplicable. This problem was obviated by considering only the first matings in each experimental unit and computing odds ratios. After submitting the paper, we continued to perform experiments identical in design to those we reported. In the table below, we combined the results of those additional replicate experiments with those already reported. From the new analysis, we now find that experiment 4, in which flies were infected with a mixture of Lactobacillus spp., assortative mating was not restored. Otherwise, the conclusions of the article were not changed by our reanalysis. We acknowledge the statistical advice of Dan Yekutieli and thank Tal Lahav for calculating the odds ratios and their 95% confidence intervals, and for performing the chi-squared tests presented in the corrected Table 1.”

The corrected Table 1 appears below.

Table 1. The role of bacteria in diet-induced mating preference of D. melanogaster

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Fly treatment*</th>
<th>N†</th>
<th>OR‡</th>
<th>95% CI</th>
<th>P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Starch-grown × CMY-grown</td>
<td>18</td>
<td>3.21</td>
<td>2.14–4.81</td>
<td>1.8 × 10⁻⁹</td>
</tr>
<tr>
<td>2</td>
<td>Experiment 1 after antibiotics</td>
<td>11</td>
<td>1.04</td>
<td>0.63–1.71</td>
<td>0.9888</td>
</tr>
<tr>
<td>3</td>
<td>Experiment 2 after infection of starch-grown flies with homologous bacteria§</td>
<td>6</td>
<td>2.68</td>
<td>1.40–5.11</td>
<td>0.0477</td>
</tr>
<tr>
<td>4</td>
<td>Experiment 3 with Lactobacillus spp. replacing homologous bacteria</td>
<td>4</td>
<td>1.76</td>
<td>0.74–4.19</td>
<td>0.2912</td>
</tr>
<tr>
<td>5</td>
<td>Experiment 3 with Lactobacillus plantarum replacing homologous bacteria</td>
<td>7</td>
<td>2.14</td>
<td>1.35–3.39</td>
<td>0.0019</td>
</tr>
<tr>
<td>6</td>
<td>Infection control (no added bacteria)</td>
<td>4</td>
<td>1.26</td>
<td>0.53–3.00</td>
<td>0.7712</td>
</tr>
</tbody>
</table>

*After all treatments, the flies were grown for one generation in CMY medium before performing the mating preference test.
†N is the number of replicate experiments.
‡Cochran-Mantel-Haenszel Odds Ratio and P value are from the Cochran-Mantel-Haenszel Chi-squared test (34, 35).
§Antibiotic-treated starch- and CMY-grown flies were infected with bacteria isolated from their respective growth medium (before antibiotic treatment).


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MEDICAL SCIENCES

The authors note that the author name Vadim Kapulkin should instead appear as Wadim Jan Kapulkin. The corrected author line appears below. The online version has been corrected.

Virginia Fonte, Wadim Jan Kapulkin, Andrew Taft, Amy Fluet, David Friedman, and Christopher D. Link

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SYSTEMS BIOLOGY

The authors note that, within the corresponding author footnote on page 9715, the email address “colaneria@niehs.nih.gov” should instead appear as “acolaneri_2000@yahoo.com.ar”.

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Direct asymmetric vinylogous Michael addition of cyclic enones to nitroalkenes via dienamine catalysis

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Edited by David W. C. MacMillan, Princeton University, Princeton, NJ, and accepted by the Editorial Board May 29, 2010 (received for review February 1, 2010)

In spite of the many catalytic methodologies available for the asymmetric functionalization of carbonyl compounds at their α and β positions, little progress has been achieved in the enantioselective carbon–carbon bond formation at a to a carbonyl group. Here, we show that primary amine catalysis provides an efficient way to address this synthetic issue, promoting vinylogous nucleophilicity upon selective activation of unmodified cyclic α,β-unsaturated ketones. Specifically, we document the development of the unprecedented direct and vinylogous Michael addition of β-substituted cyclohexenone derivatives to nitroalkenes proceeding under dienamine catalysis. Besides enforcing high levels of diastereo- and enantioselectivity, chiral primary amine catalysts derived from natural cinchona alkaloids ensure complete γ-site selectivity. The resulting, highly functionalized vinylogous Michael adducts, having two stereocenters at the γ and β positions, are synthesized with very high fidelity. Finally, we describe the extension of the dienamine catalysis-induced vinylogous nucleophilicity to the asymmetric γ-amination of cyclohexene carbaldehyde.

The stereoselective functionalization of carbonyl compounds, particularly while concomitantly forming a new carbon–carbon bond, represents one of the more efficient and potent chemical ways to produce valuable chiral molecules. This target has inspired generations of synthetic chemists to design unique chiral catalysts able to enantioselectively forge a stereocenter α or β to a carbonyl group (1–3). In this context, intense investigations into the aldol (4, 5) and Michael reactions (6, 7) have made them invaluable tools in modern organic chemistry. Recently, the classical organometallic-based approach has been enriched by the possibility of using chiral primary or secondary amines as efficient catalysts for the asymmetric functionalization of carbonyl compounds. This strategy is known as “asymmetric aminocatalysis” (8–11). Among the many advantages of this synthetic approach (12), one of its more attractive features is the ability to directly generate, in situ, the catalytically active intermediates from unmodified carbonyl compounds (13, 14).

Both metal- and organic-based approaches have achieved levels of reliability such that synthetic chemists can now address even the most daunting issues connected with the asymmetric catalytic functionalization of carbonyl compounds at their α and β positions. In contrast, little progress has been reported in the corresponding enantioselective carbon–carbon bond formation at a to a carbonyl group (15). Among the few useful approaches devised to date, the concept of vinylogous nucleophilicity is the most powerful (16–19). Formulated by Fuson in 1935 as the transmission of electronic effects through a conjugated π system (20), this principle accounts for the use of γ-enolizable α,β-unsaturated carbonyl compounds as precursors of nucleophilic dienolate equivalents, formally inverting the usual reactivity of this compound class. Vinylogous processes offer an efficient entry onto functionalized building blocks having high level of structural complexity; however, designing asymmetric catalytic versions is not simple. Indeed, every approach to vinylogous reactions overlays the challenge of site-selectivity onto the already present issue of stereo-selectivity. In general, the critical regiochemical issue can be addressed by judiciously preparing preformed, stable dienolate equivalents. This strategy has been successfully applied to asymmetric vinylogous aldol (17, 21), Mannich (18, 22), and Michael reactions (19, 23). Avoiding the stoichiometric preactivation of the vinylogous nucleophilic components would logically improve this approach, particularly from the standpoint of atom economy (24). However, examples of direct, catalytic, and asymmetric vinylogous reactions are rare: Recently, Trost and Hitce reported on the direct vinylogous Michael addition of 2(SH)-furane to nitroalkenes under dinuclear zinc catalysis (25), whereas chiral Brønsted base catalysis proved successful to activate specific reactive alkenes, such as α,α-dicyano olefins, toward vinylogous nucleophilicity (26).

Within this context, we wondered whether asymmetric aminocatalysis could solve the challenge of a direct vinylogous nucleophilic addition of unmodified γ-enolizable carbonyl compounds. We were inspired by a recent report by Jørgensen and coworkers on the direct, enantioselective γ amination of α,β-unsaturated aldehydes using azodicarboxylates as the electrophilic nitrogen source (27). The process is based on a unique activation mode, dienamine catalysis, which exploits the condensation of a chiral secondary amine catalyst with β-aliphatic-substituted unsaturated compounds. This condensation leads to the formation of the expected electrophilic iminium ion intermediate, which is in equilibrium with an electron-rich dienamine intermediate. The dienamine, exploiting its γ-nucleophilic character, actually represents the catalytic active species. In principle, the ability to promote the in situ formation of a dienamine from γ-enolizable carbonyl compounds while enforcing γ-site selectivity during the nucleophilic path might offer a unique and potent way to design direct vinylogous processes (Fig. 1).

Author contributions: P.M. designed research; G. Bencivenni and P.G. performed research; G. Bartoli contributed new reagents/analytic tools; A.M. analyzed data; and P.M. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission. D.W.C.M. is a guest editor invited by the Editorial Board.

Data deposition: The atomic coordinates have been deposited in the Cambridge Structural Database, Cambridge Crystallographic Data Centre, Cambridge CB2 1EZ, United Kingdom (CSD reference nos. 763174, 763175, and 763176).

1To whom correspondence should be addressed. E-mail: pmelchiorre@iciq.es.

This article contains supporting information online at www.pnas.orglookup/suppl/doi:10.1073/pnas.1001150107/DCSupplemental.
In spite of the potential to address important synthetic issues, such as the effective catalytic generation of a new carbon–carbon bond and a new stereocenter $\gamma$ to a carbonyl group, dienamine catalysis has found limited application (28, 29). Accordingly, a recently published perspective on the advent of organocatalysis did not include dienamine catalysis among the generic modes of activation and induction (30). This lack was probably due to the fact that $\gamma$-amination of unsaturated aldehydes was originally proposed to follow a $[4 + 2]$ cycloaddition (27), instead of a more generalizable nucleophilic addition manifold. Moreover, some recent studies suggest that chiral secondary amines, such as proline (31) and its derivatives (32, 33), can activate $\gamma$-enolizable unsaturated aldehydes toward the formation of the dienamine intermediate, but generally promoting an $\alpha$-site-selective alkylation step via enamine catalysis in the presence of suitable electrophiles. Nonetheless, a recent inspiring report by Christmann and coworkers has highlighted the potential of dienamine catalysis for enforcing a direct nucleophilic $\gamma$-addition path, albeit in an intramolecular way (34).

Here, we show that dienamine catalysis, induced by chiral primary amines, can efficiently promote the direct, intermolecular vinylogous Michael addition of unmodified $\beta$-substituted cyclohexenone derivatives to nitroalkanes, imparting high levels of diastereo- and enantioselectivity, and ensuring exclusive $\gamma$-site selectivity. Notably, the two stereocenters at the $\gamma$ and $\delta$ positions of the carbonyl moiety are formed with very high fidelity (Scheme 1).

Results and Discussion

Background. Our laboratory and others, independently, have recently introduced 9-amino(9-deoxy)epicinchona alkaloids (Fig. 2), chiral primary amines easily derived from natural sources, as general and effective catalysts for a wide variety of asymmetric $\alpha$ and $\beta$ functionalizations of ketones (35, 36). We have further demonstrated the ability of catalyst A, derived from hydroquinine, to combine orthogonal aminocatalytic modes (iminium and enamine activations) into one mechanism, thus promoting cascade reactions with $\alpha,\beta$-unsaturated ketones (37, 38) and even with the challenging $\alpha,\beta$-disubstituted enals (39).

Next, we decided to investigate the behavior of this versatile catalyst in the context of the elusive $\gamma$-site activation of unmodified enones, in order to design a dienamine-catalyzed direct, vinylogous Michael reaction. From the outset, we were fully aware of the inherent difficulties of our target, because the presence of multiple potential sites of enolization has greatly hampered the use of $\alpha,\beta$-unsaturated ketones in even the stoichiometric version of vinylogous reactions (40). We decided to attack this problem by selecting $\beta$-substituted cyclohexenone derivatives as a model substrate. At first glance, this compound class seems highly challenging, because it further enhances the task of regioselectivity (Fig. 3). The condensation of a chiral primary amine catalyst with cyclic enones would lead to the formation of the iminium ion, which could equilibrate, upon selective $\alpha'$-deprotonation or $\gamma$- and $\gamma'$-deprotonation, with the kinetic cross-conjugated dienamine intermediate I or the thermodynamic extended dienamine II and III, respectively. Although the former would open an avenue for $\alpha'$-site alkylation (path a in Fig. 3), the extended dienamines could be alkylated at three different positions, namely $\alpha$, $\gamma$, and even $\gamma'$, behaving as $d^2$ or $d^4$ reagents (paths b, d, and c, respectively).

Despite the increased complexity posed by $\beta$-substituted cyclic enones, our choice was motivated by a variety of considerations. Our experience in designing of cascade reactions (37, 38) strongly indicated that, when reacted with acyclic, linear $\alpha,\beta$-unsaturated ketones, catalyst A easily facilitates the equilibrium between the iminium ion and the nucleophilic cross-conjugated dienamine intermediate of type I, selectively directing the reaction manifold toward an $\alpha$-site alkylation (path a in Fig. 3). We thus considered using cyclohexenone derivatives to coax the regiocontrolled formation of extended dienamines within a more thermodynamically favored six-membered ring scaffold. This idea is based upon related enolization studies demonstrating that, under certain conditions, the selective formation of the thermodynamic $exo$-cycloenolate of type III is strongly favored over both the $endo$-isomer and the kinetic cross-conjugated dienolate (41–45). This inherent behavior of $\beta$-substituted cyclohexenones has found a wonderful application in the conceptually unique, direct, vinylogous aldol reaction reported by Yamamoto and coworkers (46, 47): The complete $\gamma$-site selectivity induced by the nonchiral, bulky aluminum-based catalyst has been rationalized on the basis of catalyst steric effects (48, 49), which inhibit base deprotonation at the $\alpha'$ position, whereas thermodynamic factors account for the formation of the reactive $exo$-dienolate isomer of the $\beta$-methyl 2-cyclohexen-1-one (46). On these grounds, we considered the unique

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Scheme 1. The direct vinylogous Michael addition developed in this study.

Fig. 2. Primary amine catalysts used within this study.

Fig. 3. Challenges arising from the site-selective formation of dienamines.
ability of catalyst A, in combination with an acidic cocatalyst, to perturb the iminium-dienamine equilibrium, taken together with thermodynamic factors, that may govern the regioselective formation of the exo-cyclic dienamine intermediate. We wondered if this ability might be exploited to develop the challenging γ-site-selective, direct stereoselective addition of β-methyl 2-cyclohexen-1-one to nitrostyrene derivatives (following the nucleophilic pathway in Fig. 3). Theoretical calculations accounting for a thermodynamically driven site-selective formation of a dienamine of type III are reported in the SI Appendix.

**Organocatalytic Vinylogous Michael Addition.** The vinylogous Michael addition under dienamine catalysis was first evaluated by mixing 2 equivalents of β-methyl 2-cyclohexen-1-one 1 and nitrostyrene 2a in toluene (1 M, 48 h, 40 °C). In accordance with our mechanistic postulate, the chiral primary amine A (20 mol%), in combination with 30 mol % of 2-fluorobenzoic acid as the cocatalyst, directed the reaction manifold toward a γ-site-selective addition, leading to compound 3a as the unique product of the process and with a good level of enantiomeric control (Table 1, entry 1). Examination of the reaction media revealed that the catalytic process was greatly influenced by polarity, with solvents with a high dielectric constant strongly affecting both reactivity and enantioselectivity (Table 1, entries 1–5). The nature of the acidic cocatalysts was also a crucial parameter, with stronger acids leading to worse results (Table 1, entries 1, 6, and 7). This evidence suggests that fine tuning the carboxylic acid cocatalyst is essential to modulate the perturbation of the delicate equilibrium between iminium ion, cross-conjugated and extended dienamine intermediates during the reaction.

These results further consolidate A as a general, highly versatile catalyst for the activation of keto compounds, even toward dienes during the reaction.

Table 1. Optimization studies of the vinylogous Michael addition under dienamine catalysis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Acid</th>
<th>Solvent</th>
<th>Conversion, %</th>
<th>ee, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>2F-C₆H₄CO₂H</td>
<td>Toluene</td>
<td>&gt;95</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>2F-C₆H₄CO₂H</td>
<td>CHCl₃</td>
<td>52</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>2F-C₆H₄CO₂H</td>
<td>THF</td>
<td>30</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>2F-C₆H₄CO₂H</td>
<td>MeOH</td>
<td>&lt;5</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>2F-C₆H₄CO₂H</td>
<td>MeCN</td>
<td>12</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>A</td>
<td>TFA</td>
<td>Toluene</td>
<td>&lt;5</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>A</td>
<td>2NO₂-C₆H₄CO₂H</td>
<td>Toluene</td>
<td>45</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>B</td>
<td>2F-C₆H₄CO₂H</td>
<td>Toluene</td>
<td>&gt;95</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>B</td>
<td>2F-C₆H₄CO₂H</td>
<td>Toluene</td>
<td>&gt;95 (77)</td>
<td>98*</td>
</tr>
</tbody>
</table>

Table 2. Vinylogous Michael addition: Scope of the nitrostyrene derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>R</th>
<th>3</th>
<th>Yield, %</th>
<th>ee, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B</td>
<td>Ph</td>
<td>a</td>
<td>77</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>C</td>
<td>Ph</td>
<td>a</td>
<td>57</td>
<td>95*</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>4-MeO-Ph</td>
<td>b</td>
<td>70</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>4-Me-Ph</td>
<td>c</td>
<td>70</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>4-Br-Ph</td>
<td>e</td>
<td>73</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>B</td>
<td>2-CI-Ph</td>
<td>e</td>
<td>84</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>B</td>
<td>2-F-Ph</td>
<td>f</td>
<td>83</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>B</td>
<td>2-thiophenyl</td>
<td>g</td>
<td>68</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>B</td>
<td>2-OBn-Ph</td>
<td>h</td>
<td>87</td>
<td>97</td>
</tr>
<tr>
<td>10</td>
<td>C</td>
<td>2-OBn-Ph</td>
<td>h</td>
<td>68</td>
<td>96*</td>
</tr>
</tbody>
</table>

Bn, benzyl; reactions carried out using two equivalents of enone 1. *Yield of the isolated compounds 3.

The opposite (S) enantiomer has been obtained using catalyst C.
enriching the established reactivity profile of secondary amine catalysis. Within this context, a recent report has demonstrated that a chiral secondary amine behaves in a completely different way when exposed to the very same reagents combination, namely  \( \beta \)-methyl cyclohexenone and nitrostyrene, catalyzing a Diels-Alder reaction between 1 and 2a via the selective formation of cross-conjugated dienamine of type 1 (52).

Our vinylogous protocol could be successfully extended to a  \( \beta,\beta \)-disubstituted nitrostyrene, leading to the stereocentered generation of compound 4 having an all-carbon quaternary (53) stereocenter (Scheme 2). Moreover, a different class of Michael acceptor has proven to be a viable component of the dienamine-catalyzed direct vinylogous addition. Mixing  \( \beta \)-methyl 2-cyclohexen-1-one with  \( \beta \) -methyl cyclohexenone and nitrostyrene, catalyzing a Diels-Alder reaction between 1 and 2a via the selective formation of cross-conjugated dienamine of type 1 (52).

Next, we studied the possibility of forging two contiguous stereogenic centers at the  \( \gamma \) and  \( \delta \) positions, examining the vinylogous Michael addition of differently  \( \beta \)-substituted cyclohexanones to a variety of nitrostyrene derivatives under the catalysis of the salt made by combining 20 mol % of the chiral primary amine B with 30 mol % of 2-fluorobenzoic acid. In line with previous observations, the nature of the carboxylic acid cocatalyst strongly influenced both the reactivity and the stereochémical outcome of the process: Carrying out the reaction in the presence of 40 mol % of salicylic acid afforded higher enantiocontrol and an increased reaction rate, albeit with slightly lower diastereoselectivity (Table 3, entries 1 and 2). Thus, both catalyst salt combinations, where B is mixed with 2-fluoro- or 2-hydroxybenzoic acids, have been evaluated. Selected results are reported in Table 3. In general, a variety of substrate combinations can be realized, leading to products 6, readily amenable to further functionalizations, with high levels of  \( \gamma \)-site, diastereo- and enantioselectivity.

Crystals from bromide 6i and from compound 6l were suitable for X-ray analysis, which established the absolute configuration of the vinylogous reaction as well as its anti-stereochémical outcome. Interestingly, the observed sense of relative stereoinduction is not common in the corresponding enamine-catalyzed Michael addition of carbonyls to nitroalkenes, which generally leads to a syn-relationship (55, 56).

Finally, to explore the potential of the chiral primary amine-induced vinylogous nucleophilicity, we wondered whether this unique reactivity concept may be translated to an aldehyde derivative adorned with a six-membered ring scaffold, reminiscent of the  \( \beta \)-substituted cyclohexanone framework. Although the vinylogous Michael addition of 1-cyclohexene-1-carboxaldehyde 7 to nitrostyrene 2a did not proceed at all, the combination with tert-butylazodicarboxylate under the catalysis of A furnished compound 5 with complete control over the relative stereochemistry and high enantioselectivity (54).

Table 3. Stereoselective creation of vicinal stereocenters under dienamine catalysis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst salt combination</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>6</th>
<th>Yield, %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>dr</th>
<th>ee, %&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>Me</td>
<td>Ph</td>
<td>a</td>
<td>72</td>
<td>9:1</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>Me</td>
<td>Ph</td>
<td>a</td>
<td>80</td>
<td>6:1</td>
<td>94&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>a</td>
<td>Me</td>
<td>4-MeO-Ph</td>
<td>b</td>
<td>78</td>
<td>10:1</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>a</td>
<td>a</td>
<td>4-Me-Ph</td>
<td>c</td>
<td>76</td>
<td>10:1</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>b</td>
<td>Me</td>
<td>4-Br-Ph</td>
<td>d</td>
<td>81</td>
<td>5:1</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>b</td>
<td>Me</td>
<td>4-NO&lt;sub&gt;2&lt;/sub&gt;-Ph</td>
<td>e</td>
<td>65</td>
<td>3:1</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>b</td>
<td>Me</td>
<td>2-F-Ph</td>
<td>f</td>
<td>80</td>
<td>6:1</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>b</td>
<td>Me</td>
<td>2-thiophenyl</td>
<td>g</td>
<td>90&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3:3:1</td>
<td>94</td>
</tr>
<tr>
<td>9</td>
<td>b</td>
<td>Bn</td>
<td>Ph</td>
<td>h</td>
<td>65&lt;sup&gt;d&lt;/sup&gt;</td>
<td>7:1</td>
<td>85</td>
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<tr>
<td>10</td>
<td>b</td>
<td>allyl</td>
<td>Ph</td>
<td>i</td>
<td>44</td>
<td>11:5:1</td>
<td>94&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>b</td>
<td>propyl</td>
<td>Ph</td>
<td>j</td>
<td>86&lt;sup&gt;e&lt;/sup&gt;</td>
<td>11:5:1</td>
<td>95</td>
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<td>b</td>
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<td>4-MeO-Ph</td>
<td>k</td>
<td>72</td>
<td>13:5:1</td>
<td>91&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>b</td>
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<td>4-Br-Ph</td>
<td>l</td>
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<td>10:1</td>
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</tr>
<tr>
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<td>b</td>
<td>Ph</td>
<td>Ph</td>
<td>m</td>
<td>86&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2:1</td>
<td>90&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
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</table>

Bn, benzyl; reactions carried out using two equivalents of enones 1.  
<sup>a</sup>1<sup>H</sup>NMR analysis of the crude mixture indicated a highly  \( \gamma \)-site-selective alkylation pathway, other products arising from different reaction manifolds (e.g.,  \( \alpha \)-alkylation under enamine catalysis, see ref. 52) being sporadically detected in negligible amounts.

<sup>b</sup>Refers to the isolated single, major diastereoisomer.

<sup>c</sup>The enantiomeric excess (ee) was determined by HPLC analysis on chiral stationary phases.

<sup>d</sup>Refers to the isolated mixture of diastereoisomers.

<sup>g</sup>Enantiomerically pure products obtained after a single crystallization.
the γ-amination product 8 with perfect regio- and enantioselectivity (Scheme 4).

Concluding Remarks

The direct, γ-site-selective addition of β-substituted cyclohexene-none derivatives to nitroalkenes represents one of the few examples of catalytic, asymmetric vinylogous Michael reactions of unmodified carbonyl compounds. This unprecedented chemical transformation affords highly functionalized compounds, having two stereocenters at the γ and δ positions, with high enantiomeric purity. In addition to its synthetic interest, this study confirms the ability of chiral primary amine catalysis to impart unique reactivity profiles, thus expanding the potential of asymmetric aminocatalysis. Specifically, dienamine catalysis has been exploited to promote vinylogous nucleophilicity within addition reaction manifolds. We believe this reactivity may be further extended to a variety of vinylogous donors and acceptors as well as to nucleophilic substitution reactions.

Methods and Materials

All the vinylogous adducts were fully characterized: Structural proofs and spectral data for all compounds are provided in the SI Appendix.

The reactions were carried out in the undistilled solvent without any precautions to exclude moisture. To a solution of 9-amino(9-deoxy)leucopinchoninic acid alkalds A–C (0.08 mmol) in 0.8 mL of toluene, ortho-fluorobenzoic acid (0.16 mmol, 22.4 mg) was added at room temperature under stirring. After 10 min, the reaction was started with the addition of β-substituted cyclohexene derivative 1 (0.8 mmol, 2.0 equiv) immediately followed by the addition of 2 (0.4 mmol, 1.0 equiv), and the mixture was allowed to reach 40 °C. Stirring was continued for 24 h in the vinylogous reaction of the starting material (24–48 h, checked by thin layer chromatography). The reaction mixture was then directly purified by flash column chromatography (SiO2, 20–30% ethyl acetate in hexane) to yield the vinylogous adducts 3 or 6.

Acknowledgments.

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