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](image)

**Fig. 6.** Procaspase-12 forms a complex with caspase-1 and is partially autoprocessed in the complex. HEK293T cells were cotransfected with expression vectors harboring Flag-tagged procaspase-1 (all lanes) plus either procaspase-12 (lanes 1 and 4) or the catalytically incapacitated C299A mutant (lanes 2 and 5). After 24 h, cells were harvested and lysed. One tenth of the lysate was directly applied to SDS/PAGE (lanes 1 and 2), and the remainder was immunoharvested with antibodies directed against the caspase-1 Flag epitope tag (lanes 4 and 5; lane 3 was processed in the same way, except that only lysis buffer was used). Immunoblotting for the large subunit (p20) of caspase-12 revealed that procaspase-12 and the resulting autocleavage product were both immunoharvested with caspase-1. The asterisk indicates a band of unknown identity that is detected by prebleed control serum.

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 nucleophilic addition 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-butylazodicarboxylate 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.

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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‡ 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 2.14–4.81</td>
<td>1.8 × 10⁻⁸</td>
</tr>
<tr>
<td>2</td>
<td>Experiment 1 after antibiotics</td>
<td>11</td>
<td>1.04 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 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 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 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 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).


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

Systems Biology

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

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

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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 γ 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 diastereoselectivity 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 δ 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 organic methods 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 γ 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)-furanone 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).
moting cascade reactions with (iminium and enamine activations) into one mechanism, thus pro-
hydroquinine, to combine orthogonal aminocatalytic modes
γ-protonation or presence of multiple potential sites of enolization has greatly
favored six-membered ring scaffold. This idea is based upon related
enalization studies demonstrating that, under certain conditions, the selective formation of the thermodynamic exo-cyclo-
enate of type III is strongly favored over both the endo-isomer and the kinetic cross-cyclo
diolate (41–45). This inherent behavior of β-substituted cyclohexenones has found a wonderful
application in the conceptually unique, direct, vinylogous aldol reaction reported by Yamamoto and coworkers (46, 47): The complete γ-site selectivity induced by the nonchiral, bulky alumi-
num-based catalyst has been rationalized on the basis of catalyst stereic effects (48, 49), which inhibit base deprotonation at the α’-position, whereas thermodynamic factors account for the formation of the reactive exo-dienolate isomer of the β-methyl 2-cyclo-
hexen-1-one (46). On these grounds, we considered the unique

Results and Discussion

Background. Our laboratory and others, independently, have recently introduced 9-amino(9-deoxy)epi-cinchona alkaloids (Fig. 2), chiral primary amines easily derived from natural sources, as general and effective catalysts for a wide variety of asymmetric α and β 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 prom-
moting cascade reactions with α,β-unsaturated ketones (37, 38) and even with the challenging α,β-disubstituted enals (39).

Next, we decided to investigate the behavior of this versatile catalyst in the context of the elusive γ-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 α,β-unsaturated ketones in even the stoichiometric version of vinylogous reactions (40). We decided to attack this problem by selecting β-substituted cyclohexenone deriva-
tives 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 α-deprotonation or γ- and γ’-deprotonation, with the kinetic cross-conjugated dienamine intermediate I or the thermodynamic extended dienamines II and III, respectively. Although the for-
mer would open an avenue for α’-site alkylation (path a in Fig. 3), the extended dienamines could be alkylated at three different positions, namely α, γ, and even γ’, behaving as d² or d⁴ reagents (paths b, d, and c, respectively).

Despite the increased complexity posed by β-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 α,β-unsaturated ketones, catalyst A easily facilitates the equilibrium between the iminium ion and the nucleophilic cross-conjugated dienamine inter-
mediate of type I, selectively directing the reaction manifold toward an α’-site alkylation (path a in Fig. 3). We thus considered using cyclohexenone derivatives to coax the regiocontrolled for-
mation of extended dienamines within a more thermodynamically

Scheme 1. The direct vinylogous Michael addition developed in this study.
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 path d 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 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 co-catalyst, 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 enantiocontrol (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 vinylogous nucleophilicity. However, we were not satisfied with the level of stereocencentration in the present chemistry. We speculated that using a bifunctional catalyst capable of simultaneously activating both the electrophilic and nucleophilic components might lead to higher catalytic activity and, more importantly, to better stereocenters (S9). To this end, we tested the potential of 6′-hydroxy-9-amino-9-deoxyepiquinine B to synergistically and productively bind the two reaction partners of the vinylogous Michael addition. B has recently been introduced by Chen et al. as an efficient bifunctional catalyst of the asymmetric 1,3-dipolar cycloaddition of cyclic enones (S1). Catalyst B greatly improved the enantioselectivity as well as the reaction rate of the vinylogous addition of 1 to 2a while maintaining a complete γ-selectivity (Table 1, entry 8). The enhanced catalytic activity allowed us to lower the catalyst loading to 10 mol % (Table 1, entry 9), delineating a more practical synthetic protocol (extensive optimization studies can be found within the SI Appendix).

The best result was obtained with the catalytic salt made by combining B (10 mol %) and 2-fluorobenzoic acid (20 mol %) in toluene (0.2 M). These conditions were selected to examine the scope of the vinylogous Michael addition by evaluating a variety of nitroalkenes (Table 2). Different substituents at the aromatic moiety of β-nitrostyrene derivatives were well tolerated, regardless of their electronic properties, because the corresponding adducts 3 were obtained in good to high yield and almost perfect stereocenters (enantiomeric excesses ranging from 95% to 98%). The pseudoenantiomeric catalyst C, derived from quinidine, accounted for the possibility of accessing both antipodes of the products (Table 2, entries 2 and 10).

As limitations of the direct vinylogous Michael reactions, aliphatic nitroalkenes did not react under the described conditions. Moreover, modifying the cyclic scaffold of the nucleophilic component (i.e., 3-methyl 2-cyclopenten-1-one) resulted in a complete loss of reactivity, a result that highlights how strongly the cyclic scaffold geometry influences (and drives) the selective formation of the thermodynamic, extended dienamine intermediate.

The absolute configuration of the stereogenic center was unambiguously determined to be R by anomalous dispersion X-ray crystallographic analysis of the bromide derivative 3d. The ability of the catalyst to communicate its inherent stereochemical information while forging the new stereocenter at the δ position, several atoms apart from the catalyst binding point within the covalent dienamine intermediate, seemed noteworthy to us. It is also intriguing to consider how primary amine catalysis can impart unique mechanistic pathways, thus complementing and

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**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-C6H5CO2H</td>
<td>Toluene</td>
<td>&gt;95</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>2F-C6H5CO2H</td>
<td>CHCl₃</td>
<td>52</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>2F-C6H5CO2H</td>
<td>THF</td>
<td>30</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>2F-C6H5CO2H</td>
<td>MeOH</td>
<td>&lt;5</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>2F-C6H5CO2H</td>
<td>MeCN</td>
<td>12</td>
<td>99</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-C6H5CO2H</td>
<td>Toluene</td>
<td>45</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>B</td>
<td>2F-C6H5CO2H</td>
<td>Toluene</td>
<td>&gt;95</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>B</td>
<td>2F-C6H5CO2H</td>
<td>Toluene</td>
<td>&gt;95 (77)</td>
<td>98</td>
</tr>
</tbody>
</table>

TFA, trifluoroacetic acid; reactions carried out using two equivalents of enone 1

*Conversion determined by 1H NMR analysis of the crude mixture; only product 3a, derived from a γ-site-selective alkylation step, has always been detected.

The enantiomeric excess (ee) was determined by HPLC analysis on chiral stationary phases.

Number in parentheses refers to yield of the isolated compound 3a.

*Reaction performed in the presence of 10 mol % of B and 20 mol % of 2F-C6H5CO2H and using [Z]₀ = 0.2 M

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**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>55</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>d</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. 1H NMR analysis of the crude mixture indicated a highly γ-site-selective alkylation pathway, other products arising from different reaction manifolds (e.g., α-alkylation under enamine catalysis, see ref. S2) being sporadically detected in negligible amounts.

Yield of the isolated compounds 3.

The enantiomeric excess (ee) was determined by HPLC analysis on chiral stationary phases.

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 β-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 β,β-disubstituted nitrostyrene, leading to the stereocontrolled generation of compound 4 having an all-carbon quaternary stereocenter (Scheme 2). Moreover, a different class of Michael acceptor has been proven to be a viable component of the dienamine-catalyzed direct vinylogous addition. Mixing Michael acceptor and nitrostyrene, catalyzing a Diels-Alder reaction between 1 and 2a via the selective formation of cross-conjugated dienamine of type 1 (52).

Table 3. Stereoselective creation of vicinal stereocenters under dienamine catalysis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst salt combination</th>
<th>R¹</th>
<th>R²</th>
<th>6</th>
<th>Yield, %*</th>
<th>dr</th>
<th>ee, %†</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†</td>
</tr>
<tr>
<td>3</td>
<td>a</td>
<td>Me</td>
<td>4-Me-Ph</td>
<td>b</td>
<td>78</td>
<td>10:1</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>a</td>
<td>Me</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-NO₂-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°</td>
<td>3:1:1</td>
<td>94</td>
</tr>
<tr>
<td>9</td>
<td>b</td>
<td>Bn</td>
<td>Ph</td>
<td>h</td>
<td>65°</td>
<td>7:1</td>
<td>85</td>
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<td>b</td>
<td>allyl</td>
<td>Ph</td>
<td>i</td>
<td>44</td>
<td>11.5:1</td>
<td>94†</td>
</tr>
<tr>
<td>11</td>
<td>b</td>
<td>propyl</td>
<td>Ph</td>
<td>j</td>
<td>86°</td>
<td>11.5:1</td>
<td>95</td>
</tr>
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<td>4-Me-Ph</td>
<td>k</td>
<td>72</td>
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<td>91†</td>
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<tr>
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<td>10:1</td>
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<td>Ph</td>
<td>m</td>
<td>86°</td>
<td>2:1</td>
<td>90°†</td>
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</table>

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

†Enantioselectivity (ee) was determined by HPLC analysis on chiral stationary phases.

‡Refers to the isolated single, major diastereoisomer.

§Enantiomerically pure products obtained after a single crystallization.
the γ-amino product 8 with perfect regio- and enantioselectivity (Scheme 4).

**Concluding Remarks**

The direct, γ-site-selective addition of β-substituted cyclohexone 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.

After the reactions were carried out in the undistilled solvent without any precautions to exclude moisture. To a solution of 9-aminoo(9-deoxy)epicinchona alkaloids 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 a period of time and composition 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.

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