2,3-Dihydropyridin-4(1H)-ones and 3-Aminocyclohex-2-enones: Synthesis, Functionalization, and Applications to Alkaloid Synthesis

Hajime Seki, Gunda I. Georg*

Departments of Chemistry and Medicinal Chemistry, and the Institute for Therapeutics Discovery and Development, College of Pharmacy, University of Minnesota, 717 Delaware Street SE, Minneapolis, MN 55414, USA
Fax +1(612)6266318; E-mail: georg@umn.edu

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Abstract: This account summarizes our recent investigations into the chemistry of 2,3-dihydropyridin-4(1H)-ones and 3-aminocyclohex-2-enones (enaminones). These enaminones are exceptionally versatile chemical scaffolds that serve as valuable intermediates in the synthesis of indolizidine and quinolizidine alkaloids and other bioactive compounds. Since we reported our first method for constructing enaminones in 2006, we have developed a number of additional approaches to the synthesis and derivatization of enaminones and we have explored their applications in natural product synthesis.

1 Background

Because indolizidine, piperidine, and quinolizidine alkaloids often possess biologically interesting properties, the synthesis community has devoted significant efforts to preparing and investigating those alkaloids.1,2 In this regard, cyclic enaminones such as 2,3-dihydropyridin-4(1H)-ones 1.3 have been shown to be excellent intermediates for the synthesis of indolizidine, piperidine, and quinolizidine alkaloids (Scheme 1).3,4

![Scheme 1 Overview of enaminones](image)

The chemical properties of enaminones are quite different from those of enamines 1.1 or amides 1.2. Enamines, which are neutral nucleophiles, have been used in a number of reactions,5,6 although they can be quite unstable under hydrolytic or oxidative conditions. On the other hand, the amide group is a stable functional group and amides can be easily isolated. Because of this stability, very strong reagents are typically required to functionalize amides. The reactivities and stabilities of enaminones lie between those of enamines and amides. Under hydrolytic and oxidative conditions, enaminones are generally more stable than enamines, but they maintain a certain degree of nucleophilicity that clearly differentiates them from amides. These stable but reactive properties are what make enaminones useful as intermediates for the synthesis of alkaloids.
A number of transformations of enaminones are known (Scheme 2). The C3 position can be functionalized by enolate chemistry to give derivatives 1.7. Nucleophilic additions of soft nucleophiles such as cuprates take place at the C6 position to give products 1.8. Functionalization at the C5 position to give products 1.9 has been extensively studied; for example, halogenated derivatives have been used in palladium-catalyzed cross-coupling reactions. Triflation has been practiced in two different ways either directly from the enaminones 1.3 to give the triflates 1.11 or sequentially after double-bond reduction to form triflates 1.10.

2 Ynone Cyclization

2.1 Initial Discovery

We initially attempted to synthesize enaminones by cyclizing the amino ynone 2.3 in a 6-endo-dig fashion (Scheme 3). Although intermolecular Michael addition to ynones is well known, the intramolecular variant had not been reported, even though cyclization should be a fa-

Biographical Sketches

Dr. Hajime Seki was born in Kawasaki, Japan, in 1983. In 2005, he received his B.S. degree from Keio University, Japan, where he studied ruthenium-catalyzed C−H activation chemistry under the guidance of Professor Fumitoshi Kakiuchi. Soon after, he entered graduate school at Keio University before moving to the U.S.A. and joining the chemistry Ph.D. program at the University of Minnesota. In 2011, he obtained his Ph.D., directed by Professor Gunda I. Georg. For his Ph.D. studies, he worked on the development of new methodologies, alkaloid synthesis, and the construction of libraries of anticancer agents, some of which are covered in this review. Since May 2012, he has continued his academic career as a research associate in the laboratory of Professor Kim D. Janda at the Scripps Research Institute, where he develops and evaluates inhibitors for the zinc protease of botulinum neurotoxin A. Inside the lab, he enjoys chemical biology, and outside, he enjoys nice weather and badminton.

Professor Gunda I. Georg was born in Herborn in the state of Hesse, Germany. She received a degree in pharmacy in 1975 and a Dr. rer. nat. degree in medicinal chemistry in 1980 from the Philipps University of Marburg in Germany under the direction of Professor Manfred Haake. After postdoctoral studies at the University of Marburg and in the Department of Chemistry at the University of Ottawa, Canada, in the laboratory of Professor Tony Durst, she accepted a one-year post as assistant professor at the University of Rhode Island. She then moved to the University of Kansas in 1984 to become a faculty member in the Department of Medicinal Chemistry in the School of Pharmacy. In 2007, she moved to the Department of Medicinal Chemistry in the College of Pharmacy at the University of Minnesota. She is currently head of the department and is the founding director of the Institute for Therapeutics Discovery and Development. She holds the Vince and McKnight Endowed Chairs. She has published 200 scientific contributions in organic and medicinal chemistry, and has trained 100 students, fellows, and scientists in her laboratory. She is currently co-editor-in-chief of the Journal of Medicinal Chemistry.
favorable transformation according to Baldwin’s rules. The investigation started by synthesizing the quinolizidine system 2.4. N-(tert-Butoxycarbonyl)pipecolic acid (2.1) was converted into the homologated Weinreb amide 2.2 by a Wolff rearrangement. This amide was reacted with an ethynyl Grignard reagent to give the N-tert-butoxycarbonylamino ynone 2.3. When we screened conditions for deprotection of the tert-butoxycarbonyl group and subsequent cyclization we found that the desired quinolizidine system 2.4 was obtained by treating the ynone with hydrochloric acid or iodo(trimethyl)silane, followed by potassium carbonate in methanol.16

![Scheme 3](image)

**Scheme 3** Protocol for forming enaminone 2.4 from the N-tert-butoxycarbonylamino ynone 2.3 at room temperature

Chiral HPLC analysis revealed that the enantiomeric ratio of the product was 97:3 when hydrochloric acid was used for the deprotection. Because deprotection with trifluoroacetic acid gave only modest yields, if any, we concluded that halides must play an important role in this reaction. We therefore proposed a mechanism involving halide activation (Scheme 4). We posited that under the deprotection conditions, cationic vinylogous acid halide 2.5 and dihalogenated 2.6 form as intermediates, possibly preventing intermolecular reactions.

When the scope of this method was investigated, however, significant racemization was observed in some cases (Figure 1). For example, the enaminones 2.7 and 2.8, derived from hydroxyproline, racemized during the cyclization, to give diastereomeric ratios of 80:20 and 86:14, respectively.15 Because proline-derived enaminones are useful as indolizidine scaffolds, this racemization might jeopardize the usefulness of the chiral-pool approach.

![Figure 1](image)

**Figure 1** Racemized enaminones 2.7 (HCl, 1,4-dioxane) and 2.8 (TMSI)

### 2.2 Optimization of Reaction Conditions

Given the short duration of the cyclization reaction, racemization is likely to have occurred during the tert-butoxycarbonyl deprotection step. Because racemization was observed at the α- and β-positions in ynones 2.10, two different pathways were proposed (Scheme 5).16 One possible mechanism is a retro-Mannich reaction that cleaves the C−C bond and racemizes the α-stereocenter. The other path is a retro-Michael reaction that cleaves the C−N bond and racemizes the β-stereocenter. On the assumption that strong acidity in the deprotection step is responsible for these racemizations, several acids were screened (Table 1).16 A combination of formic acid as a weak acid and sodium iodide as an external source of halide was found to be optimal for the reaction. Under these conditions, racemization was minimized, and the enantio-
merically enriched enaminone 2.12 was obtained in >95:5 er.

**Table 1** Optimization of Cyclization Step\(^{16}\)

<table>
<thead>
<tr>
<th>Reaction conditions</th>
<th>Yield (%)</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 N HCl–1,4-dioxane</td>
<td>77</td>
<td>85:15</td>
</tr>
<tr>
<td>TFA</td>
<td>31</td>
<td>67:33</td>
</tr>
<tr>
<td>TFA–CH(_2)Cl(_2) (1:1)</td>
<td>18</td>
<td>88:12</td>
</tr>
<tr>
<td>1 N HCl, Et(_2)O</td>
<td>36</td>
<td>67:33</td>
</tr>
<tr>
<td>TESOTf, 2,6-lutidine, CH(_2)Cl(_2)</td>
<td>21</td>
<td>83:17</td>
</tr>
<tr>
<td>TMSI (3 equiv), CH(_2)Cl(_2)</td>
<td>99</td>
<td>75:25</td>
</tr>
<tr>
<td>HCO(_2)H, r.t.</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>NaI (3 equiv), HCO(_2)H, r.t.</td>
<td>93</td>
<td>&gt;95:5</td>
</tr>
</tbody>
</table>

2.3 **Scope and Limitations**

Two series of bicyclic and monocyclic enaminones were prepared by using the optimized protocol (Tables 2 and 3, respectively).\(^{16}\)

**Table 2** Substrate Scope for Bicyclic Enaminones\(^{16}\)

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Method(^{a})</th>
<th>Yield(^{b}) (%)</th>
<th>er(^{c}) or dr(^{d})</th>
</tr>
</thead>
<tbody>
<tr>
<td>H (2.13)</td>
<td>A</td>
<td>87</td>
<td>97:3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>90</td>
<td>&gt;98:2</td>
<td></td>
</tr>
<tr>
<td>Me (2.14)</td>
<td>A</td>
<td>87</td>
<td>73:27</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>80</td>
<td>73:27</td>
<td></td>
</tr>
<tr>
<td>Ph (2.15)</td>
<td>A</td>
<td>91</td>
<td>58:42</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>85</td>
<td>69:31</td>
<td></td>
</tr>
<tr>
<td>H (2.16)</td>
<td>A</td>
<td>89</td>
<td>70:30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>96</td>
<td>98:2</td>
<td></td>
</tr>
<tr>
<td>Me (2.17)</td>
<td>A</td>
<td>87</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Ph (2.18)</td>
<td>A</td>
<td>89</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>H (2.19)</td>
<td>A</td>
<td>94</td>
<td>67:33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>92</td>
<td>&gt;95:5</td>
<td></td>
</tr>
<tr>
<td>Me (2.20)</td>
<td>B</td>
<td>94</td>
<td>63:37</td>
<td></td>
</tr>
<tr>
<td>Ph (2.21)</td>
<td>A</td>
<td>85</td>
<td>63:37</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>88</td>
<td>60:40</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2** Substrate Scope for Bicyclic Enaminones\(^{16}\) (continued)

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Method(^{a})</th>
<th>Yield(^{b}) (%)</th>
<th>er(^{c}) or dr(^{d})</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-OH (2.12)</td>
<td>A</td>
<td>77</td>
<td>85:15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>93</td>
<td>&gt;95:5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>94</td>
<td>96:4</td>
<td></td>
</tr>
<tr>
<td>β-OH (2.8)</td>
<td>A</td>
<td>60</td>
<td>60:40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>95</td>
<td>92:8</td>
<td></td>
</tr>
<tr>
<td>cis (2.7)</td>
<td>A</td>
<td>80</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>95</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>trans (2.23)</td>
<td>A</td>
<td>99</td>
<td>&gt;95:5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>82</td>
<td>&gt;95:5</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) Method A: (i) 4 N HCl–1,4-dioxane, 15 min, (ii) K\(_2\)CO\(_3\), MeOH; Method B: (i) NaI (3 equiv), HCO\(_2\)H, 6–24 h, (ii) K\(_2\)CO\(_3\), MeOH; Method C: (i) TMSI, CH\(_2\)Cl\(_2\), (ii) K\(_2\)CO\(_3\), MeOH.

\(^{b}\) Isolated yield.

\(^{c}\) Determined by HPLC.

\(^{d}\) Determined by \(^1\)H NMR spectroscopy.

**Table 3** Substrate Scope for Monocyclic Enaminones\(^{16}\)

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Method(^{a})</th>
<th>Yield(^{b}) (%)</th>
<th>er(^{c})</th>
</tr>
</thead>
<tbody>
<tr>
<td>H (2.24)</td>
<td>A</td>
<td>50</td>
<td>&gt;99:1</td>
<td></td>
</tr>
<tr>
<td>Me (2.25)</td>
<td>A</td>
<td>92</td>
<td>&gt;95:5</td>
<td></td>
</tr>
<tr>
<td>Me (2.26)</td>
<td>A</td>
<td>96</td>
<td>&gt;95:5</td>
<td></td>
</tr>
<tr>
<td>H (2.27)</td>
<td>A</td>
<td>70</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>CH(_2)Ph (2.28)</td>
<td>A</td>
<td>50</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Ph (2.29)</td>
<td>B</td>
<td>86</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) Method A: (i) 4 N HCl–1,4-dioxane, 15 min, (ii) K\(_2\)CO\(_3\), MeOH, r.t.; Method B: (i) NaI (3 equiv), HCO\(_2\)H, r.t., 6–24 h, (ii) K\(_2\)CO\(_3\), MeOH, r.t.

\(^{b}\) Isolated yield.

\(^{c}\) Determined by HPLC.
The use of formic acid and sodium iodide markedly suppressed the racemization in most cases; however, these conditions were ineffective for the cyclization of substituted ynones, leading to β-racemization in products 2.20 and 2.21. The strategy also allowed the synthesis of several seven-membered enamiones (Scheme 6). Although the expected decrease in yield was observed, no general method was previously available for synthesizing seven-membered enamiones; in this regard, our new protocol has a unique advantage.

**Scheme 6** Substrate scope for seven-membered enamiones

### 2.4 Mechanistic Studies

With regard to the mechanism of cyclization, two pathways were proposed after the formation of the vinylogous acid chloride 2.34 (Figure 2). Initially, a simple 6-endo-trig cyclization followed by liberation of hydrogen chloride was proposed (Pathway A). However, when the reaction was carried out in bulky alcoholic solvents (s-BuOH or i-PrOH) or a non-nucleophilic solvents (CH₂Cl₂ or THF), the reaction was significantly impaired. This observation was suggestive of an alternative mechanism (Pathway B), in which the solvent ROH displaces chloride and leads to 6-exo-trig cyclization.

To determine whether an alcohol was required for the cyclization, the reaction was conducted by using triethylamine as a base in three different solvents (Scheme 7). All three conditions provided the enamione 2.41, suggesting that a nucleophilic solvent is not necessary.

**Scheme 7** Ynone cyclization using triethylamine as the base

To rule out the possibility that the cyclization is promoted by residual water, ynone 2.42, lacking an amine group, was prepared (Scheme 8). When ynone 2.42 was treated with hydrochloric acid, two intermediates 2.43 and 2.44 were formed in a ratio of 1:6. When these two species were subjected to basic conditions, the vinylogous acid chloride 2.43 was obtained as the sole product (Scheme 8). Upon addition of excess water, this compound remained intact. These results suggest that trace amounts of water do not promote the cyclization.

**Scheme 8** Treatment of ynone 2.42 with hydrochloric acid

In a further exploration of the reaction mechanism, the two intermediates 2.43 and 2.44 were treated with potassium carbonate in methanol (Scheme 9). After two hours, only a 33% conversion was detected, suggesting that the addition of methanol to the vinylogous acid chloride is much slower than the cyclization. It is therefore reason-
able to assume that the cyclization takes a 6-endo-trig mode (Pathway A). We postulated that the reason for failure to achieve cyclization in nonprotic solvents is insufficient solubility of potassium carbonate, whereas this base readily dissolves in methanol.

**Scheme 9** Treatment of intermediates 2.43 and 2.44 with potassium carbonate in methanol

### 2.4 Application to Quinolone Synthesis

The ynone cyclization strategy was then used for the synthesis of a quinolone library. The synthesis of the ynones started from the anthranilic acids 2.46, which were protected with a tert-butoxycarbonyl group and converted into Weinreb amides 2.47 in one flask (Scheme 10). These amides were reacted with organomagnesium or organolithium reagents to give the desired ynones 2.48.

Next, the cyclization was conducted by using a one-flask procedure (Scheme 11). First, the N-tert-butoxycarbonyl ynone was treated with hydrochloric acid to remove the protecting group, and secondly, the resulting crude mixture was subjected to basic conditions by using potassium carbonate in methanol. Interestingly, this cyclization was slow enough to permit the observation of the Michael-attack intermediate 2.49, formed by addition of methanol to the vinylogous acid chloride. In this case, therefore, a plausible mechanism involves a 6-endo-dig mode with methanol as the catalytic nucleophile. Because of the stability of intermediate 2.49 and the weaker nucleophilicity of the amino group, the cyclization requires heating at 50 °C for four days.

**Scheme 11** Synthesis of quinolones from ynones

### 2.6 N-Butoxycarbonyl β-Lactam Approach

Having established a protocol for cyclizing ynones to enamiones, we turned our focus on the synthesis of functionalized ynones. Specifically, it was envisioned that the ynone could be derived by nucleophilic ring opening of a β-lactam (Scheme 12). This synthesis started with the reaction of acid chloride 2.51 and imine 2.52 under Staudinger reaction conditions to give the N-p-methoxyphenyl (PMP) protected β-lactam 2.53 with cis-configuration. The acetate group was cleaved, the resulting hydroxy group was protected with a silyl group, and the PMP N-protecting group was removed. The nitrogen was reprotected with a tert-butoxycarbonyl group to give the β-lactam 2.55, which was treated with an ethynyl Grignard reagent to afford the ynone 2.56.

**Scheme 12** Synthesis of functionalized ynones via a β-lactam
Next, the ynones 2.56 were subjected to the one-flask procedure to provide the desired enaminones 2.57 in good yield (Scheme 13).

The nitrogen atom of the vinyl enaminones 2.57 was then functionalized with various terminal alkenes (Scheme 14). The resulting enaminones 2.58 were subjected to ring-closing metathesis conditions using the Grubbs II catalyst to give a variety of five-, six-, and seven-membered bicyclic enaminones 2.59. It is of interest that an \( N \)-acylated 2-phenyl analogue of 2.57 has recently been identified as an androgen receptor modulator.19

Although this approach is similar to our previous enamine synthesis, the use of a protected hydroxylamine enabled us to synthesize aldehyde 2.70 with high enantioselectivity by employing MacMillan’s organocatalytic method.21 We hypothesized that enaminone 2.66 might be readily synthesized from aldehyde 2.70 by means of our previous strategy and that the hydroxy group of 2.67 might be cleaved in a reductive fashion to provide enaminone 2.66.

With the aid of an imidazolidinone catalyst, protected hydroxylamine 2.71 underwent Michael addition to aldehyde 2.72 to give amino aldehyde 2.70 with excellent enantioselectivity (Scheme 16). The amino aldehyde 2.70 was then treated with a Grignard reagent, and the resulting propargyl alcohol 2.69 was oxidized with manganese dioxide to give the corresponding ynone. However, the desired product was not obtained under cyclization conditions. On the assumption that the \( \text{tert} \)-butyl(dimethyl)silyl group might attenuate the nucleophilicity of the amine group in the cyclization, we attempted a deprotection of the silyl group from the ynone. Interestingly, the resulting free hydroxy group underwent 7-endo-dig cyclization to afford the seven-membered product 2.74.

Although scaffold 2.74 had not previously been reported, we sought conditions to convert it into the enaminone 2.66. We found that the weak N–O bond could be cleaved reductively with samarium(II) iodide, and upon deprotection of the \( \text{tert} \)-butoxyacarbonyl group, an intermediate with the tentative diketone structure 2.75 underwent cyclization to provide enantiomerically enriched enaminone 2.66 (Scheme 17).

### Scheme 13 Cyclization of ynones to enaminones

![Scheme 13](image)

### Scheme 14 Derivatization of enaminones to form bicyclic nitrogenous compounds

![Scheme 14](image)

### Scheme 15 Retrosynthetic plan to obtain enantiomerically-enriched enaminones

![Scheme 15](image)
3 Ketene Cyclization

As discussed above, our approach to synthesizing enamiones has a unique advantage in its use of amino acids. In some instances, however, partial racemization of the product occurred during the cyclization. Also, not all β-amino acids are readily available. To address these issues, we sought a different approach.

### 3.1 Chiral-Pool Approach

In the ynone cyclization, a retrosynthetic disconnection was made at C–N bond of the enamione (Scheme 18, bond a). As an alternative approach, a disconnection might be made at the α–C–C bond of the enamione (bond b). We hypothesized that for a pendent enamine, a ketene should be an excellent electrophile that might be generated by Wolff rearrangement of the corresponding diazo ketone 3.3.

#### Scheme 16 Synthesis of an ynone and its cyclization

![Chemical structure](image1)

#### Scheme 17 One-flask reductive cleavage of 3,4-dihydro-1,2-oxazepin-5(2H)-one 2.74 to obtain enamione 2.66

![Chemical structure](image2)

<p>| Table 4 Optimization of the Reaction Conditions |</p>
<table>
<thead>
<tr>
<th>Run</th>
<th>Catalyst</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ag₂O</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>AgO₂CCF₃</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>AgOA nghiên.</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>AgOBz</td>
<td>99</td>
</tr>
</tbody>
</table>

* Isolated yield.
of diazo ketone 3.8 (Table 4). First, N-benzylglycine hydrochloride (3.7) was treated with ethyl propiolate under basic conditions, to give a vinylogous carbamate. In the same flask, after evaporation of the solvent, the acid was subsequently converted into the diazo ketone 3.8. This process requires only a single purification by column chromatography. Having obtained the diazo ketone 3.8, we tested various silver salts that are frequently used in Arndt–Eistert homologations; several of these silver salts gave the desired product 3.9 in excellent yield.

On the basis of this study, we selected silver benzoate in dichloromethane as our standard conditions, and we subjected a variety of alkyne and amino acids to these optimized conditions to give the desired diazo ketones 3.12–3.18 (Scheme 19).

Each of the diazo ketones 3.12–3.18 was subjected to the conditions for the Wolff rearrangement to give various piperidine, indolizidine, and quinolizidine ring systems in high yields (Scheme 20).

**Scheme 19** Synthesized diazo ketones

<table>
<thead>
<tr>
<th>Reaction conditions</th>
<th>diazo ketone</th>
<th>Products and yieldsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) CO2Et MeOna, MeOH 0 °C, 20 min</td>
<td>3.12</td>
<td>53%</td>
</tr>
<tr>
<td>2) CICO2 i-Bu, THF; CH2N2, Et2O r.t., overnight</td>
<td>3.13</td>
<td>31%</td>
</tr>
</tbody>
</table>

**Scheme 20** Synthesized enaminones. *Reaction conditions*: diazo ketone, PhCO2Ag (10 mol%), CH2Cl2 (0.2 M), r.t., overnight. * Isolated yields. **PhCO2Ag (20 mol%) was used. † The ee was determined by 19F NMR (Mosher ester derivatives); only one isomer was observed. ‡ Ag2O (10 mol%) and DCE (0.2 M) were used. § The dr was determined by 1H NMR; one isomer was observed.

### 3.2 Three-Component Synthesis

For the ketene cyclization, the appropriate diazo ketone precursors were prepared from amino acids by using diazomethane. Although the incorporation of chirality derived from an amino acid into the enaminone is attractive, the scale and scope of this method are limited by the need to use diazomethane, as well as by the limited solubility of amino acids in organic solvents. For example, N-methylglycine could not be used as a substrate because of its insufficient solubility in methanol. Such shortcomings were addressed by an alternative retrosynthetic analysis. We speculated that the diazo ketones might be derived from three components: a primary amine 3.31, an alkyne 3.30, and 1-bromo-3-diazoacetone (3.32) (Scheme 21).

By applying this disconnection, it should be possible to vary the substituents on the enaminone structure in a simple and convergent fashion, and to limit the use of diazomethane to the preparation of the common diazoacetone intermediate 3.32. To examine this hypothesis, we set our...
initial goal as the synthesis of known diazo ketone 3.8 (Scheme 22). The desired intermediate 3.8 was obtained by the Michael addition of 1-(benzylamine)-3-diazoacetonitrile (3.33) in ethanol; the diazo compound 3.33 was, in turn, synthesized by treatment of 1-bromo-3-diazoacetone (3.32) with an excess of benzylamine.

Subsequently, several amino diazo ketones were prepared in a similar fashion from 1-bromo-3-diazoacetone (3.32) and alkyl amines 3.31 (Table 5). Several primary alkyl amines 3.31, including a chiral amine and tryptamine, were converted into the corresponding amino diazo ketones 3.29 in good yields.

The clean conversion of diazo ketone 3.33 into the azo keto ester 3.8 led us to attempt a Michael addition of the amino diazo ketone to an alkyne and a subsequent Wolff rearrangement in a single flask. We found that the use of two solvents (ethanol and dichloromethane) maximized the conversion and the yield. Under these conditions, a wide variety of enaminones were prepared in a single step from the corresponding amino diazo ketones (Scheme 23). In a few instances, silver oxide gave superior yields to silver benzoate.

4 C5 Functionalization

4.1 Suzuki Coupling of Iodoenaminones

If we consider the embedded enamine functionality in enaminones, it is not surprising that the C5 position exhibits nucleophilicity. In fact, iodination occurs readily at the C5 position unless the substituent on the nitrogen is an electron-withdrawing group. Comins and Joseph and Kranke and Kunz have shown that this iodoenaminones undergo a variety of palladium-catalyzed reactions, such as Stille or Negishi cross-couplings, although the reaction conditions have not been optimized.

We found that the iodoenaminones underwent Suzuki coupling with arylboronic acids under microwave conditions in good to excellent yields (Scheme 24).

4.2 Suzuki-Type Direct Cross-Coupling

Once a two-step protocol was available for functionalizing the C5 position, a more direct method was envisaged that would eliminate the need for preactivation of the enaminone. We surmised that, by taking advantage of the innate nucleophilic character of enaminone, a palladium-enaminone species might be derived from the nonactivat-
ed enaminone; this would be followed by C–C bond formation with a suitable coupling partner to permit the two-step process to become a catalytic one-step method. A direct palladium(II)-catalyzed arylation of enaminone 4.13 was successfully achieved by using an aryl(trifluoro)borate as a coupling partner in a mixture of three solvents (Scheme 25) to give the aryl derivative 4.14.26 Acetic acid was used to promote palladation by increasing the electrophilicity of the palladium(II) center. Consequently, trifluoroborates, known to be robust equivalents of organoboronic acids, were chosen as coupling partners because other coupling partners, including boronic acids or organozinc reagents, are sensitive to acidic conditions. Slow addition of the trifluoroborate was necessary to avoid its dimerization.

The scope for the aryl(trifluoro)borate was then investigated under the optimized conditions (Scheme 26). As expected, electron-rich aryl(trifluoro)borates coupled efficiently. Electron-deficient or sterically hindered aryl(trifluoro)borates gave moderate yields in extended periods of time. Notably, halo groups on the aryl moieties remained intact, potentially serving as positions for further derivatization.

Next, we examined the scope of enaminones for the reaction (Scheme 27). We found that monocyclic or bicyclic...
enaminones were viable substrates. The N-butoxycarbonyl-protected enaminone 4.32, however, was inactive in the cross coupling.

It is possible that the coupling is initiated by nucleophilic attack of the enaminone 4.33 on palladium to give the palladium–enaminone intermediate 4.34 (Scheme 28).26 This palladium species might then undergo transmetalation with the aryltrifluoroborate followed by reductive elimination to give the arylated enaminone 4.36. Alternatively, the catalytic cycle might start with transmetalation between the palladium species and the aryl(trifluoro)borate species. The palladium–aryl intermediate would then serve as an electrophile for the enaminone 4.33. The formation of a biaryl byproduct was observed, which supports the formation of the palladium–aryl intermediate.

Scheme 27 Scope of enaminones

4.27 98% 4.28 70% 4.29 79% 4.30 86% 4.31 77% 4.32 0%

Scheme 28 Proposed catalytic cycle for direct arylation of enaminones

4.33 Suzuki-Type Direct Cross-Coupling with Arylboronic Acids

Although the direct Suzuki-type cross-coupling of the enaminone with aryltrifluoroborates was successful, it was necessary to explore other partners for the coupling reaction because of the limited number of aryl(trifluoroborates) that are commercially available. Boronic acids were selected as the most promising alternative, and conditions for their cross-coupling reactions were investigated. Smooth coupling was observed under optimized conditions when copper(II) acetate and copper(II) chloride were used with various boronic acids in N,N-dimethylformamide (Scheme 29).27

Scheme 29 Scope of the boronic acids

This protocol was applied to various enaminones (Scheme 30), confirming the wide scope and broad functional-group compatibility of this approach.

We found that, in most cases, the electronic nature of boronic acids did not affect the coupling yield, which is a considerable advantage over the previous method with ar-
The scope of the Hiyama coupling proved to be highly versatile, as a variety of aryl triethoxysilanes were viable substrates for coupling with various enaminones. However, the double bond of the enaminone might remain intact under the reaction conditions, but would serve as a Heck donor to afford C6 arylated enaminones. This problem of regioselectivity was overcome by careful optimization of the reaction conditions using silver salts (Scheme 32).29 The silver salts and dimethyl sulfide presumably contribute to the production of an electrophilic arylpalladium(1+) species by abstracting iodide and stabilizing the cation, leading to the suppression of carbopalladation (the Heck pathway). The scope of this reaction was explored with respect to both the aryl iodide coupling partners for the C5 functionalization of enaminones and the aryl group onto the palladium–enaminone species through a putative aryl-copper intermediate.

4.5 Direct Coupling with Aryl Iodides

Because they are available commercially or can be readily synthesized, aryl iodides appeared to be the most practical coupling partners for the C5 functionalization of enaminones. However, the double bond of the enaminone might also serve as a Heck donor to afford C6 arylated enaminones. This problem of regioselectivity was overcome by careful optimization of the reaction conditions using silver salts (Scheme 32).29 The silver salts and dimethyl sulfide presumably contribute to the production of an electrophilic arylpalladium(1+) species by abstracting iodide and stabilizing the cation, leading to the suppression of carbopalladation (the Heck pathway). The scope of this reaction was explored with respect to both the aryl iodide and the enaminone.
4.6 Alkenylation by the Fujiwara–Moritani Reaction

Encouraged by our success in direct arylation of the enamiones, we investigated their direct alkenylation. This was unsuccessful under Suzuki reaction conditions because of the rapid homocoupling of alkenyl(trifluoro)borates. To address this problem, we considered the Fujiwara–Moritani reaction (Scheme 33). The Fujiwara–Moritani reaction starts with the formation of an aryl–palladium complex that undergoes by carbopalladation by an olefin and subsequent reductive elimination to give the alkene. By assuming that a palladium-enaminone intermediate exists in our catalytic cycle and has an aryl–palladium-like property, we surmised that alkenylation might be possible by using a terminal alkene as a coupling partner. The reaction conditions were optimized by screening various palladium catalysts, oxidants, and additives.

By using an activated olefin as the coupling partner and potassium trifluoroacetate as an additive, we obtained the alkenylated enamione product (Scheme 34). A wide variety of olefins with electron-withdrawing groups were found to be viable substrates in this reaction. However, acrylic acid and vinyl ethers failed to afford the desired products and respectively.

Next, we carried out this alkenylation by using various enamiones (Scheme 35), and we found that the protocol is applicable to mono- and bicyclic enamiones. Impor-
tantly, stereochemical integrity was retained during the transformation, yielding enaminones 4.100 and 4.101 without epimerization. As previously observed in the Suzuki and Hiyama reactions, N-unsubstituted and N-benzylxoycarbonyl enaminones were not viable substrates (4.102 and 4.103). 1-Benzylpyridin-4(1H)-one was also a poor substrate for this coupling reaction (4.104).

During the course of this study, we conducted NMR experiments in an attempt to identify the palladium–enaminone intermediate, presumed to be the key intermediate species for the coupling reactions (Scheme 36). The enaminone 4.37 was treated with 0.5 or 1.0 equivalents of palladium(II) acetate in dimethyl sulfoxide for 20 minutes. The disappearance of the two doublet peaks at 7.62 and 4.79 ppm and the appearance of a singlet peak at 7.72 ppm indicated that the enaminone was converted into the palladium–enaminone intermediate 4.105.

This intermediate 4.105 was then subjected to alkenylation in dimethyl sulfoxide (Scheme 37). Upon heating the reaction to 140 °C, the alkenylated product 4.80 was observed.

We found that 1,3-dimethyluracil (4.106) underwent coupling with tert-butyl acrylate in N,N-dimethylformamide in the presence of palladium(II) acetate as a catalyst to give the C5-alkenyl derivative 4.107 in 92% yield (Scheme 38). The key additives were silver(I) acetate, which acts as an effective palladium oxidant, and pivalic acid, which presumably lowers the energy of the transition state and facilitates palladation of the uracil.34 We examined the scope of this reaction with various olefins (Scheme 38) and various 1,3-disubstituted uracils 4.121 (Scheme 39).

4.7 Alkenylation of Uracils

We also applied the Fujiwara–Moritani protocol (see Section 4.6) to olefination of uracils at the C5 position.34 Although C5 alkenylation had been reported previously in the context of biological investigations on uracil derivatives, preactivated uracils and metalated alkenes were used in most cases.35,36 With the aim of streamlining these inefficient processes, we developed a direct dehydrogenative coupling, based on results from our enaminone chemistry.

Scheme 36 NMR studies to detect the palladium–enaminone intermediate

Scheme 37 Stoichiometric alkenylation for mechanistic investigation

Scheme 38 Alkenylation of 1,3-dimethyluracil. Scope of the alkene component.

4.8 Aerobic Alkenylation and its Application to the Synthesis of 1,3,5-Trisubstituted Benzenes

Having developed a series of direct C–H functionalizations of enaminones at the C5 position, we turned our attention to the use of molecular oxygen as a green and mild oxidant.37 Our previous methods required the use of stoichiometric amounts of heavy-metal or organometallic coupling partners, which was inconsistent with the original aim of C–H functionalization.

We therefore explored some known biomimetic approaches to bypassing the high activation energy of mo-
lecular oxygen. We found that a catalytic amount of catechol and copper(II) acetate effectively oxidized palladium, leading to multiple turnovers of the catalyst. Under optimized conditions, the coupling reactions of enamines with alkenes proceeded smoothly under aerobic oxygen at room temperature in the presence of molecular sieves (Scheme 40).

Next, we attempted to convert the alkenylated products into the corresponding hydroquinolines by means of the Diels–Alder reaction. Unexpectedly, we obtained the trisubstituted benzenes 4.131–4.140 as the exclusive reaction products, presumably through a cascade sequence involving Diels–Alder reaction, aromatization, and retro-Michael reaction (Scheme 41).

Although this outcome was unexpected, the products are nevertheless quite valuable because few general methods are currently available for synthesizing nonsymmetrical 1,3,5-substituted benzenes. Also, the products are highly electron-deficient in character and cannot, therefore, be synthesized efficiently by classical methods, such as electrophilic reactions. Finally, the products are chalcones, a group of compounds that are known to show a variety of biological effects, including antiinflammatory effects.

Scheme 39  Alkenylation reactions of various 1,3-disubstituted uracils with tert-butyl acrylate

Scheme 40  Scope of the aerobic alkenylation
4.9 Lithium Perchlorate-Catalyzed Alkylation

We have shown that cyclic enamines are viable substrates for various palladium-catalyzed C5 functionalization reactions, provided that the nitrogen atom is a part of a cyclic system. However, enamines 4.142 bearing nitrogen atoms outside the cyclic carbon skeleton (Figure 3) could not be used in any of the methods described above.

Although our main focus had been on the chemistry of enamines 4.141, which can be readily converted into structurally diverse nitrogenous heterocyclic compounds, structural motifs such as 4.142 can also be found in a variety of bioactive compounds. We therefore began efforts to functionalize enamines of type 4.142. To this end, we turned our attention to the Knoevenagel reaction (Scheme 42). We devised a novel variant of this reaction using paraformaldehyde (Scheme 43). Because of the reactivity of formaldehyde, the dimerization product 4.156, derived from condensation of the enamine and formaldehyde, was obtained as the major product. This problem was overcome by increasing the rate of the initial reaction between formaldehyde and the reactive methylene (malonate) moiety by the addition of lithium perchlorate as a Lewis acid.

Under acidic conditions in the presence of trifluoroacetic acid, the products of the reaction cyclized to provide the bicyclic system 4.148 (R1 = H) (Scheme 42). In addition, we found that triphenylphosphine catalyzed the reaction between enamines and cyanoacetates to give the cyclized products directly (Scheme 44). The precise role of triphenylphosphine is obscure, but we assume that it is involved in both the Knoevenagel-type condensation and the cyclization steps. When a malonate was used instead of a cyanoacetate in this reaction, the desired product was not obtained.

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5 Applications to Total Synthesis

The development of the enaminone chemistry provided an opportunity to synthesize several indolizidine and quinolizidine alkaloids in a concise manner.

5.1 Total Synthesis of (+)-Ipalbidine and (+)-Antofine

The enaminone chemistry was first applied to a synthesis of (+)-ipalbidine (Scheme 45), which is a nonaddictive analgesic, an oxygen-free radical scavenger, and an inhibitor of the respiratory burst of leukocytes. By using the ynone cyclization, we obtained enaminone 5.1 with an enantiomeric ratio of 98:2. This enaminone was subjected to the direct arylation protocol to give the arylated product 5.2. The arylated enaminone was reduced with L-selectride, and the resulting boron enolate was trapped with the Comins reagent \( \text{N-(5-chloro-2-pyridyl)bis[(trifluoromethane)sulfonimide]} \). The methyl group was then installed by Negishi coupling. Finally, the methyl group of the 4-methoxyphenyl substituent was removed by treatment with boron tribromide to give (+)-ipalbidine (Scheme 45) with an enantiomeric ratio of 98:2, indicating that stereochemical integrity was retained throughout this synthetic process.

Having established a synthetic route to (+)-ipalbidine, we selected (+)-antofine (Scheme 45) as our next target. Antofine exhibits low nanomolar antiproliferative activity against drug-sensitive and multidrug-resistant cancer cell lines, as well as antiviral activity. The (+)-antofine enantiomer

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was synthesized by subjecting triflate 5.3 to Negishi coupling with the arylzinc bromide 5.6 to give the biaryl product 5.7 (Scheme 46). This biaryl intermediate was oxidized with [bis(trifluoroacetoxy)iodo]benzene to give (+)-antofine (5.8).39

5.2 Total Synthesis of (R)- and (S)-Boehmeriasin A

We also succeeded in a synthesis of boehmeriasin A (5.14; Scheme 47),47 which had previously been isolated without assignment of its absolute stereochemistry.48 This compound was found to be more potent than paclitaxel in most cancer cell lines, with GI50 values ranging from 0.8 to 265 nM.49 Because the configuration of the stereocenter of boehmeriasin A was unknown at the time when we began our study,50 we synthesized both enantiomers of the compound.

We adopted a similar strategy to that which we used in our synthesis of ipalbidine, and we obtained triflate 5.12 in two steps from enaminone 5.9 (Scheme 47). Triflate 5.12 was subjected to Negishi coupling to provide the biarylamine 5.13, which was oxidized by using vanadyl trifluoride to give boehmeriasin A (5.14). The (R)- and (S)-enantiomers were obtained in enantiomeric ratios of 97.5:2.5 and 98:2, respectively. By comparison with the literature,48,50 we confirmed that the (R)-product is the natural product.

Finally, we tested our synthetic compounds in three cancer cell lines, with paclitaxel as a control (Table 6). The (R)-enantiomer was more potent than the (S)-enantiomer and, most importantly, it showed activity in the taxol-resistant cancer cell line NCI-ADR-RES.

5.3 Total Synthesis of Tylocrebrine and Related Phenanthropiperidines

Among the more than 60 known phenanthropiperidines, tylocrebrine (5.18, Scheme 48) is the only compound that has been tested in a clinical trial; however, this trial was terminated because patients experienced ataxia and disorientation, clearly indicating that the compound affects the central nervous system. Nevertheless, because of the
potency of tylocrebine, interest persists in developing phenanthropiperidines for chemotherapeutic purposes. In pursuit of developing a safe phenanthropiperidine as an anticancer agent, we embarked on the synthesis of tylocrebrine and several closely related analogues. The difficult problem of regioselectivity in the synthesis of tylocrebrine was solved by a unique disconnection that involved an aryl–alkene C−C bond-forming reaction to construct the pentacyclic ring system.

As shown in Scheme 48, indolizidine triflate was linked with a variety of biaryl groups by using a Negishi coupling; subsequent vanadyl trifluoride-mediated oxidative C−C bond formation gave various phenanthroindolizidines. The aryl–alkene C−C bond-forming reaction has few precedents in the literature.

The synthesized alkaloids were then tested against three cancer cell lines to evaluate their antiproliferative activities (Table 7). The alkaloids showed very potent cytotoxicities with broad spectra. The results show that removal or relocation of each of the methoxy groups affects the activity of the resulting analogue against NCI/ADR-RES, although most of the compounds remained potent against COLO-205 and MCF-7, with the exception of compound 5.21.

Table 7 Antiproliferative Activity of Phenanthroindolizidines

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6 Summary and Outlook

We have shown that enaminones can be synthesized from amino acids in two complementary ways. Ynone cyclization provided a variety of enaminones, including seven-membered azepinones, in a scalable manner. Although racemization occurred in some cases, the reaction was shown to proceed in the 6-endo-trig mode; this led to the identification of reaction conditions that minimized the racemization. The ynone cyclization enabled us to generate a quinoline library, to synthesize functionalized enaminones from β-lactams, and to obtain unique seven-membered 3,4-dihydro-1,2-oxazepin-5(2H)-ones.

The ketene cyclization gave enantiopure enaminones carrying carbonyl groups at the C5 position that can as handles for further functionalization. The use of diazomethane limited the scale and applicability of this reaction, a shortcoming that prompted us to develop a three-component strategy for synthesizing enaminones in a simple manner. Note that this ketene cyclization represents a rare example of a case in which a carbon nucleophile is used to react with a ketene electrophile.

Considerable efforts were also devoted to the development of C5 functionalization. Inspired by direct arylation using aryl(trifluoro)borates, we developed several superior or complementary protocols. A Suzuki-type coupling with boronic acids was found to be general and of wide scope for C5 arylation of enaminones, presumably as a result of the neutral reaction conditions and the use of copper additives to facilitate transmetalation. A Hiyama-type coupling with silicon reagents was developed as a complementary method. The conditions for Heck-type coupling were also investigated, leading to the alkenylation of enaminones and uracils by using the Fujiwara–Moritani reaction conditions.

After we had developed the synthetic methods and the various derivatization strategies, we applied our enaminone chemistry in syntheses of several phenanthropiperidine natural products.

Since we first reported our enaminone chemistry in 2006, we have been fascinated by the exceptional versatility and utility of enaminones. Not only did we enjoy developing new synthetic methods and derivatizations, but we were also pleased to discover that the resulting enaminones provide unique opportunities for synthesizing biologically active compounds, which significantly broadened the scope of our research.

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References


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