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Catalytic Use of Elemental Gallium for Carbon–Carbon Bond Formation

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Supporting Information Placeholder

ABSTRACT: The first catalytic use of Ga(0) in organic synthesis has been developed by using a Ag(I) co-catalyst, crownether ligation, and ultrasonic activation. Ga(I)-catalyzed C–C bond formations between allyl or allenyl boronic esters and acetals, ketals, or aminals have proceeded in high yields with essentially complete regio- and chemoselectivity. NMR spectroscopic analyses have revealed novel transient Ga(I) catalytic species, formed in situ through partial oxidation of Ga(0) and B–Ga transmetalation, respectively. The possibility of asymmetric Ga(I) catalysis has been demonstrated.

Advances in synthetic chemistry and/or catalysis rely on innovative concepts and the exploration of unprecedented chemical species. In this context, gallium (Ga) is an interesting main group metal; it is fairly abundant and relatively inexpensive; it also displays good functional group compatibility and low toxicity. In turn, species such as Ga clusters, Ga and GaP nanoparticles, GaAs crystals, or Ga phosphate frameworks have been recently exploited in various domains. In the field of organic chemistry, gallium in its stable high-oxidation state +III has been thoroughly explored (Scheme 1a–i). Indeed, due to its strong Lewis acidity, gallium(III) has been widely used in catalysis.

In contrast, the chemistry of gallium in the less stable low-oxidation state +I is largely underexplored (Scheme 1a–ii). One reason may be the propensity to undergo disproportionation to form gallium(III) and gallium(0). Intriguingly, however, gallium(I) may display both Lewis acidity and basicity because of the presence of both vacant p orbitals and a lone pair. Depending on the ligand/counteranion by which it is coordinated, gallium(I) has been shown to act as stoichiometric Lewis acid, Lewis base, or ambiphilic reagent. While not commercially available, gallium(I) has been synthesized from gallium(III) or sub-valent gallium species using strong reductants. Recently, Krossing and Slattery et al. have reported a seminal access to gallium(I) through partial oxidation of gallium(0) by a perfluorinated silver aluminate. Gallium(0) itself is not Lewis acidic or basic, and has been used as a stoichiometric reagent in Barbier chemistry. However, gallium(0) displays several attractive features; it has a relatively low first ionization potential, and is fairly air- and moisture-stable; furthermore, it can be easily handled as it is liquid at ≈ 30 °C.

Scheme 1. Background and concept.

We envisioned that gallium(0) may be exploited in catalysis if it can be converted in situ to gallium(I) (Scheme 1b). Thereby, a potentially Lewis acidic and basic catalyst may be generated, which may activate both Lewis basic and acidic reagents for subsequent bond formation. We report here the first catalytic use of elemental gallium in organic synthesis through in situ oxidation by silver(I) to generate a potentially ambiphilic gallium(I) species.

In initial proof-of-concept experiments for a model reaction between acetal 1a and allyl boronic ester 2, we used gallium(0) (50 mol%) and silver triflate (10 mol%) in dioxane at 30–40 °C for 24 h (Table 1, entries 1 and 2). Although the virtual gallium(I) loading was only 10 mol%, homoallyl ether 3a was obtained in 50–55% yield; other solvents proved to be less efficient (see SI). Significantly, the use of gallium(0) or silver triflate alone
resulted only in the recovery of starting materials (entries 3 and 4). The reaction time was substantially decreased by switching from conventional heating and stirring to ultrasonication (8 h; entry 5); this result represents a rare example for ultrasonic activation in catalysis. The Ga(0)/Ag ratio and the virtual Ga(I) loading were decreased to 2:1 and 5 mol%, respectively, without loss of activity (67% yield; entries 6 and 7). The use of [18]crown-6 ([18]c-6) as a ligand to stabilize the anticipated in situ gallium(I) catalyst proved to be critical for the full conversion of 1a to 3a (95–99% yield; entries 8 and 9). This reaction could be carried out on a gram scale by switching from conventional heating and stirring to ultrasonication (8 h; entry 5); this result was supported by unsuccessful reactions using four-coordinate boron species 4 and 5 (Table 1). While toluene was shown to be a compatible solvent (90% yield; entry 10), other silver salts or ligands displayed lower reactivity (see SI). Control experiments in the absence of Ga(0) or AgOTf failed to give 3a, thus confirming the necessity of both catalyst components to generate in situ a gallium(I) catalyst (entries 11 and 12). Likewise, a control experiment with gallium(III) gave very poor reactivity (entry 13); similar results were obtained in control reactions with other metal triflates or Ag(0) (see SI).

### Table 1. Initial results and reaction optimization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ga(0) [mol%]</th>
<th>AgOTf [mol%]</th>
<th>[18]c-6 [mol%]</th>
<th>Conditions</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50</td>
<td>10</td>
<td>–</td>
<td>dioxane, 30 °C, 24 h</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>10</td>
<td>–</td>
<td>dioxane, 40 °C, 24 h</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>–</td>
<td>–</td>
<td>dioxane, 40 °C, 24 h</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>10</td>
<td>–</td>
<td>dioxane, 40 °C, 24 h</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>10</td>
<td>–</td>
<td>dioxane, 40–45 °C, 8 h</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>10</td>
<td>–</td>
<td>dioxane, 40–45 °C, 8 h</td>
<td>67</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>5</td>
<td>–</td>
<td>dioxane, 40–45 °C, 8 h</td>
<td>61</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>dioxane, 40–45 °C, 8 h</td>
<td>95</td>
</tr>
<tr>
<td>9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>dioxane, 40–45 °C, 8 h</td>
<td>61</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>dioxane, 40–45 °C, 8 h</td>
<td>90</td>
</tr>
<tr>
<td>11</td>
<td>–</td>
<td>10</td>
<td>10</td>
<td>dioxane, 40–45 °C, 8 h</td>
<td>NR</td>
</tr>
<tr>
<td>12</td>
<td>–</td>
<td>5</td>
<td>10</td>
<td>dioxane, 40–45 °C, 8 h</td>
<td>NR</td>
</tr>
<tr>
<td>13&lt;sup&gt;c&lt;/sup&gt;</td>
<td>–</td>
<td>5</td>
<td>10</td>
<td>dioxane, 40–45 °C, 8 h</td>
<td>3</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields are 1H NMR yields determined with an alkane as internal standard.  <sup>b</sup> The use of other solvents gave 3a in 28–38% yields (see SI).  <sup>c</sup> The use of other silver salts or ligands gave 3a in 0–73% yields (see SI).  

Next, the scope of this catalytic C–C bond formation was examined (Scheme 2). Various aromatic, heteroaromatic, aliphatic, and even cyclic acetals were converted to homoallyl ethers 3 in high yields under mild conditions. Remarkably, sensitive or challenging functionalities, such as ester, hydroxyl, and amino groups, were tolerated by the catalyst system (c, h, i). Likewise, in case of substrates bearing aryl chloride or bromide units, catalyst decomposition via “classic” Barbier reactivity<sup>13</sup> was not observed (e, f). In addition, the transformations using propargyl and allyl acetals proved to be fully regioselective (v, w). Finally, challenging ketals reacted smoothly to give quaternary carbon centers (z, z'); in this context, a reactive ketone group could be chemoselectively preserved (z').

### Scheme 2. Scope of acetals and ketals.<sup>ab</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Condition</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a:</td>
<td>X = H; 91% yield</td>
<td></td>
</tr>
<tr>
<td>3b:</td>
<td>X = Cl; 92% yield</td>
<td></td>
</tr>
<tr>
<td>3c:</td>
<td>X = CO₂Me; 92% yield</td>
<td></td>
</tr>
<tr>
<td>3d:</td>
<td>X = F; 86% yield</td>
<td></td>
</tr>
<tr>
<td>3e:</td>
<td>X = Cl; 92% yield</td>
<td></td>
</tr>
<tr>
<td>3f:</td>
<td>X = Br; 92% yield</td>
<td></td>
</tr>
<tr>
<td>3g:</td>
<td>X = Me; 94% yield</td>
<td></td>
</tr>
<tr>
<td>3h:</td>
<td>X = CH₃OH; 57% yield</td>
<td></td>
</tr>
<tr>
<td>3i:</td>
<td>X = Me₂; 54% yield</td>
<td></td>
</tr>
<tr>
<td>3j:</td>
<td>X = OMe; 93% yield</td>
<td></td>
</tr>
<tr>
<td>3k:</td>
<td>X = OMe; 95% yield</td>
<td></td>
</tr>
<tr>
<td>3l:</td>
<td>X = OMe; 99% yield</td>
<td></td>
</tr>
<tr>
<td>3m:</td>
<td>X = OMe; 91% yield</td>
<td></td>
</tr>
<tr>
<td>3n:</td>
<td>X = OMe; 95% yield</td>
<td></td>
</tr>
<tr>
<td>3o:</td>
<td>X = OMe; 97% yield</td>
<td></td>
</tr>
<tr>
<td>3p:</td>
<td>X = OMe; 95% yield</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 1. Ga(0) (10 mol%), AgX (X = OTf or F; 5 mol%), [18]c-6 (10 mol%), 2 (1.1–1.5 equiv), dioxane or toluene, (11–12 h), 80–120 °C.  

Next, we investigated catalytic intermediates and the reaction mechanism (Scheme 3). In the absence of 1 and 2, Ga(0) was reacted with AgOTf and [18]c-6 in dioxane under standard conditions resulting in a single resonance at 71 ppm ([18]Ga NMR, Scheme 3a–i). Based on literature,<sup>19</sup> this chemical shift is consistent with a novel Ga(I) species;<sup>19</sup> we assume the Ga(I) center being coordinated by dioxane in analogy to [18]c-6 complexes.<sup>20</sup> A solution of 6 was used to trigger C–C bond formation between 1a and 2<sup>11</sup> [11B NMR: 33 ppm; Scheme 3a–ii]. Product 3a and by-product 7 were formed quantitatively (<sup>11</sup>B NMR: 22 ppm), and the regeneration of gallium(I) catalyst 6 was confirmed ([11]Ga NMR: 587 ppm).<sup>19</sup>

Next, 6 was reacted with acetal 1a to form oxocarbenium ion species 8 as detected by HRMS (EIS)<sup>11</sup> and the assumed [Ga(I)–OMe] species<sup>9</sup> (Scheme 3b–i). Subsequent addition of 6 resulted in the smooth production of 3a (not shown). In contrast, 6 proved to be unreactive toward boronic ester 2 as confirmed by NMR analyses (Scheme 3b–ii). Thus, prior to the activation of Ga(I) catalyst 6 may activate 1a as a Lewis acid (C–O bond cleavage, i.e., abstraction of OMe). In order to probe this scenario, 6 was reacted with boron–ate complex 10<sup>11</sup> [11B NMR: 7 ppm], formed in situ from 2 and K–OMe (Scheme 3b–iii). A down-field shift was observed suggesting the formation of three-coordinate boron species 7<sup>11</sup> [11B NMR: 22 ppm], which provided unambiguous proof for C–B bond cleavage. Moreover, we detected a...
single resonance at ~624 ppm (\(^{71}\text{Ga} \text{NMR}\)), ascribed to novel allyl gallium(I) species 11 (B–Ga transmetalation).

We also carried out a deuterium labeling experiment using 2–[d\(_2\)] (Scheme 3c). Under standard conditions, regioisomers 3\(_a\)–[d\(_2\)] and 3\(_3\)–[d\(_2\)] were obtained in a 1:1 ratio. This result indicated that deuterium scrambling must have occurred prior to C–C bond formation, which again supports B–Ga transmetalation.

Scheme 3. Mechanistic experiments.

(a) Generation, characterization, and regeneration of \([\text{Ga}=(\text{I})]^{11} \text{Ga} \text{ \& }^{11} \text{B} \text{ NMR})\): 

(b) Reactivity of \([\text{Ga}=(\text{I})]^{11} \text{Ga} \text{ \& }^{11} \text{B} \text{ NMR})\): 

(c) Deuterium labelling experiment \((^{1} \text{H} \text{ \& }^{1} \text{H} \text{ NMR})\): 

Based on these experiments, we propose a catalytic cycle (Scheme 4). Ga(II) catalyst 6, formed in situ from Ga(0), may activate acetal or ketal 1 as a Lewis acid to abstract an alkoxide (C–O bond cleavage). This process would lead to two transient species, oxocarbenium ion 8 and [Ga(II)]–OR 9. This electron-rich Ga(II) intermediate may convert boronic ester 2 to the active nucleophile, either allyl gallium(I) species 11 or the corresponding boron–ate complex (C–B activation). The active nucleophile would undergo C–C bond formation with 8 to give product 3 with regeneration of 6. It is noted that the original concept of direct Ga(I) dual catalysis is not borne out by this mechanism.

This in situ gallium(I) catalysis was successfully extended to the use of aminal rac-12 to give homoallyl amide rac-13 (Scheme 5a); ultrasonic activation was not required. This concept proved to be also applicable to the use of allenyl boronic ester 14 (Scheme 5b). Aromatic or aliphatic acetals 1a or 1x were converted regioselectively to homopropargyl ethers 15a or 15x; AgF proved to be the best co-catalyst. These transformations highlight the synthetic utility of this novel catalysis method.

Scheme 4. Proposed catalytic cycle.
method is a rare example for ultrasonic activation in catalysis, and may open up a new field in organic synthesis.

ASSOCIATED CONTENT

Supporting Information

Additional experiments, experimental details, and characterization data (PDF).

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Notes

The authors declare no competing financial interest.

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(14) (http://chemglobel.org/ptoe/31.php


(17) Seminal report on the use of allyl silanes and acetals: (a) Hossami, S.; Endo, M.; Sakurai, H. Chem. Lett. 1976, 5, 941; (b) see also references cited in ref. 15.

(18) In the absence of Ga(0), reactions did not occur.


(21) In the absence of Ga(0), 8 was not detected when AgOTf, [18]c-6, and 1a were reacted under identical conditions.

(22) Unlike in 6, no signal was observed in the 7Ga NMR spectrum of 9; for similar cases, see refs. 9b–c.

(23) C–C bond formation between 10 and 1a did not proceed in the absence of Ga(1) catalyst 6.

(24) 2-[d3], 3a–[d3], and 3a–[d3] proved to be stable; deuteration scrambling via 1,3-boratropic rearrangement [2–[d3]] or product interconversion [3a–[d3], 3a–[d3]] were not detected.

(25) Control experiments using 6 in the presence of Hg(0) or after hot filtration strongly suggest homogeneous Ga(I) catalysis.

(26) The use of 1a, under Ga(I) catalysis, with a pro-nucleophile such as Ph–B(pin), octyl–B(pin), or a keto-derivived silyl enol ether failed to give C–C bond formation.

Ga(0) (catalytic) + Ag(I) → in situ Ag(0)

potentially ambiphilic catalyst

Lewis basic reagent  Lewis acidic reagent