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Catalytic Use of Elemental Gallium for Carbon–Carbon Bond Formation

Bo Qin and Uwe Schneider*

The University of Edinburgh, EaStCHEM School of Chemistry, The King's Buildings, David Brewster Road, EH9 3FJ Edinburgh, UK

Supporting Information Placeholder

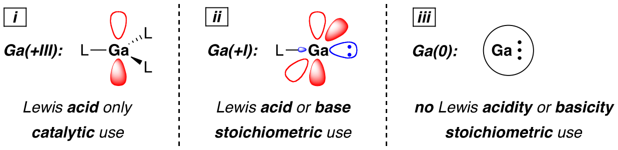
ABSTRACT: The first catalytic use of Ga(0) in organic synthesis has been developed by using a Ag(I) co-catalyst, crownether ligation, and ultrasonic activation. Ga(I)-catalyzed C–C bond formations between allyl or allenyl boronic esters and acetals, ketals, or aminals have proceeded in high yields with 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;[1] it also displays good functional group compatibility and low toxicity.[1] In turn, species such as Ga clusters,[2] Ga and GaP nanoparticles,[3] GaAs crystals,[4] or Ga phosphite frameworks[5] 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.[6]

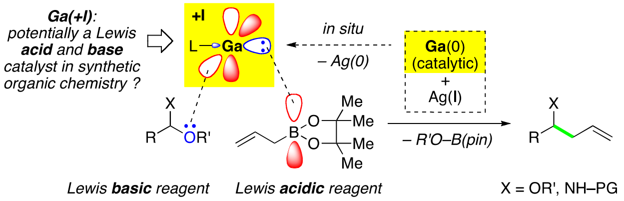
In contrast, the chemistry of gallium in the less stable low-oxidation state +I is largely underexplored (Scheme 1a–*ii*). One reason may be the propensity to undergo disproportionation to form gallium(III) and gallium(0). Intriguingly, however, gallium(I) may display both Lewis acidity and basicity because of the presence of both vacant p orbitals and a lone pair.[7,8] Depending on the ligand/counteranion by which it is coordinated, gallium(I) has been shown to act as *stoichiometric* Lewis acid,[9,10] Lewis base,[11] or ambiphilic reagent.[12] While not commercially available, gallium(I) has been synthesized from gallium(III) or sub-valent gallium species using strong reductants.[11f] 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.[9a] Gallium(0) itself is not Lewis acidic or basic, and has been used as a *stoichiometric* reagent in Barbier chemistry (Scheme 1a–*iii*).[13] However, gallium(0) displays several attractive features; it has a relatively low first ionization potential,[1,14] and is fairly air- and moisture-stable; furthermore, it can be easily handled as it is liquid at ≈ 30 °C.[1,14]

Scheme 1. Background and concept.

(a) Chemistry of gallium in its oxidation states +III, +I, and 0:



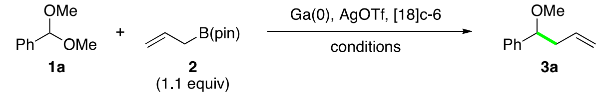
(b) Our concept for catalytic use of Ga(0) – *in situ* ambiphilic Ga(I) catalysis:



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**,[15] 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.[16] 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 at low catalyst loading (0.1 mol%; see SI). The prerequisite of a three-coordinate boron reagent, such as **2**, 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).

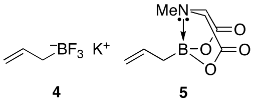
Table 1. Initial results and reaction optimization.[a]



1a **2** (1.1 equiv) **3a**

entry	Ga(0) [mol%]	AgOTf [mol%]	[18]c-6 [mol%]	conditions	yield [%][a]
1[b]	50	10	–	dioxane, 30 °C, 24 h	50
2	50	10	–	dioxane, 40 °C, 24 h	55
3	50	–	–	dioxane, 40 °C, 24 h	NR
4	–	10	–	dioxane, 40 °C, 24 h	NR
5	50	10	–	dioxane,))), 40–45 °C, 8 h	57
6	20	10	–	dioxane,))), 40–45 °C, 8 h	67
7	10	5	–	dioxane,))), 40–45 °C, 8 h	67
8	10	5	5	dioxane,))), 40–45 °C, 8 h	95
9[c,d]	10	5	10	dioxane,))), 40–45 °C, 8 h	99
10	10	5	10	toluene,))), 40–45 °C, 8 h	90
11	10	–	10	dioxane,))), 40–45 °C, 8 h	NR
12	–	5	10	dioxane,))), 40–45 °C, 8 h	NR
13[e]	$Ga(OTf)_3$ (5)		10	dioxane,))), 40–45 °C, 8 h	3

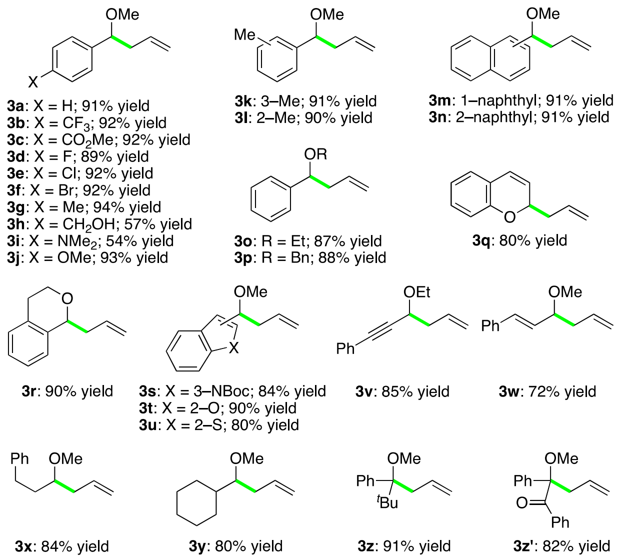
[a] Yields are ^1H NMR yields determined with an aliquot vs. Bn_2O as internal standard. [b] The use of other solvents gave **3a** in 12–36% yields (see SI). [c] The use of other silver salts and ligands gave **3a** in 0–73% yields (see SI). [d] When four-coordinate allyl boron species **4** and **5** were used (instead of **2**), no reaction occurred. [e] Control experiments with other metal triflates or Ag(0) gave **3a** in 0–4% yields (see SI).



4 **5**

Next, the scope of this catalytic C–C bond formation was examined (Scheme 2).[17] Various aromatic, heteroaromatic, aliphatic, and even cyclic acetals **1** were converted to homoallyl ethers **3** in high yields under mild conditions.[18] 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[13] 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.[a,b]



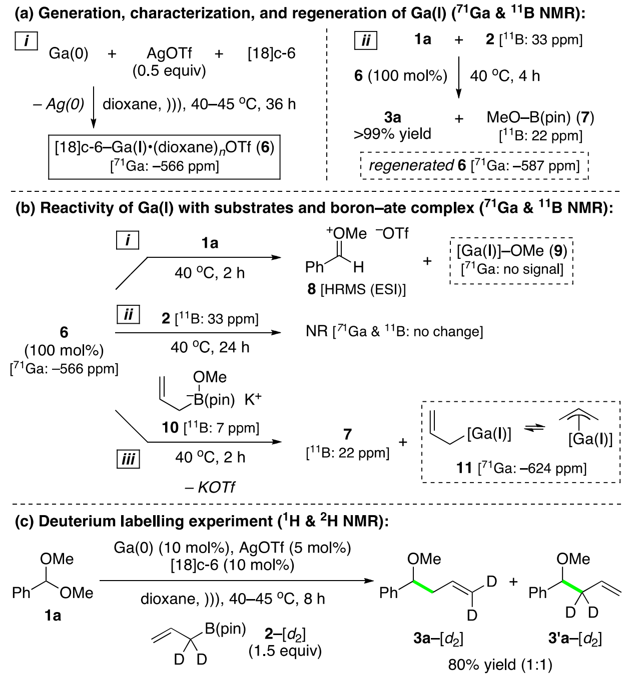
[a] Reaction conditions: **1**, Ga(0) (10 mol%), AgX (X = OTf or F; 5 mol%), [18]c-6 (10 mol%), **2** (1.1–1.5 equiv), dioxane or toluene,))), 40–50 °C, 8–78 h. [b] All yields are isolated yields after preparative thin-layer chromatography (PTLC) on silica gel.

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 –566 ppm (^{71}Ga NMR; Scheme 3a–*i*). Based on literature,[9a] this chemical shift is consistent with a novel Ga(I) species;[19] we assume the Ga(I) center being coordinated by dioxane in analogy to arene η^6 complexes:[20] [18]c-6–Ga(I)•(dioxane)$_n$OTf (**6**; *n* = 1,2,3). A solution of **6** was used to trigger C–C bond formation between **1a** and **2** (^{11}B NMR: 33 ppm; Scheme 3a–*ii*). Product **3a** and by-product **7** were formed quantitatively (^{11}B NMR: 22 ppm), and the regeneration of gallium(I) catalyst **6** was confirmed (^{71}Ga NMR: –587 ppm).[19]

Next, **6** was reacted with acetal **1a** to form oxocarbenium ion species **8** –as detected by HRMS (ESI)[21]– and the assumed [Ga(I)]–OMe species **9**[19,22] (Scheme 3b–*i*). Subsequent addition of **2** 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 **2**, 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** (^{11}B 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** (^{11}B NMR: 22 ppm), which provided unambiguous proof for C–B bond cleavage. Moreover, we detected a single resonance at –624 ppm (^{71}Ga NMR), ascribed to novel allyl gallium(I) species **11** (B–Ga transmetallation).[19,23]

We also carried out a deuterium labeling experiment using **2**–[*d*$_2$] (Scheme 3c). Under standard conditions, regioisomers **3a**–[*d*$_2$] and **3'a**–[*d*$_2$] were obtained in a 1:1 ratio. This result indicated that deuterium scrambling must have occurred prior to C–C bond formation,[24] which again supports B–Ga transmetalation.

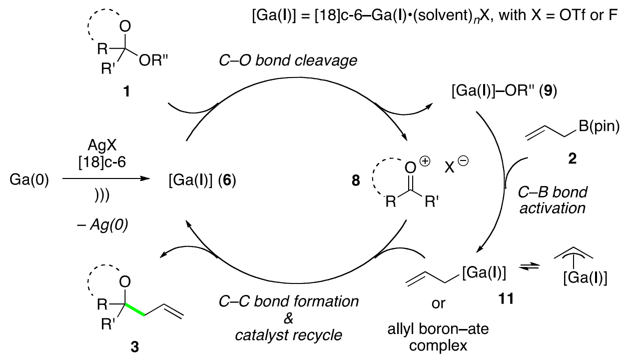
Scheme 3. Mechanistic experiments.



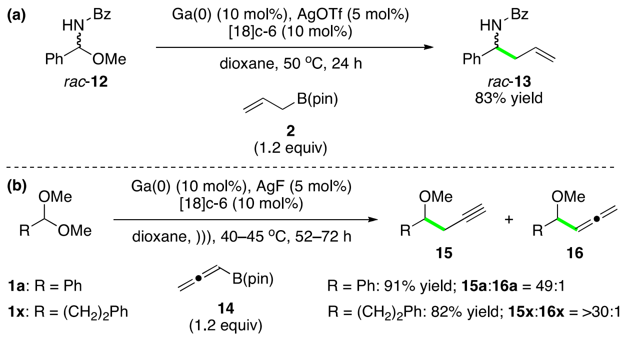
Based on these experiments[25] we propose a catalytic cycle (Scheme 4). Ga(I) catalyst **6**, formed *in situ* from Ga(0), may activate acetal or ketal **1** as a Lewis acid to abstract an alkoxide (C–O bond cleavage). This process would lead to two transient species, oxocarbenium ion **8** and [Ga(I)]–OR **9**. This electron-rich Ga(I) intermediate may convert boronic ester **2** to the active nucleophile, either allyl gallium(I) species **11** or the corresponding boron–ate complex (C–B bond 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);[18] ultrasonic activation was not required. This concept proved to be also applicable to the use of allenyl boronic ester **14** (Scheme 5b).[15] Aromatic or aliphatic acetals **1a** or **1x** were converted regioselectively to homopropargyl ethers **15a** or **15x**; AgF proved to be the best co-catalyst.[18] These transformations highlight the synthetic utility of this novel catalysis method.[26]

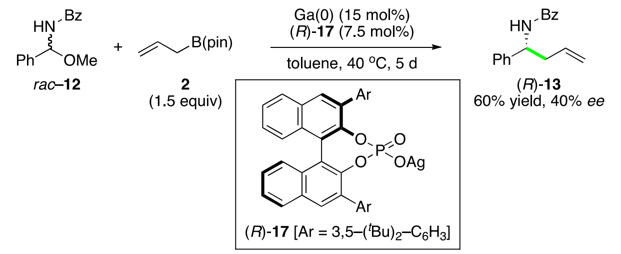
Scheme 4. Proposed catalytic cycle.



Scheme 5. Additional scope.



Scheme 6. Asymmetric induction.



Finally, we investigated the possibility of an asymmetric version (Scheme 6). The combined use of Ga(0) and silver salt (*R*)-**17** for the reaction between *rac*-**12** and **2** gave product (*R*)-**13** in 60% yield with 40% *ee*.[27] Control experiments confirmed that the presence of both elemental gallium and (*R*)-**17** were critical to both reactivity and selectivity (see SI). This transformation represents the first example of asymmetric induction for the catalytic use of Ga(0) and for Ga(I) catalysis.

In summary, we have developed the first catalytic use of Ga(0), which relies on a mildly oxidizing Ag(I) co-catalyst. Crownether ligation and ultrasonic activation have proved to be critical to the catalyst's activity. Ga(I)-catalyzed C–C bond-forming reactions between allyl or allenyl boronic esters and acetals, ketals, or aminals have proceeded in high yields with essentially complete chemo- and regioselectivity. NMR spectroscopic analyses have revealed the *in situ* generation of novel Ga(I) catalytic species, which distinguishes our work from Ga(II) chemistry.[19] Likewise, in contrast to Ga(I), other metal triflates including Ga(III) have proved to be catalytically inactive. We have also demonstrated the possibility of asymmetric Ga(I) catalysis. This novel scalable method is a rare example for ultrasonic activation[16] in catalysis, and may open up a new field in organic synthesis.

ASSOCIATED CONTENT

Supporting Information

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

AUTHOR INFORMATION

Corresponding Author

***uwe.schneider@ed.ac.uk**

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Downs, A. J.; Himmel, H.-J., New Light on the Chemistry of the Group 13 Metals. In *The Group 13 Metals Aluminium, Gallium, Indium and Thallium: Chemical Patterns and Peculiarities*; Aldridge, S.; Downs, A. J., Eds.; John Wiley & Sons, Ltd.: Chichester, 2011 (1st edition); p 1.

(2) Breaux, G. A.; Hillman, D. A.; Neal, C. M.; Benirschke, R. C.; Jarrold, M. F. *J. Am. Chem. Soc.* **2004**, *126*, 8628.

(3) (a) Sun, J.; Liu, C.; Yang, P. *J. Am. Chem. Soc.* **2011**, *133*, 19306. (b) Yarema, M.; Wörle, M.; Rossell, M. D.; Erni, R.; Caputo, R.; Protesescu, L.; Kravchyk, K. V.; Dirin, D. N.; Lienau, K.; von Rohr, F.; Schilling, A.; Nachtegaal, M.; Kovalenko, M. V. *J. Am. Chem. Soc.* **2014**, *136*, 12422.

(4) Fahrenkrug, E.; Gu, J.; Maldonaldo, S. *J. Am. Chem. Soc.* **2013**, *135*, 330.

(5) Sie, M.-J.; Lin, C.-H.; Wang, S.-L. *J. Am. Chem. Soc.* **2016**, *138*, 6719.

(6) Examples for Ga(III) catalysis: (a) Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783. (b) Simmons, E. M.; Sarpong, R. *Org. Lett.* **2006**, *8*, 2883. (c) Prakash, G. K. S.; Mathew, T.; Panja, C.; Alconcel, S.; Vaghoo, H.; Do, C.; Olah, G. A. *Proc. Nat. Acad. Sci.* **2007**, *104*, 3703. (d) Mihara, H.; Xu, Y.; Shepherd, N. E.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 8384. (e) Bour, C.; Gandon, V. *Coord. Chem. Rev.* **2014**, *279*, 43. (f) Li, L.; Fan, S.; Mu, X.; Mi, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2014**, *136*, 7793. (g) Abdalla, J. A. B.; Riddlestone, I. M.; Tirfoin, R.; Aldridge, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 5098.

(7) Aldridge, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 8097.

(8) Ga(I) is not to be mistaken with "GaI", which is a mixture of sub-valent gallium iodides: (a) Baker, R. J.; Jones, C. *Dalton Trans.* **2005**, 1341. (b) Malbrecht, B. J.; Dube, J. W.; Willans, M. J.; Ragogna, P. J. *Inorg. Chem.* **2014**, *53*, 9644.

(9) Examples for stoichiometric Ga(I) Lewis acidity: (a) Slattery, J. M.; Higelin, A.; Bayer, T.; Krossing, I. *Angew. Chem., Int. Ed.* **2010**, *49*, 3228. (b) Higelin, A.; Haber, C.; Meier, S.; Krossing, I. *Dalton Trans.* **2012**, *41*, 12011. (c) Higelin, A.; Keller, S.; Göhringer, C.; Jones, C.; Krossing, I. *Angew. Chem., Int. Ed.* **2013**, *52*, 4941.

(10) While our work was in progress, Ga(I)-initiated isobutene polymerization was reported: (a) Lichtenthaler, M. R.; Higelin, A.; Kraft, A.; Hughes, S.; Steffani, A.; Plattner, D. A.; Slattery, J. M.; Krossing, I. *Organometallics* **2013**, *32*, 6725. (b) Lichtenthaler, M. R.; Maurer, S.; Mangan, R. J.; Stahl, F.; Mönkemeyer, F.; Hamann, J.; Krossing, I. *Chem. – Eur. J.* **2015**, *21*, 157.

(11) Examples for stoichiometric Ga(I) Lewis basicity: (a) Kuchta, M. C.; Bonanno, J. B.; Parkin, G. *J. Am. Chem. Soc.* **1996**, *118*, 10914. (b) Schmidt, E. S.; Jockisch, A.; Schmidbaur, H. *J. Am. Chem. Soc.* **1999**, *121*, 9758. (c) Hardman, N. J.; Power, P. P.; Gorden, J. D.; Macdonald, C. L. B.; Cowley, A. H. *Chem. Commun.* **2001**, 1866. (d) Baker, R. J.; Jones, C.; Platts, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 10534. (e) Jones, C.; Junk, P. C.; Platts, J. A.; Stasch, A. *J. Am. Chem. Soc.* **2006**, *128*, 2206. (f) Dange, D.; Choong, S. L.; Schenk, C.; Stasch, A.; Jones, C. *Dalton Trans.* **2012**, *41*, 9304.

(12) Stoichiometric Ga(I) ambiphilicity: Prabusankar, G.; Gemel, C.; Parameswaran, P.; Flener, C.; Frenking, G.; Fischer, R. A. *Angew. Chem., Int. Ed.* **2009**, *49*, 5526.

(13) (a) Araki, S.; Ito, H.; Butsugan, Y. *Appl. Organomet. Chem.* **1988**, *2*, 475. (b) Lee. P. H. *Bull. Korean Chem. Soc.* **2007**, *28*, 17. (c) Goswami, D.; Chattopadhyay, A.; Sharma, A.; Chattopadhyay, S. *J. Org. Chem.* **2012**, *77*, 11064.

(14) http://chemglobe.org/ptoe/_/31.php

(15) Precedent for this reaction: Schneider, U.; Dao, H. T.; Kobayashi, S. *Org. Lett.* **2010**, *12*, 2488.

(16) Ultrasonic activation in catalysis: Ahmed-Ohmer, B.; Barrow, D.; Wirth, T. *Chem. Engin. J.* **2008**, *135S*, S280.

(17) Seminal report on the use of allyl silanes and acetals: (a) Hosomi, A.; 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.

(19) Evidence for Ga(II) or Ga(III) was not found under standard conditions; key reference for Ga(II): Protchenko, A. V.; Dange, D.; Harmer, J. R.; Tang, C. Y.; Schwarz, A. D.; Kelly, M. J.; Phillips, N.; Tirfoin, R.; Birjkumar, K. H.; Jones, C.; Kaltsoyannis, N.; Mountford, P.; Aldridge, S. *Nat. Chem.* **2014**, *6*, 315.

(20) (a) Schmidbaur, H. *Angew. Chem., Int. Ed.* **1985**, *24*, 893. (b) Dohmeier, C.; Loos, D.; Schnöckel, H. *Angew. Chem., Int. Ed.* **1996**, *35*, 129. (c) see ref. 9a.

(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 ^{71}Ga NMR spectrum of **9**; for similar cases, see refs. 9b–c.

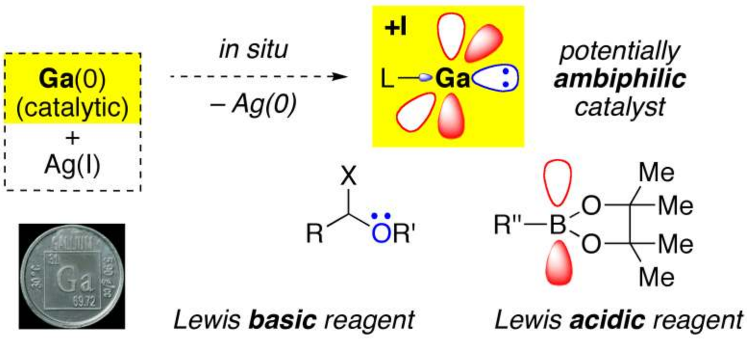
(23) C–C bond formation between **10** and **1a** did *not* proceed in the absence of Ga(I) catalyst **6**.

(24) **2**-[d_2], **3a**–[d_2], and **3'a**–[d_2] proved to be stable; deuterium scrambling *via* 1,3-boratropic rearrangement {**2**-[d_2]} or product interconversion {**3a**–[d_2], **3'a**–[d_2]} 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 ketone-derived silyl enol ether failed to give C–C bond formation.

(27) Precedent for this reaction: Huang, Y.-Y.; Chakrabarti, A.; Morita, N.; Schneider, U.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11121.


Ga(0)
(catalytic)
+
Ag(I)
in situ
– Ag(0)
+I
L
Ga
potentially
ambiphilic
catalyst
X
R
OR'
R''
B
O
O
Me
Me
Me
Me
GALLIUM
Ga
69.72
Lewis basic reagent
Lewis acidic reagent