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Tertiary and Quaternary Carbon Formation via Gallium-Catalyzed Nucleophilic Addition of Organoboronates to Cyclopropanes

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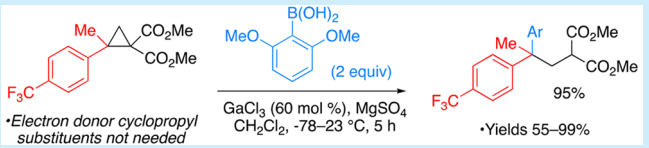
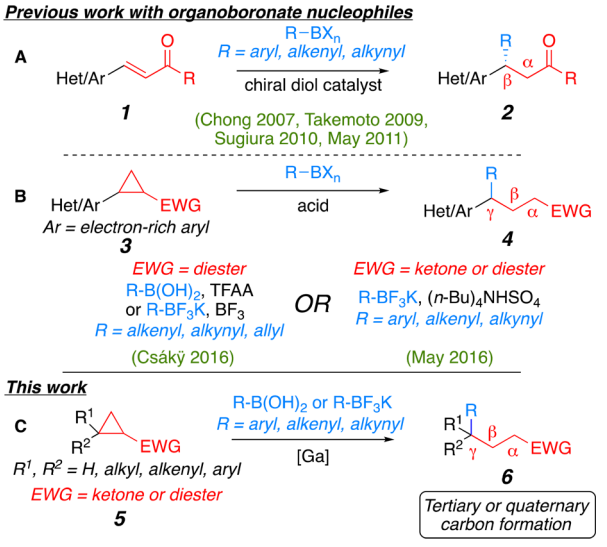
Supporting Information

ABSTRACT: $GaCl_3$ and $(IPr)GaCl_3/AgSbF_6$ formed γ-tertiary and γ-quaternary carbons via homoconjugate addition of organoboron nucleophiles to diester- and ketone-functionalized cyclopropanes. Electron donor group cyclopropane substituents were not needed, allowing electron-deficient aryl, alkenyl, alkyl, and hydrogen-substituted cyclopropanes to be used. The catalytic conditions were compatible with alkenyl, alkynyl, and aryl nucleophiles, including ortho-substituted aromatics, to synthesize highly hindered quaternary carbons. Alkynyl nucleophiles formed substituted cyclopentenes. A control experiment supports an intermediate carbocation in quaternary carbon center formation.



A significant synthetic challenge in organic chemistry is the controlled formation of quaternary carbon centers, especially via robust reactions from easily obtained starting materials.[1] To form these hindered carbons in a fixed relationship to versatile functional group handles such as carbonyls is key to generating synthetic building blocks for molecular targets. In general, the formation of carbonyl compounds with α-[2] and β-quaternary carbons[3] has seen greater success than the formation of all-carbon quaternary centers at the carbonyl γ-position.[4] Given recent successes in β-[5] and γ-C−C bond forming reactions[6] using neutral organoboronate π-nucleophiles (Scheme 1A,B, respectively), where the boron substituent controls the site of bond formation instead of Friedel−Crafts or Markovnikov considerations, we saw an opportunity for the controlled formation of γ-quaternary centers via Lewis acid catalysis (Scheme 1C). This plan was predicated on access to stabilized tertiary cationic intermediates formed from opening the disubstituted donor/acceptor cyclopropane **5**.

Scheme 1. Reactions with Organoboron Nucleophiles



Having recently reported an approach to tertiary carbon formation using the cheap Brønsted acid catalyst $(n\text{-}Bu)_4NHSO_4$[6b] and found that it was not suitable for the formation of quaternary carbon centers, we looked to Lewis acid catalysts to promote the nucleophilic ring opening of donor/acceptor cyclopropane **7a** with organoboronate nucleophile **8a** (Table 1). For preliminary studies, the formation of tertiary carbon centers was attempted, though the use of the sterically encumbered *o*,*o*-disubstituted aryl **8a** was employed to ensure that hindered C−C bonds could be formed. Unfortunately, experiments with many common Lewis acids failed to provide any product (entry 1). The only initial encouraging results were the use of $Bi(OTf)_3$ or $Sc(OTf)_3$ (entries 2 and 3). Gallium[11] has been shown to catalyze transformations utilizing organo-

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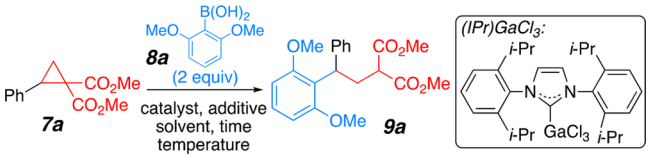
Table 1. Probing the Reaction Components



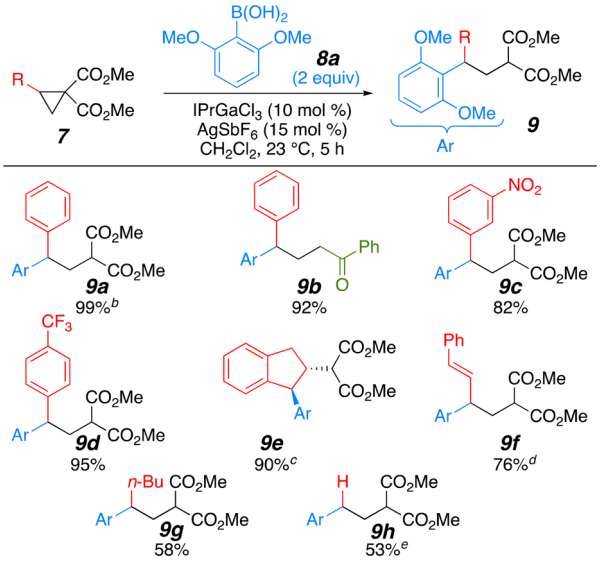
entry	catalyst (equiv)	additive	solvent	temp (°C)	time (h)	yield (%)[a]
1	Lewis acid[b] (0.20)	3 Å MS	DCE[c]	40	24	<2
2	$Bi(OTf)_3$ (0.20)	3 Å MS	DCE	40	24	7
3	$Sc(OTf)_3$ (0.20)	3 Å MS	DCE	40	24	30
4	$GaCl_3$ (1.0)	3 Å MS	CH_2Cl_2	23	0.25	45
5[d]	$GaCl_3$ (0.60)	$MgSO_4$	CH_2Cl_2	0–23	1	91
6	$(IPr)GaCl_3$ (0.10)	$AgSbF_6$	CH_2Cl_2	23	5	99

[a]Yield determined by ^1H NMR integration relative to an internal standard. [b]Lewis acid = $Yb(OTf)_3$, $Sn(OTf)_2$, $Cu(OTf)_2$, $InCl_3$, $SnCl_4$, $ZnCl_2$, $EtAlCl_2$, $FeCl_2$, $La(OTf)_3$, and $Gd(OTf)_3$. [c]DCE = Cl-$(CH_2)_2$Cl. [d]$MgSO_4$ did not catalyze the reaction in the absence of $GaCl_3$. Cyclopropane added dropwise for 30 min.

stannanes[12] and organoboronates;[13] therefore, it was employed in this screen. $GaCl_3$ turned out to promote the reaction at lower temperature and much more rapidly than $Bi(OTf)_3$ or $Sc(OTf)_3$ (15 min vs 24 h), though initial trials used a full equivalent (entry 4). Analysis of reaction temperature, catalyst equivalents, and additive led to a highly productive transformation using $GaCl_3$ (0.6 equiv) in CH_2Cl_2 in the presence of $MgSO_4$ while warming from 0 to 23 °C (entry 5). Slow addition of the cyclopropane to a solution of $GaCl_3$ and the boronic acid significantly increased the yield by preventing substrate dimerization. Exploring the use of a cationic *N*-heterocyclic carbene (NHC)-ligated gallium catalyst, generated from $(IPr)GaCl_3$ and $AgSbF_6$, also proved to be highly amenable to forming the γ-substituted product **9a** (entry 6). $(IPr)GaCl_3$ offers many benefits in its ease of handling and stability, so this was the preferred catalyst where possible.

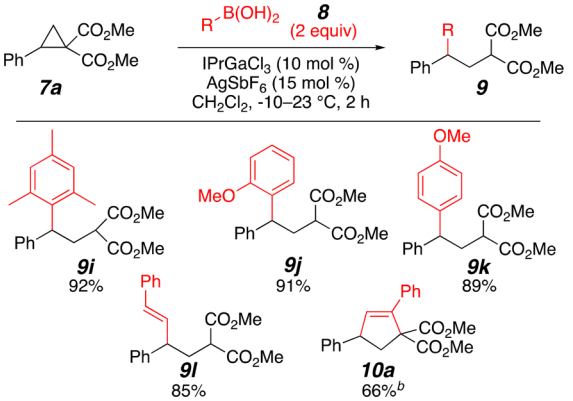
Reaction scope exploration focused on substrates that reacted poorly for our Brønsted acid-catalyzed addition to cyclopropanes:[6b] substrates bearing neutral or electron poor groups at the site of bond formation. $(IPr)GaCl_3$ catalyzed the reaction well for nearly all of these substrates. These new conditions accommodated an unsubstituted phenyl substituent, and **9a** was obtained in excellent isolated yield even when the reaction was performed on larger scale and the catalyst loading was reduced to 1 mol % (Scheme 2; footnote b). In general, diester-functionalized substrates were examined because of the ease of cyclopropane synthesis, but bis-activation was not required for a successful reaction. The acceptor group could also be a ketone (**9b**) as was the case with a Brønsted acid.[6b] Remarkably, substrates bearing electron-deficient aromatics at the point of attack performed as well as those with a relatively neutral phenyl ring (**9c** and **9d**). An additional ring fused to the cyclopropane had little impact on the reaction, and complete diastereoselectivity was observed for *trans*-indane **9e**. Products **9a–e** exhibited impeded rotation about the *o*,*o*-disubstituted aryl–C bond as evidenced by the symmetry of the dimethoxyphenyl being broken in the ^1H NMR. Complete regioselectivity was observed in generating the γ-addition product **9f**, though there was the potential for isomers to be formed from a putative allylic cationic intermediate generated from a styrenyl cyclopropane. Two

Scheme 2. Tertiary Carbons: Cyclopropyl Substituents[a]



[a]Isolated yields (average of ≥2 trials). [b]Five millimoles of **7a**, $IPrGaCl_3$ (1 mol %), $AgSbF_6$ (2 mol %), 48 h, 91% yield. [c]Product was a single diastereomer. [d]Cyclopropane added dropwise at −10 °C. [e]$GaCl_3$ (1 equiv), −10–23 °C gave 65% yield of **9h**.

Scheme 3. Tertiary Carbons: Nucleophile Diversity[a]



[a]Isolated yields (average of ≥2 trials). Cyclopropane added dropwise over 30 min. [b]Reaction run at −40 °C.

remarkable substrates gave **9g** and **9h**, which bore only an alkyl chain or hydrogens as substituents at the reactive carbon. Only a few existing cationic methods react with the latter substrate (i.e., 7 h) to form C–C bonds from cyclopropanes.[8a,14]

There was significant flexibility in the unsaturated nucleophiles that were useful. Aryl rings with or without ortho substituents worked well with $(IPr)GaCl_3$ (Scheme 3). Thus, aryl rings with electron-donating groups were excellent nucleophiles (**9i–9k**), and a styrene boronic acid also reacted well (**9f**). The use of alkenylboronic acids provides an orthogonal approach to starting from vinyl cyclopropanes like that which gave **9f**. While alkynylboronic acids are inherently unstable, the alkynyl trifluoroborate salt could be used successfully. The γ-substituted adduct apparently undergoes an additional 5-endo-dig cyclization, however, to form cyclopentene **10a**.[15] In general, organotrifluoroborate congeners of **8** were productive nucleophiles, but did not function as well as the boronic acids (see Supporting Information for examples).

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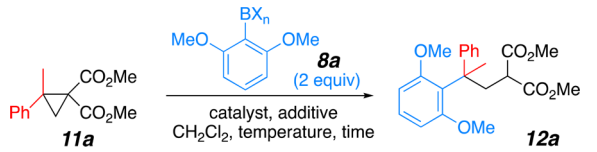
Table 2. Optimization for Quaternary Carbon Formation



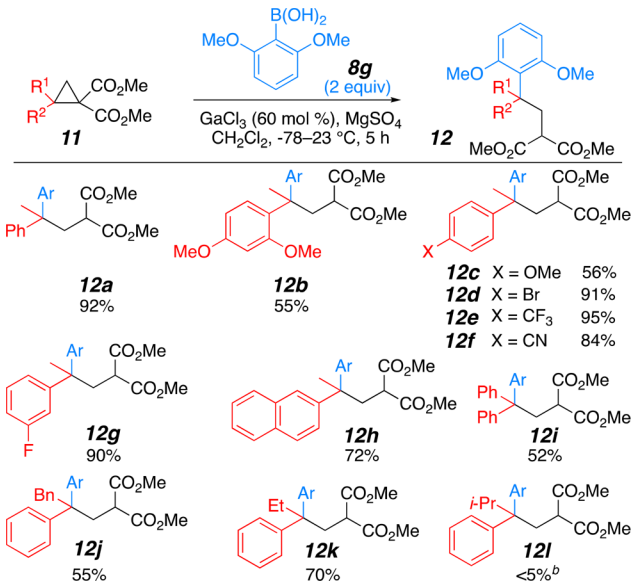
entry	BX_n	catalyst (equiv)	additive	temp (°C)	time (h)	yield (%)[a]
1	$B(OH)_2$	(IPr)$GaCl_3$ (0.10)	$AgSbF_6$	23	5	30
2	$B(OH)_2$	$GaCl_3$ (0.60)	$MgSO_4$	0–23	1	35
3	BF_3K	$GaCl_3$ (0.60)	$MgSO_4$	0–23	1	42
4	BF_3K	$GaCl_3$ (0.60)	$MgSO_4$	−40–23	3	60
5	BF_3K	$GaCl_3$ (0.60)	$MgSO_4$	−78–23	5	94

[a]Yield determined by ^{1}H NMR integration relative to an internal standard. Cyclopropane added dropwise over 30 min.

One of the most significant challenges in organic synthesis is the controlled formation of quaternary carbons.[1] Examples of cyclopropanes as precursors for quaternary carbons are very rare,[9] despite the ease with which these building blocks may be synthesized. Yet when the tetrasubstituted cyclopropane **11a** was examined, it was found that the high reactivity of Ga as a catalyst extended to that of a highly substituted cyclopropane, forming the γ-quaternary carbon center in diester **12a** in an efficient manner (Table 2). Both (IPr)$GaCl_3$ and $GaCl_3$ initially produced identifiable amounts of **12a**, though the latter was more reactive (entries 1 and 2). The trifluoroborate salts produced more product than the boronic acids below room temperature (entry 3), and starting the reaction at lower temperatures improved the outcome even more (entries 4 and 5).

A β-methyl-β-phenyl-substituted cyclopropane provided the γ-functionalized **12a** in 92% yield after 5 h (Scheme 4). In general, a variety of electron-donating and electron-withdrawing aryl variations were viable in the reaction (**12b**–**12g**). Both aryl groups in product **12b** bear ortho substitution, and so formation of that highly hindered C–C bond occurred in a lower but useful

Scheme 4. Quaternary Carbons: Cyclopropyl Substituents[a]

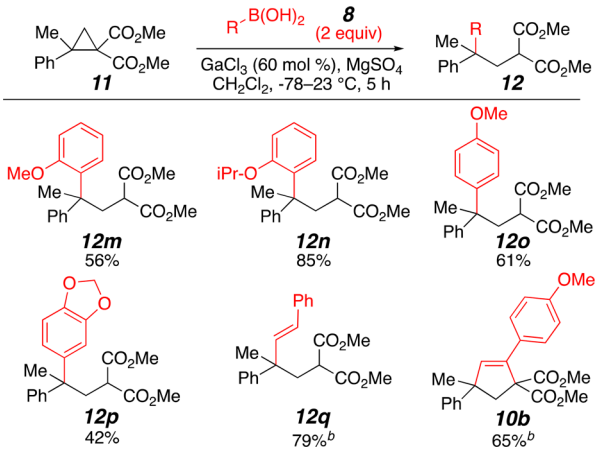


[a]Isolated yields (average of ≥2 trials). Cyclopropane added dropwise over 30 min. [b]Product observed by ^{1}H NMR, but not isolated.

yield. More sterically hindered quaternary centers, resulting from replacing the methyl with a phenyl or benzyl group, afforded **12i** or **12j**, respectively. The yields were somewhat lower for these highly hindered carbon centers, but the products were again obtained in useful quantities. If a larger *i*-propyl group was incorporated, though, little of the product **12l** was obtained.

As was the case for the tertiary centers, several additional nucleophiles were used with the gallium catalyst to form quaternary carbons. Thus, the conditions identified in Table 2 could give the mono-*ortho* methyl or isopropyl aryl ether adduct **12m** or **12n**, respectively (Scheme 5). Interestingly, the

Scheme 5. Quaternary Carbons: Nucleophile Diversity[a]



[a]Isolated yields (average of ≥2 trials). Cyclopropane added dropwise over 30 min. [b]Used $GaBr_3$ (60 mol %) at −40–23 °C.

nucleophile with the larger isopropyl substituent gave a higher yield of product. The use of a styrenyl boronate was still tolerated to give the allylic quaternary carbon in **12p**. Lastly, an alkynyl trifluoroborate generated the γ-substituted product of cyclopropane opening, but again underwent a 5-endo-dig cyclization to cyclopentene **10b** having two quaternary carbons.

For cyclopropanes with substituents, products derived from nucleophilic attack at the unsubstituted carbon were not detected. This observation suggests that the stabilization of positive charge controls regioselectivity in the reaction, although nucleophilic attack can take place in the absence of cyclopropane substitution (see **9h**, Scheme 2). Our current hypothesis is that the degree of intermediate cationic character at the electrophilic carbon varies according to cyclopropane substitution. For **9h**, little charge buildup occurs, and the reaction is likely S_N2-like (**13**, Scheme 6A). At the other end of the spectrum are the quaternary carbon-forming substrates, which can form a carbocation/enolate 1,3-dipole (**14**) that is typically invoked in cycloadditions to donor/acceptor cyclopropanes (Scheme 6B).[16] The latter supposition is supported by a control experiment using the enantioenriched cyclopropane **11e**, which gave racemic γ-substituted **12e** in 75% yield (Scheme 6C).

In conclusion, the use of $GaCl_3$ and (IPr)$GaCl_3$/$AgSbF_6$ facilitated the formation of γ-tertiary and γ-quaternary carbon center formation via homoconjugate addition of organoboron nucleophiles to diester- and ketone-functionalized cyclopropanes. Unlike previous homoconjugate additions, electron donor group-substituents were not needed on the cyclopropanes, allowing electron-deficient aryl, alkyl, alkenyl, and hydrogen-substituted cyclopropanes to be viable. The catalytic conditions were compatible with alkenyl, alkynyl, and aryl nucleophiles,

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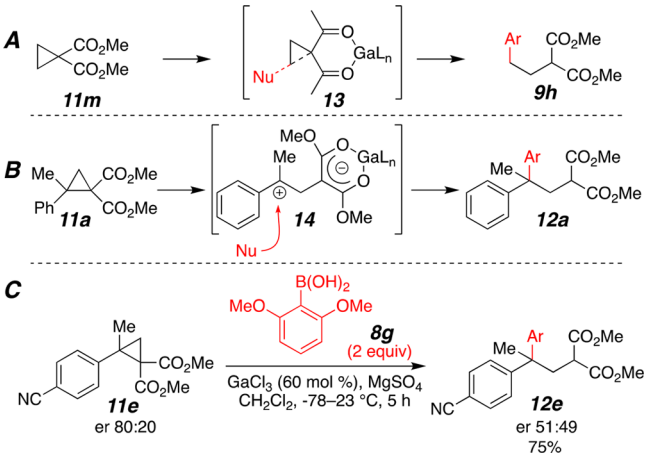
Scheme 6. Mechanistic Considerations



including the use of ortho-substituted aromatics to synthesize highly hindered quaternary carbons. The mechanism likely varies with the substrate, depending on the degree of cation stabilization. The use of alkynyl nucleophiles generated reaction intermediates that underwent an additional 5-endo-dig cyclization to form substituted cyclopentenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03349.

Complete experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(15) A 1,3-dipole formation (see **14**)/alkyne cycloaddition/protodeboronation could also be operative to form **10**.

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