Constructing All-Carbon Quaternary Centers from Ketones via Titanacyclobutanes: Rapid Access to Azaspiro[3.*n*]alkanes

Tyler D. Weinhold, James A. Law, and James H. Frederich*

Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL 32306, United States

ABSTRACT: Quaternary carbon centers pose a significant challenge in chemical synthesis. Harnessing the underexplored reactivity of titanacyclobutane intermediates, a strategy to construct functionalized all-carbon quaternary centers from ketones is described. This methodology streamlines access to a wide variety of azaspiro[3.*n*]alkanes that have emerged as valuable three-dimensional inputs for drug discovery.

The synthesis of all-carbon quaternary centers is an enduring challenge in organic chemistry.[1,2] This hydrocarbon motif is prevalent in bioactive natural products,[3] and recently, there is a growing demand for novel quaternary carbon building blocks for medicinal chemistry.[4] Introduced in this context by Müller and Carreira,[5,6] nitrogen-containing spiro[3.*n*]alkanes featuring a quaternary center have generated interest across academia and industry (Figure 1).[6,7] This structural class includes the 2,6-diazaspiro[3.3]heptane ring system, which has been championed as a bioisostere for piperazine.[8,9] Incorporation of this heterocycle into drug-like small molecules has been shown to increase conformational rigidity, improve solubility, and importantly, occupy chemical space that is inaccessible any other way.[5,10] Exploiting these features, Mach and co-workers demonstrated that replacing the piperazine ring of olaparib (**1**) with a 2,6-diazaspiro[3.3]heptane (i.e., **2**) enhanced target selectivity and reduced off-mechanism cytotoxicity in human cell culture.[11] Together, these studies highlight the significant potential of azaspiro[3.*n*]alkanes and their congeners as three-dimensional inputs for drug discovery.[12]

While unassuming at first glance, azaspirocycles are intricate structures that continue to inspire new advances in heterocyclic chemistry.[13,14] Nevertheless, as a consequence of the quaternary center embedded within azaspiro[3.*n*]alkanes, this substructure remains laborious to prepare. For example, monoprotected 2,6-diazaspiro[3.3]heptanes require an 8-step synthesis that begins from a quaternary carbon fragment.[15,16] In contrast, the related 2,6-diazaspiro[3.4]octane and -[3.5]nonane motifs are prepared along a 6-step route that leverages enolate acylation to build the quaternary center.[17] While these distinct solutions can support discovery research, a modular and more concise entry point to azaspiro[3.*n*]alkanes is required to streamline their integration into medicinal chemistry programs.

Guided by this logic, we envisioned expedient access to the linchpin quaternary carbon center of azaspiro[3.*n*]alkanes using $Cp_2Ti(\mu\text{-}Cl)(\mu\text{-}CH_2)AlMe_2$ (**3**; Cp = C_5H_5) as a progenitor to titanacyclobutanes **4** (Scheme 1).[18] Building upon pioneering studies from Tebbe[19] and Grubbs,[20] we previously demonstrated that the degenerate metathesis equilibria between the titanocene methylidene unveiled from **3** (i.e., Cp_2TiCH_2) and C–C π-bonds could be used for alkene hydromethylation.[21] This methodology exploited **4** as a 1,3-dianion equivalent. In the present context, we reasoned that **4** could be generated directly from ketones via sequential carbonyl methylenation and alkene cyclometallation if an excess of **3** was employed.[22] Halogenation of **4** might then produce dihalide **5**,[23] which could be reacted subsequently with an amine to furnish 3-azetidines. The potential of this sequence to rapidly construct azaspiro[3.*n*]alkanes from readily available cyclic ketones was apparent. Moreover, in our view, the need for excess quantities of **3**[24,25] was justified by direct access to quaternary carbon fragments that are difficult to prepare.

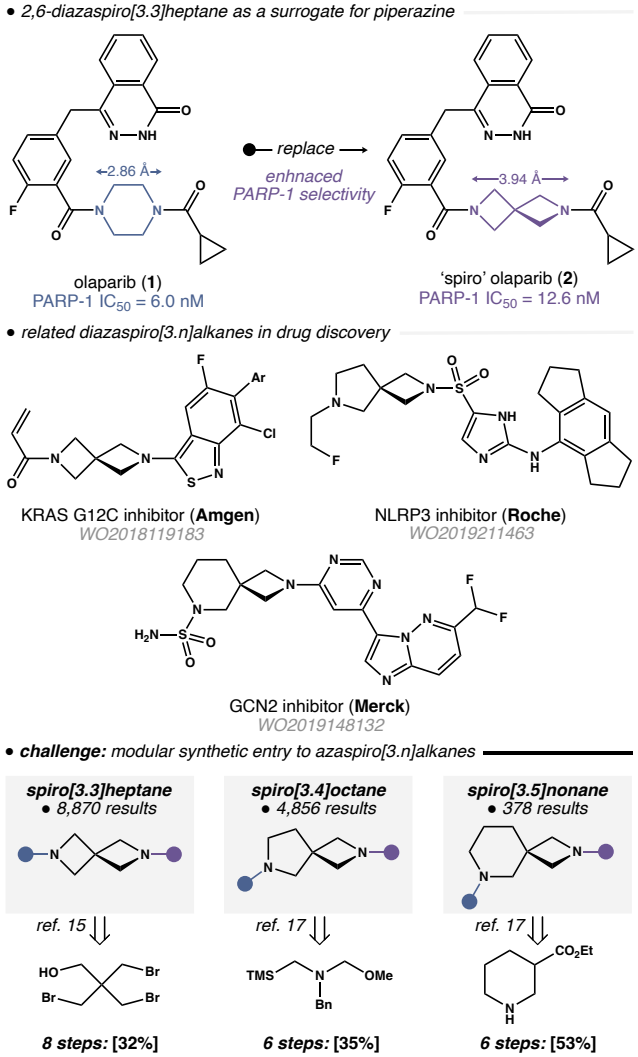
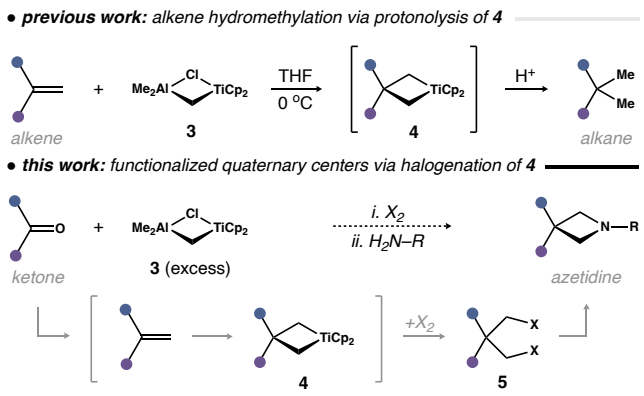


Figure 1. Examples of azaspiro[3.*n*]alkanes in drug discovery. Results from a query of the Reaxys database highlight a growing demand for 2,6-diazaspiro[3.*n*]alkanes.

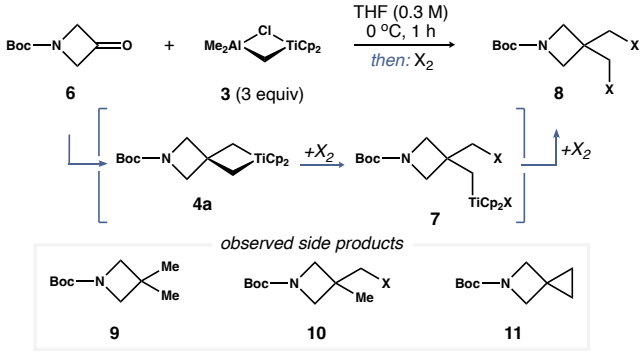
We identified commercially available *N*-Boc-3-azetidenone (**6**)[26] as an initial substrate to establish the feasibility of this idea. Thus, extending our previous study,[21] we found that reacting **6** with 3 equiv of **3** in THF (0.3 M) at 0 °C resulted in quantitative formation of titanacyclobutane **4a** after 1 h.[27] Initial attempts to intercept **4a** with various common halogen sources (e.g. NCS, NBS, etc.) gave complex mixtures of dihalide **8** alongside

Scheme 1. Approaches to All-carbon Quaternary Centers via Titanacyclobutanes **4**.



products **9**–**11** (Table 1).[28] The most useful electrophiles from this initial screen were I_2 and Br_2, which returned mixtures of **8** and cyclopropane **10** after workup. These results can be rationalized by addition of X_2 across a Ti–C bond to produce Ti(IV) complex **7**.[29] As a result, structures **8** and **11** arise from competing S_N2 processes involving (i) intermolecular capture of X_2 by **7** to furnish **8**, and (ii) an intramolecular 3-*exo*-*tet* cyclization within **7** to afford **11**. Consistent with this model, we found that the ratio of **8**:**11** was dependent on the identity and stoichiometry of X_2. For example, whereas I_2 favored the formation of **11** over **8a** (X = I, entries 1–3), Br_2 produced **8b** (X = Br) as the major product. Assuming that the cyclization of **7** was slower when X = Br than when X = I, we increased the stoichiometry of Br_2 to improve the yield of **8b** (entries 4–7).

Table 1. Optimizing the Halogenation of Titanacyclobutane **4a**.



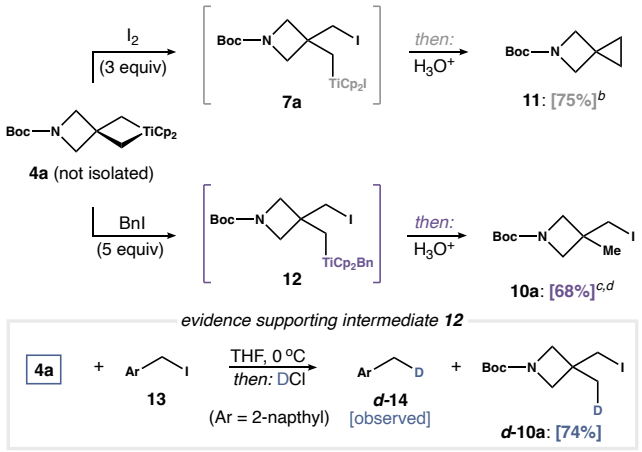
entry	X_2 (equiv)[a]	**8**	X	**8**:**11** ratio[b]	conversion to **8** (%)
1	I_2 (2)	**8a**	I	0:1	0
2	I_2 (3)	**8a**	I	1:15	6
3	I_2 (5)	**8a**	I	1:4	17
4	Br_2 (3)	**8a**	Br	2:1	45
5	Br_2 (5)	**8b**	Br	3:1	68
6	Br_2 (7)	**8b**	Br	7:1	85
7	Br_2 (10)	**8b**	Br	>20:1	95 (87)[c]

[a] Solutions of X_2 in CH_2Cl_2 or THF (1.0 M) were added via syringe to **4a** cooled to –78 °C. After 0.25 h, the reaction was warmed to 0 °C for 0.75 h before addition of SiO_2 in Et_2O. [b] The ratio of **8**:**11** was determined by ^{1}H NMR. [c] Isolated yield (% based on **6**).

Accordingly, we found that 10 equiv of Br_2 gave **8b** exclusively in 87% isolated yield (>95% conversion, >20:1 ratio of **8**:**11**).

To further investigate the reactivity of titanacyclobutane **4a**, we compared the effectiveness of I_2 and benzyl iodide (BnI) as electrophiles (Scheme 2). As anticipated, cyclopropane **11** was generated in 75% yield by treating **4a** with 3 equiv of I_2 at at 0 °C. This outcome is consistent with the facile intramolecular cyclization of Ti(IV) complex **7a**. Alternatively, when **4a** was treated with BnI (5 equiv), we observed selective formation of monoiodide **10a** (X = I, 68% yield) alongside a stoichiometric quantity of bibenzyl. This outcome suggested a radical pathway that likely intercepted alkyl Ti(IV) complex **12**. Evidence for **12** was obtained by repeating the reaction with 2-iodomethyl naphthalene (**13**). Following a workup with DCl in D_2O, this modification allowed for the simplified detection of 1,2-bis-(2-naphthyl)ethane and deuterated 2-methylnaphthalene (***d*-14**) in the reaction mixture by ^{1}H NMR and facilitated the isolation of ***d*-10a** in 74% yield.[30] Only traces of **11** were formed under these conditions. Thus, in contrast to **7a**, alkyl Ti(IV) complex **12** was persistent at 0 °C. Taken together, these observations illustrate the redox reactivity of titanacyclobutanes, which we speculate involves outer-shell electron transfer between **4a** and BnI.[31,32] They also establish a selective entry point to any of products **8**–**11** based on the reaction conditions employed.

Scheme 2. Exploring the Reactivity of Titanacyclobutane **4a.**[a]

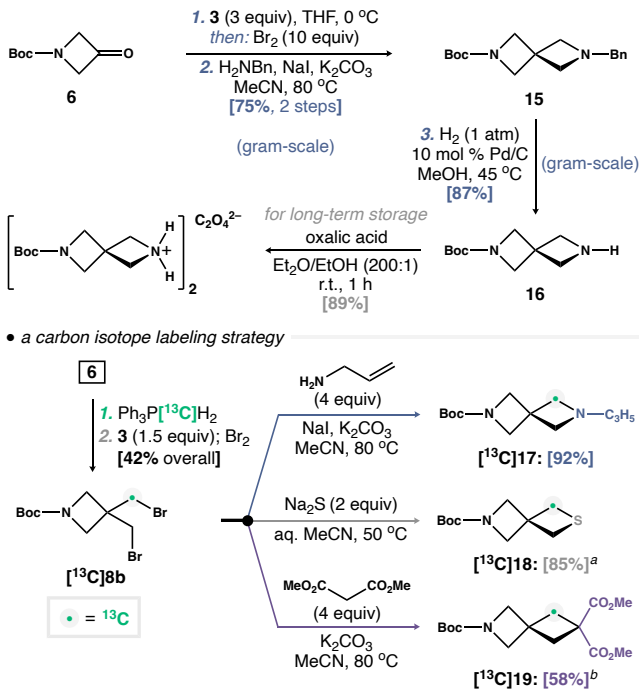


[a] **4a** was generated *in situ* from **6** using 3 equiv of **3** in THF (0.3 M) at 0 °C for 1 h prior to treatment with I_2 or BnI. [b] Dihalide **8a** was formed in 5–7% yield. [c] Bibenzyl was formed. [d] Less than 5% of **11** was observed by ^{1}H NMR.

With direct access to **8b** from ketone **6** in place, we focused on improving the assembly of azaspiro[3.3]heptane derivatives. We began with a short synthesis of 2,6-diazaspiro[3.3]heptane fragment **16** (Scheme 3).[15] Thus, **6** was converted to **4a** as noted above, then reacted with Br_2 to give **8b** in 84% yield on gram-scale.[30] Cyclization of **8b** with benzylamine afforded protected spirocycle **15** in 89% yield. Hydrogenolysis of **15** then provided **16** as a colorless solid in 87% yield. This material was stored for several weeks at 23 ºC without incident;[30] however, long-term storage resulted in slow, non-specific decomposition. This problem was avoided by converting **16** to the corresponding oxalate salt, which previously required 8 steps to prepare.[15,33]

The availability of **8b** in a single step also streamlines access to other in-demand azaspiro[3.3]heptanes. Existing approaches to this family avoid building the congested quaternary carbon center. For example, the reported 6-step synthesis of **8b** starts from diethyl bis(hydroxymethyl)malonate.[34] The *N*-tosyl

Scheme 3. Synthesis of Azaspiro[3.3]heptane Derivatives.

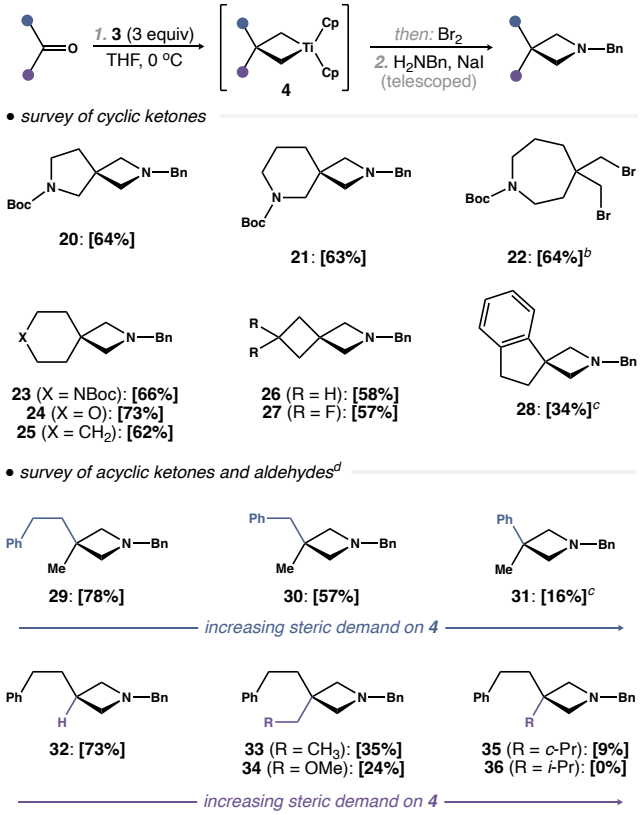


[a] The synthesis of **18** was reported in 6 steps (25% yield) from 2,2-bis(bromomethyl)-3-bromo-propanol (reference 35). [b] An *N*-tosyl equivalent of **19** was synthesized in 5 steps (50% yield) from 2,2-bis(bromomethyl)-1,3-propanediol (reference 36).

congener of **8b** was prepared in a similar manner in 4 steps.[5] In contrast, by constructing the quaternary carbon center directly, our approach expedited the diversification of **6** into a series of azaspiro[3.3]heptanes (i.e., **17**–**19**, 2 steps each from **6**) that are laborious to prepare using known chemistry (see the Supporting Information for details).[35,36] As summarized in Scheme 3, the carbon-13 isotopologs of **17**–**19** were also accessible by initially reacting azetidenone **6** with methylenetriphenylphosphorane-^{13}C. The resultant alkene was then elaborated to **[^{13}C]8b** in 57% yield (42% yield from **6**) using 1.5 equiv of **3**. This intermediate provided isotopically labeled spirocycles that would be difficult access using existing strategies. In principle, this approach can also be used to install a ^{14}C-radiolabel to facilitate metabolism and distribution studies.[37,38]

To complete a modular entry point to azaspiro[3.*n*]alkanes, we explored the scope of alternative cyclic ketones (Scheme 4). Leveraging a slight modification of our 2-step procedure that minimized purification of the initial dihalide,[30] we found that *N*-Boc-3-pyrrolidinone and -piperidone afforded the orthogonally protected 2,6-diazaspiro[3.*n*]alkane scaffolds **20** and **21** in 64% and 63% overall yield (2-steps), respectively. Alternatively, *N*-Boc-4-azacycloheptanone furnished dihalide **22** in 64% yield; however, this species could not be cyclized with benzyl amine under the reaction conditions employed, putatively because the resultant heterocycle is too strained. Conversely, azaspirocycles **23**–**25** derived from various 6-membered (hetero)cyclic ketones were prepared in good yield. This approach was also compatible with cyclobutanone and 2,2-difluorocyclobutanone, which gave 2-azaspiro[3.3]heptane derivatives **26** and **27** in 58% and 57% yield, respectively. Surprisingly, aromatic cyclic ketones were more problematic. For example, 1-indanone was not consumed in the reaction, despite affording azetidine **28** in 34% yield. This result indicated a sluggish carbonyl methylenation step between

Scheme 4. Scope and Limitations: Cyclic Ketones vs. Acyclic Ketones and Aldehydes.[a]



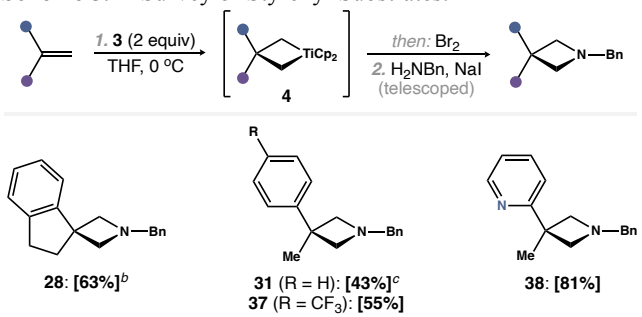
[a] Isolated overall yields from the corresponding ketone are reported for each entry. [b] Yield of dihalide **22**. This substrate could not be cyclized using benzylamine. [c] Unreacted aryl ketone was recovered in modest yield. [d] Step 1 was carried out at –10 °C.

Cp_2TiCH_2 and aromatic ketones.

Notably, whereas cyclic ketones were productive substrates, acyclic ketones gave nuanced results that can be rationalized by stability of titanacyclobutane **4**.[21,39] Thus, we evaluated a series of methyl ketones where the steric interactions imposed by the neighboring alkyl group on **4** were systematically increased. As the steric element (i.e., a phenyl group) was moved into close proximity to the Cp ligands in **4**, the stability of this species decreased. For example, whereas benzylacetone gave azetidine **29** in 78% yield, phenylacetone furnished **30** in 54% yield. The major side product in this case was the 1,2-dibromide formed via electrophilic halogenation of the alkene generated *in situ* from Cp_2TiCH_2 and the parent ketone. Consistent with this trend, acetophenone furnished **31** (16% yield) alongside several side products derived from alkylation of the corresponding 1,2-dibromide and unreacted starting material. The impact of sterics was apparent using higher-order dialkyl ketones. Here, keeping the phenethyl group constant, we found that 3-phenylpropanal gave **32** in 73% yield. However, as exemplified by products **33**–**36**, unbranched alkyl groups (e.g. **33**, R = Et) were problematic and branched alkyl groups (e.g. **36**, R = *i*-Pr) emerged as limitations. Together, these results indicate that this method can be used to prepare 3-azetidines from unhindered acyclic methyl ketones and aldehydes.[40]

As noted in Scheme 4, aryl ketones were not fully consumed by reagent **3** at 0 ºC. Warming the reaction to accelerate the methylenation step was not feasible because titanacyclobutanes (**4**) decompose between 0–23 ºC.[21,39] This issue was avoided by utilizing the corresponding styrenes (Scheme 5). In this case,

Scheme 5. A Survey of Styrenyl Substrates.[a]



[a] Isolated overall yields from the corresponding styrene are reported for each entry. [b] **28** was isolated in 34% yield from 1-indanone. [c] **31** was isolated in 16% yield from acetophenone.

the stoichiometry of **3** was reduced to 2 equiv.[41] Following this modification, using 1-methyleneindene as a substrate improved the yield of **28** to 63%. Similarly, α-methylstyrene facilitated access to **31** in 43% yield. This procedure was also compatible with other electron-deficient (hetero)arenes, as evidenced by 3-azetidines **37** and **38**, which were produced in 55% and 81% yield, respectively, from the corresponding styrenes. Notably, the pyridine-containing substrate produced azetidine **38** in good yield, suggesting that this organotitanium chemistry is tolerant to Lewis basic heterocycles. As such, the reported strategy can be extended to 1,1-disubstituted alkenes, which are superior substrates to aromatic ketones.

In summary, we have established a direct strategy to prepare quaternary carbon centers from ketones. This approach exploits titanacyclobutanes generated *in situ* from C–O π-bonds via sequential carbonyl methylenation and alkene cyclometallation mediated by an excess of Tebbe's reagent (**3**). Halogenation of these transient organotitanium species provides functionalized all-carbon quaternary centers that are laborious to prepare any other way. The utility of this method was demonstrated via a versatile platform for the synthesis of azaspiro[3.*n*]alkanes and 3-azetidines. In this regard, the rather modest stability profile of titanacyclobutanes emerged as a limiting feature in some cases. Efforts to develop less sterically hindered titanium methylidene equivalents are on-going and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, supplemental figures, and characterization data for all new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

James H. Frederich – *Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida, 32306, United States*; orcid.org/0000-0003-2077-4436;
Email: frederich@chem.fsu.edu

Authors

Tyler D. Weinhold – *Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida, 32306, United States.*

James A. Law – *Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida, 32306, United States*

Notes

The authors declare no competing financial interest.

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(24) The estimated cost to prepare Tebbe's reagent (**3**) is ~$1.3/mmol starting from Cp_2TiCl_2 and $AlMe_3$. Details for the preparation of **3** used in this study are outlined in reference 21.

(25) We recommend preparing **3** within 1–2 weeks of use. As noted in reference 21, we observed inferior results using commercial sources of **3**.

(26) *N*-Boc-3-azetidinone (**6**) was purchased from Biosynth [FB18887] for $0.9/gram.

(27) Protonolysis of **4a** prepared from **6** under these conditions afforded *gem*-dimethyl product **9** in 93% isolated yield (>95% conversion).

(28) See Table S1 in the Supporting Information for a complete survey of electrophiles.

(29) For precedent, see: Suzzy, C. H.; Straus, D. A.; Grubbs, R. H. An Alternate Path to Reductive Elimination for Group 4B Metals: Mechanism of Cyclopropane Formation from Titanacyclobutanes. *J. Am. Chem. Soc.* **1984**, *106*, 1533.

(30) See the Supporting Information (SI) for more details.

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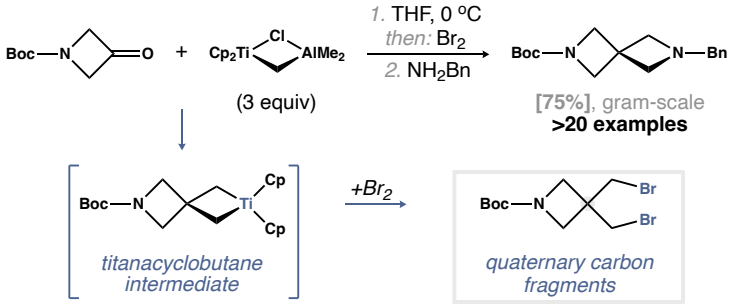
(41) As outlined in reference 21, 2 equiv of **3** are required to convert α-methylstyrene derivatives to titanacyclobutanes **4**.

TOC Graphic:


Boc—N
O
+
Cp2Ti
Cl
AlMe2
(3 equiv)
1. THF, 0 °C
then: Br2
2. NH2Bn
Boc—N
N—Bn
[75%], gram-scale
>20 examples
Boc—N
Cp
Ti
Cp
titanacyclobutane intermediate
+Br2
Boc—N
Br
Br
quaternary carbon fragments