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Site-Specific Alkene Hydromethylation via Protonolysis of Titanacyclobutanes

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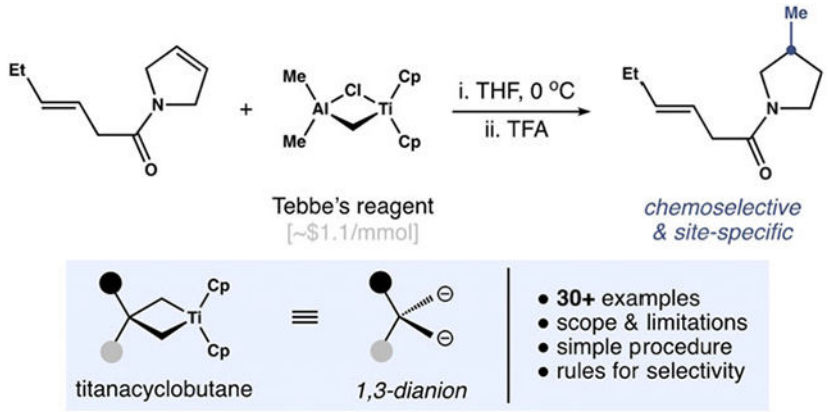
Abstract

Methyl groups are ubiquitous in biologically active molecules. Thus, new tactics to introduce this alkyl fragment into polyfunctional structures are of significant interest. With this goal in mind, a direct method for the Markovnikov hydromethylation of alkenes is reported. This method exploits the degenerate metathesis reaction between the titanium methylidene unveiled from $Cp_2Ti(\mu\text{-}Cl)(\mu\text{-}CH_2)AlMe_2$ (Tebbe's reagent) and unactivated alkenes. Protonolysis of the resulting titanacyclobutanes in situ effects hydromethylation in a chemo-, regio-, and site-selective manner. The broad utility of this method is demonstrated across a series of mono- and di-substituted alkenes containing pendant alcohols, ethers, amides, carbamates, and basic amines.

Graphical Abstract



A method for the direct Markovnikov hydromethylation of unactivated alkenes by protonolysis of titanacyclobutanes has been developed. This approach enables site-specific incorporation of a methyl group into complex, polyfunctional molecules and has been demonstrated with a series of mono- and di-substituted alkenes containing pendant alcohols, ethers, amides, carbamates, and basic amines.

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Conflict of interest

The authors declare no conflict of interest.

Keywords

hydromethylation; polyfunctional structures; site-specificity; synthetic methods; titanacyclobutanes

Site-specific methylation is a valuable strategy to optimize the pharmacology of bioactive small molecules.[1] This "magic methyl" effect has inspired new strategies for selective C–H bond methylation that facilitate the late-stage diversification of complex structures.[2,3] The addition of methane across a C–C π-system provides an appealing and complementary approach to small-molecule methylation. Nevertheless, despite advances in catalytic alkene hydrofunctionalization,[4] there are few direct methods for regioselective hydromethylation.[5–7] A procedure involving cyclopropanation and reductive C–C bond cleavage provides an indirect approach to this problem (Figure 1).[8] In contrast, the Baran group developed a more direct, branch-selective hydromethylation procedure using Fe-mediated hydrogen-atom transfer.[9,10] Herein, we describe the utility of $Cp_2Ti(\mu\text{-}Cl)(\mu\text{-}CH_2)AlMe_2$ (**1**; Cp = C_5H_5) as a hydromethylation reagent.[11] This method facilitates site-specific incorporation of methyl substituents into polyfunctional structures and circumvents several of the intrinsic limitations of existing hydromethylation tactics.

Our interest in hydromethylation strategies emerged from a program to synthesize fusicoccane diterpenes.[12] An early route intercepted structure **2**, from which the regioselective addition of methane to the C7–C8 alkene became an attractive option to install the C7 methyl group of this terpene family. In practice, the poor reactivity profile of **2** made this task challenging. For example, exposure of **2**, or protected variants, to combinations of electrophilic metals (e.g. Pd,[13] Fe,[14] Cu[15]) and nucleophilic methyl surrogates (e.g. $ZnMe_2$) returned only starting material. Cyclopropanation was also intractable, requiring 10 equiv $(TFA)ZnCH_2I$ to achieve modest conversion.[16] Conversely, the Mukaiyama-type hydromethylation reported by Baran yielded only traces of target structure **3** alongside significant quantities of the corresponding net hydrogenation product arising from competitive reduction of radical species **A**.[17]

In search of a solution, we revisited the pioneering work of Tebbe et al.[18] and Grubbs and co-workers[19] concerning reagent **1**, which serves as a progenitor to titanium methylidene **B**. While best known as an intermediate for carbonyl methylenation, **B** also participates in a degenerate metathesis reaction with unactivated alkenes.[20] In select cases, the resultant titanacyclobutanes (i.e. **C**) have been isolated and reacted with acid to give formal hydromethylation products.[20] However, these examples are largely constrained to simple hydrocarbons lacking other functional groups.[21,22] Thus, with some experimentation, we were pleased to find that the reaction of 1.5 equiv **1** with **2** afforded **3**[23] in 68% yield after addition of SiO_2 to the reaction.[24] The enhanced reactivity and regioselectivity (C7/C8 = 21:1) achieved with reagent **1** in this complex setting compelled us to explore further. Our efforts to transform this chemistry into a general method for alkene hydromethylation are summarized below.

Our study began with a detailed investigation of reaction conditions (Table 1). Reaction parameters were explored using piperidine **4**, which reacted with a solution of **1** (0.3–0.4

M in PhMe)[25] and 4-dimethylaminopyridine (DMAP) at 0°C.[19c] After 6 h, addition of HCl furnished an inseparable mixture of net Markovnikov hydromethylation product **5** (16% conversion) and **4** (entry 1). We observed no reaction in the absence of a Lewis base (entry 2). In contrast, the reaction was improved using THF as the Lewis base (entry 3), and the best results (94% yield) were obtained using THF as the solvent (entry 4). We found that HCl could be replaced by trifluoroacetic acid (TFA) without impacting the reaction efficiency (entry 5). Moreover, the reaction was executed on a gram scale to give **5** in 89 % yield (entry 6). Importantly, commercial solutions of **1** (0.5 M in PhMe) did not give comparable results (entry 7). The concentration of **1** was accurate; however, commercial **1** was darker than solutions of **1** freshly prepared from Cp_2TiCl_2 and $AlMe_3$.[26] The same problem was encountered with prepared solutions of **1** after about 120 h, which suggests the formation of impurities upon storage.[27] With this practical issue noted, we found that ketone **6** was converted into **5** in 90 % yield with 3 equiv **1** using otherwise identical conditions. As such, this method also allows the direct geminal dimethylation of ketones.[28]

A series of control reactions shed light on the properties of the titanacyclobutane **7** formed by the reaction of **1** and **4** (Scheme 1). It was unnecessary to isolate this transient species, which we observed in ^{1}H NMR spectra of unpurified reaction mixtures before protonolysis.[25] Instead, the thermal stability of **7** was established by forming the metallacycle in situ at 0°C, then warming the reaction for 1 h before the addition of HCl. This analysis revealed significant cyclo-reversion to **4** after 1 h at 35°C (50% by ^{1}H NMR spectroscopy).[29] Conversely, **7** persisted for 10 h at 0°C when precautions were taken to exclude air. The introduction of oxygen (1 atm) resulted in the rapid formation of by-products, the most significant being aldehyde **8**. However, when handled as described, **7** functions as a useful 1,3-dianion equivalent. This feature was showcased by the reaction of DCl with **7** at 0°C to furnish isotopically labeled **5**-d_2 in 90% yield and with ≥ 90 % deuterium incorporation.

As shown in Scheme 2, the regioselectivity of this method was highlighted using α-olefins (**9**). In principle, both branched (b) and linear (l) hydromethylation isomers of **10** are accessible by protonolysis of titanacycles **I** and **II**, respectively. However, using the standard procedure, 4-phenyl-1-butene (**9a**) gave branched alkane **10a** (72% yield, > 25:1 b/l), indicating the selective generation of the primary alkyl titanacycle **I**. In comparison, pyridine congener **9b** afforded **10b** in 71 % yield, but with reduced regioselectivity (3:1 b/l). In this case, the secondary alkyl titanacycle **II** is stabilized by coordination to the pendant nitrogen atom through a six-membered chelate. Increasing the reaction time to 3 h before the addition of acid improved the branched selectivity (**10b**, 3:1→6:1 b/l), which suggests that intermediates **I** and **II** equilibrate under the reaction conditions. A directing effect was not observed using homoallylic ether **9c**, as shown by the regioselective formation of **10c** after 1 h (52% yield, > 25:1 b/l). In contrast, modest branched selectivity was observed after 1 h with allyl arene derivatives **9d** and **9e**. As expected, the regioselectivity in both cases was enhanced to >25:1 by extending the reaction time. This modification allowed **10d** and **10e** to be isolated in yields of 78% and 85%, respectively.

To interrogate the role of temperature on the formation and equilibration of titanacyclobutanes **I** and **II**, we studied the conversion of methyl eugenol (**9e**) into products

10e using ^{1}H NMR spectroscopy. Thus, **9e** was reacted with 1.2 equiv **1** in THF (0.1M) for 3 h at various temperatures, then treated with TFA at −78°C. These experiments revealed a temperature window of −10°C to 10°C to achieve a high conversion into **10e** (≥95%). Using these conditions, the regioselectivity (b/l ratio) improved from 8:1 at R̂10°C to >25:1 at 0°C. Taken together, these data demonstrate the importance of time and temperature as variables for reaction optimization.

With these considerations in mind, the hydromethylation of substituted alkenes was explored. As highlighted in Scheme 3, alkenes **11** were divided into four groups (I–IV) based on the structure of the titanacyclobutane formed during the reaction. Group I included exocyclic 1,1-disubstituted alkenes derived from nitrogen heterocycles (**11a**–**g**). Substrates of this type reacted at 0°C to afford branched products exclusively. Pendent carbamates (**12a**) and amides (**12b**) were tolerated, as were small- (**12d**–**f**) and medium-sized (**12g**) ring systems. In contrast, hydroquinoline **11c** reacted slowly under the standard conditions, presumably because the resultant titanacyclobutane is more sterically hindered.

Group II consisted of endocyclic 1,2-disubstituted alkenes (**11h**–**k**), which reacted at 0°C in an identical fashion to Group I. Similarly, heterocyclic carbamates (**12h**), ethers, and alcohols (**12i**–**k**) were tolerated.[30] We observed that the methyl group was selectively delivered to the more congested position (α) within **12i** and **12j**. This outcome is consistent with a requirement to place the titanium atom in the least sterically encumbered position. In comparison, branched acyclic alkenes in Group III (**11l**–**s**) were less reactive, requiring an excess of **1** (2 equiv) and longer reaction times (3 h, −10°C) to obtain useful results. Nevertheless, 1,1-disubstituted alkyl (**11l**–**n**) and (hetero)aryl (**11o**–**s**) alkenes were transformed to branched alkanes **12l**–**s** in reasonable yield. Alkanes **12q**–**s** derived from α-methylstyrene derivatives are noteworthy, as this alkene class is a limitation of the Baran hydromethylation.[9] On the other hand, trisubstituted alkenes (e.g. **11t**) were unreactive. In addition, reactions of substrates bearing pendent aldehydes, ketones, or esters were complicated by competitive carbonyl methylenation.

With these limitations established, we set out to exploit the noted differences in alkene reactivity to achieve site-specific hydromethylation (Scheme 4). Thus, we found that the acyclic alkene in **13** reacted selectively to give **14** exclusively. We also observed complete selectivity for the α-olefin in **15** to afford **16** in 84% yield. Likewise, the cyclic alkene of **17** was functionalized, leaving the branched acyclic alkene untouched en route to amide **18**. In contrast, the α-olefin of **19** reacted preferentially to give pyrrole **20** in 72% yield following oxidation of the pyrroline ring during purification.[31] Taken together, these competition experiments established the following order of alkene reactivity: α-olefins > cyclic alkenes > acyclic branched alkenes ≫ trisubstituted alkenes.

In summary, a method for the direct hydromethylation of alkenes has been developed. This approach harnesses Tebbe's reagent (**1**) to generate titanacyclobutanes from alkenes. These transient 1,3-dianion equivalents react in situ with exogenous acid to furnish net hydromethylation products with excellent regioselectivity. In defining the scope and limitations of this method, we established a clear hierarchy for alkene reactivity that allows site-specific hydromethylation within complex, polyfunctional molecules. This feature is

especially useful for natural product synthesis and the late-stage diversification of bioactive small molecules.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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[25]. See the Supporting Information for additional details.

[26]. Reagent **1** was prepared from Cp_2TiCl_2 and $AlMe_3$ (2.0M in PhMe). Based upon current prices for these reagents, the cost of **1** was ca. $\$1.1 mmol^{-1}$ when prepared as described in the Supporting Information. In our hands, the titration of **1** with 2-*tert*-butylcyclohexanone was difficult to interpret. An alternative titration using *p*-anisaldehyde was developed. These procedures were adapted from an earlier report:Cannizzo LF, Grubbs RH, J. Org. Chem 1985, 50, 2386–2387.

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[30]. The relative stereochemistry of **12i**–**12k** was assigned by comparison to previously reported data for these structures.

[31]. Structures **17** and **19** were intrinsically sensitive to oxidation and slowly oxidized to the corresponding acyl pyrroles under ambient conditions.

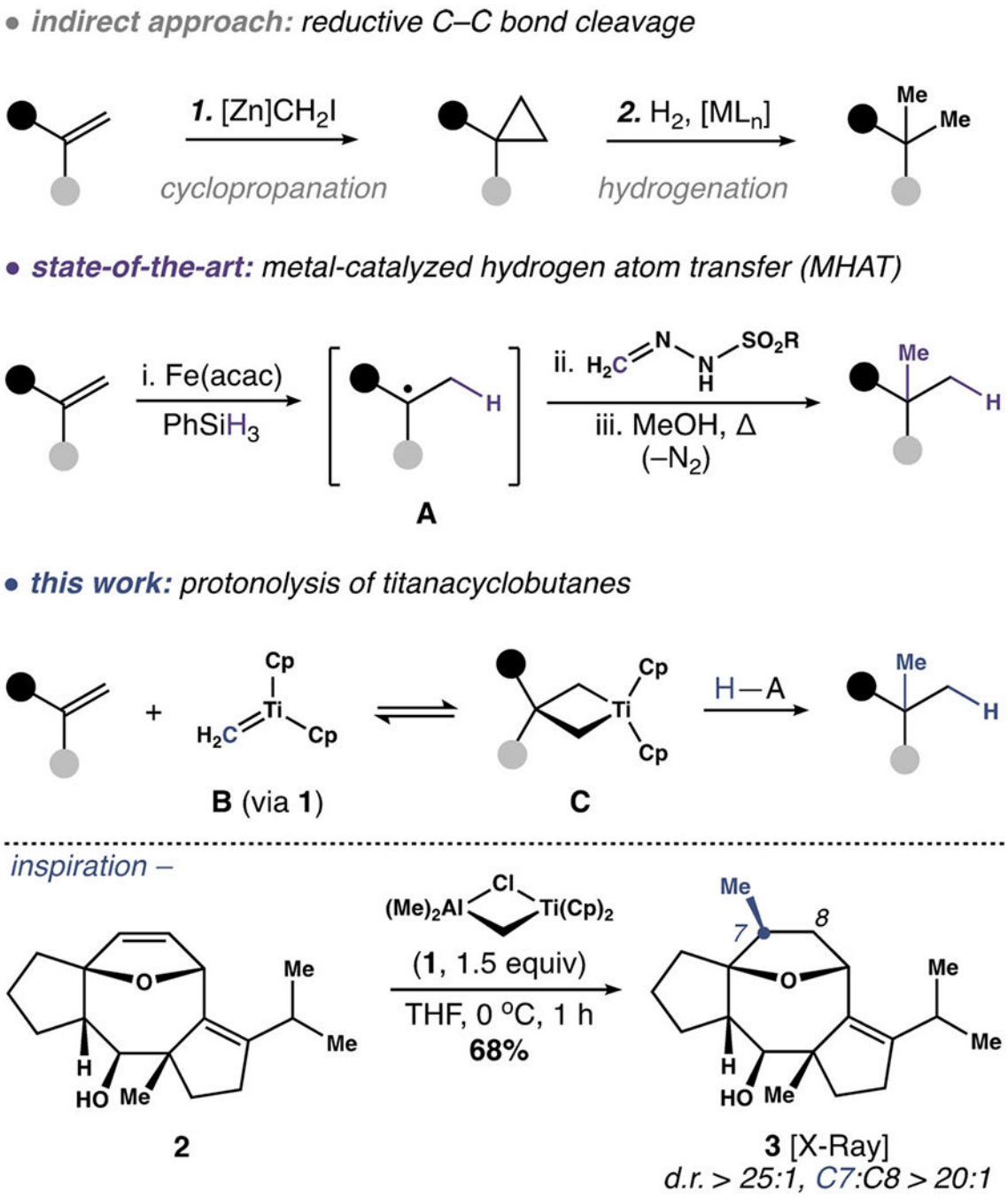
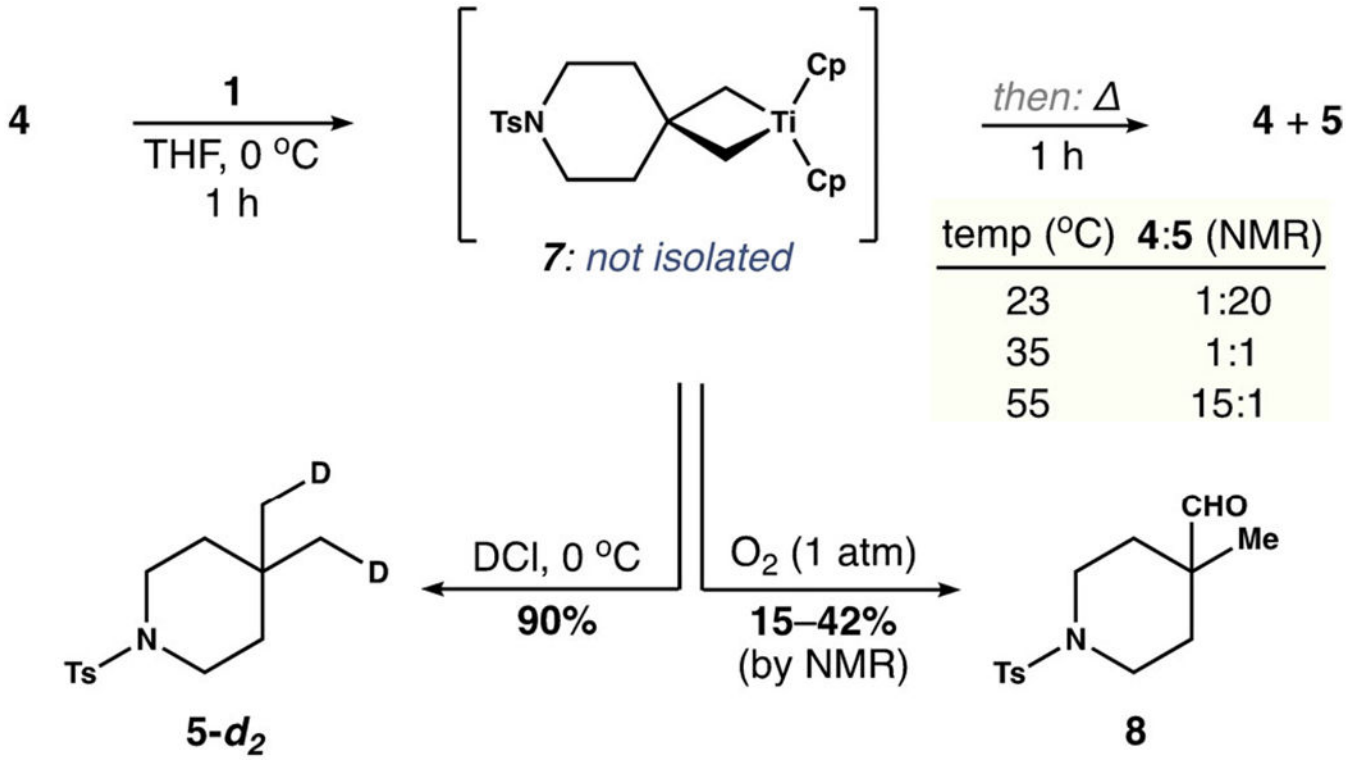
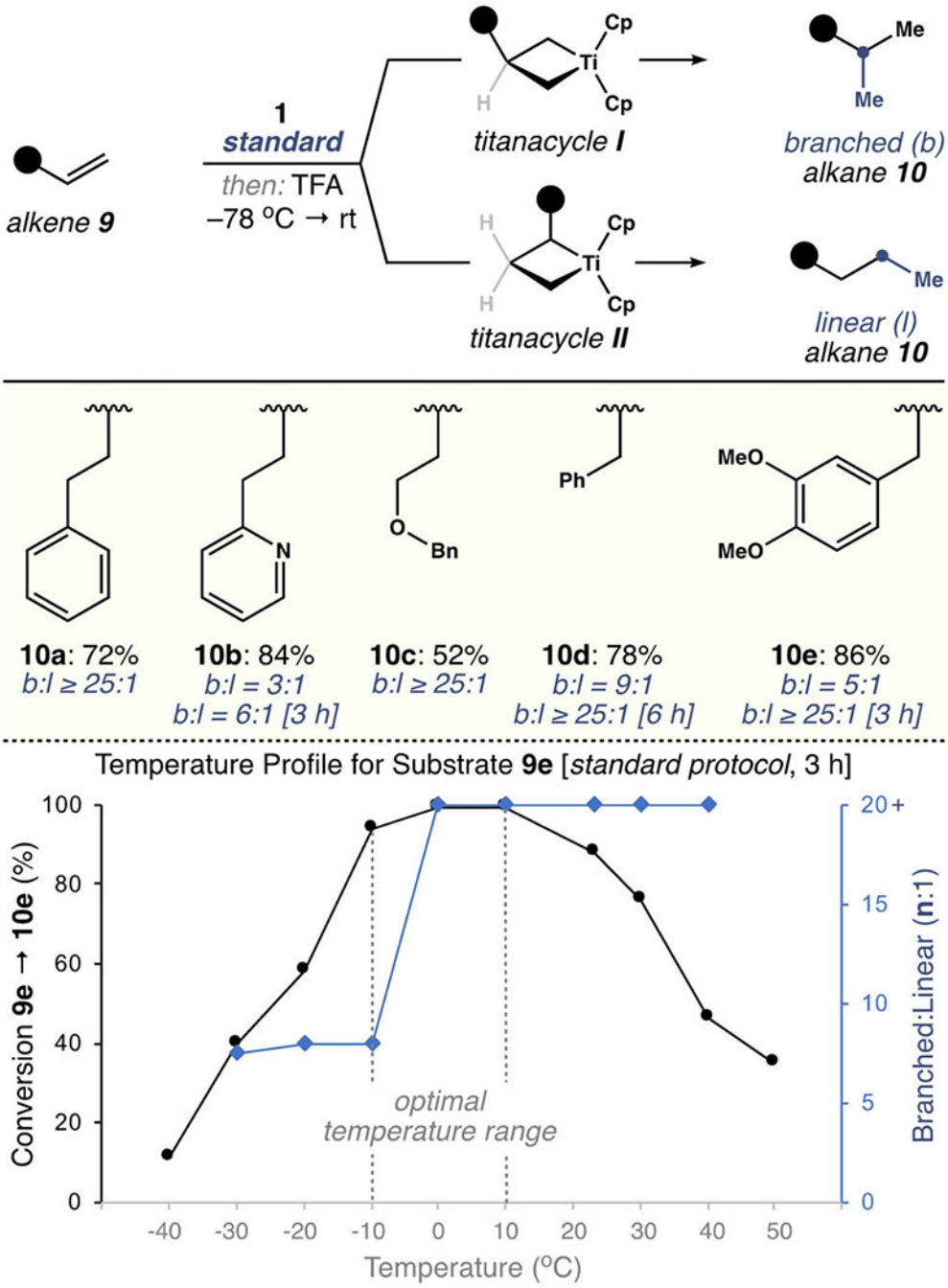


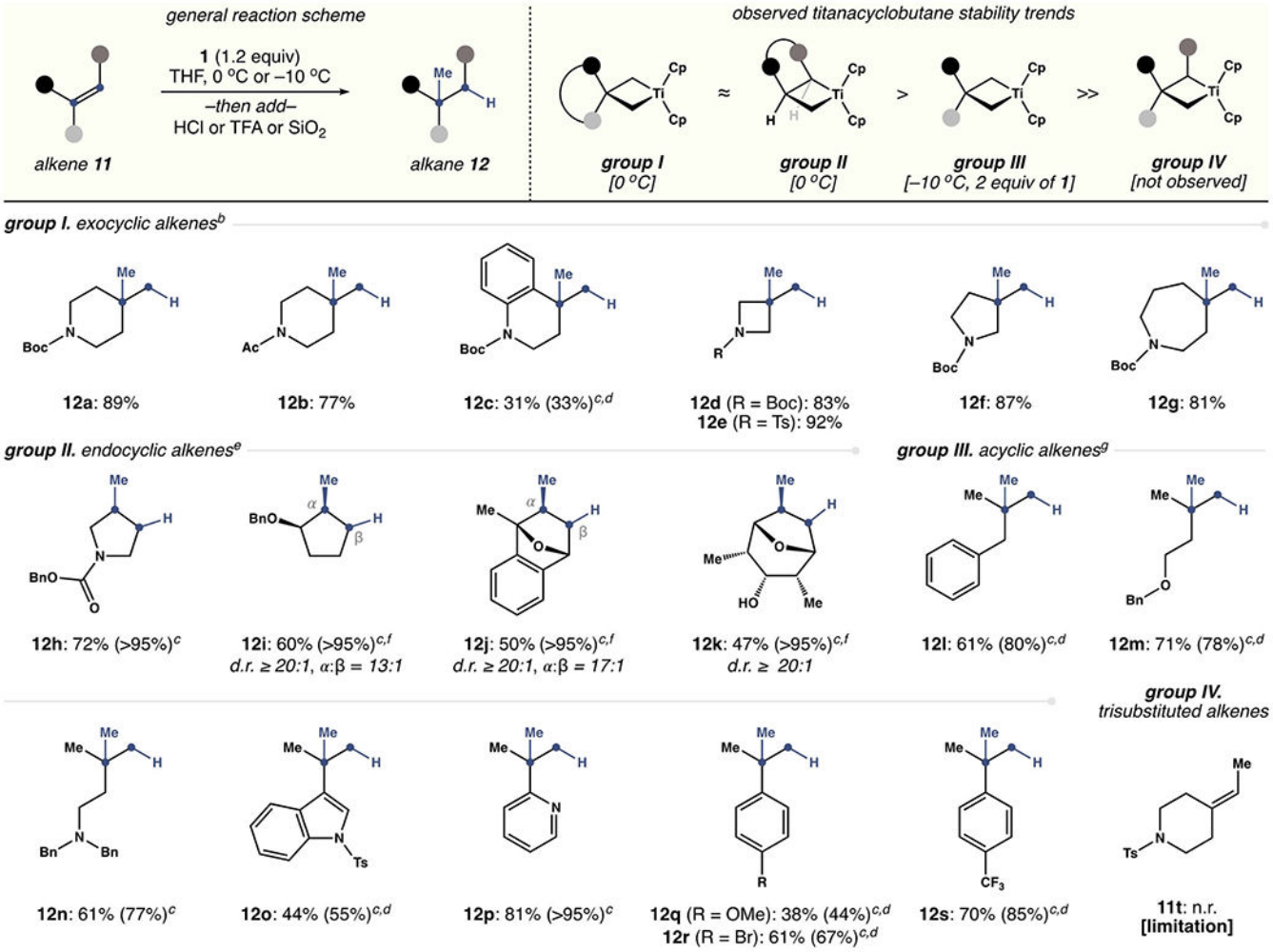
Figure 1.
Regioselective hydromethylation of unactivated alkenes explored in the context of structure **2**.



Scheme 1.
Reactivity of titanacyclobutane **7**.

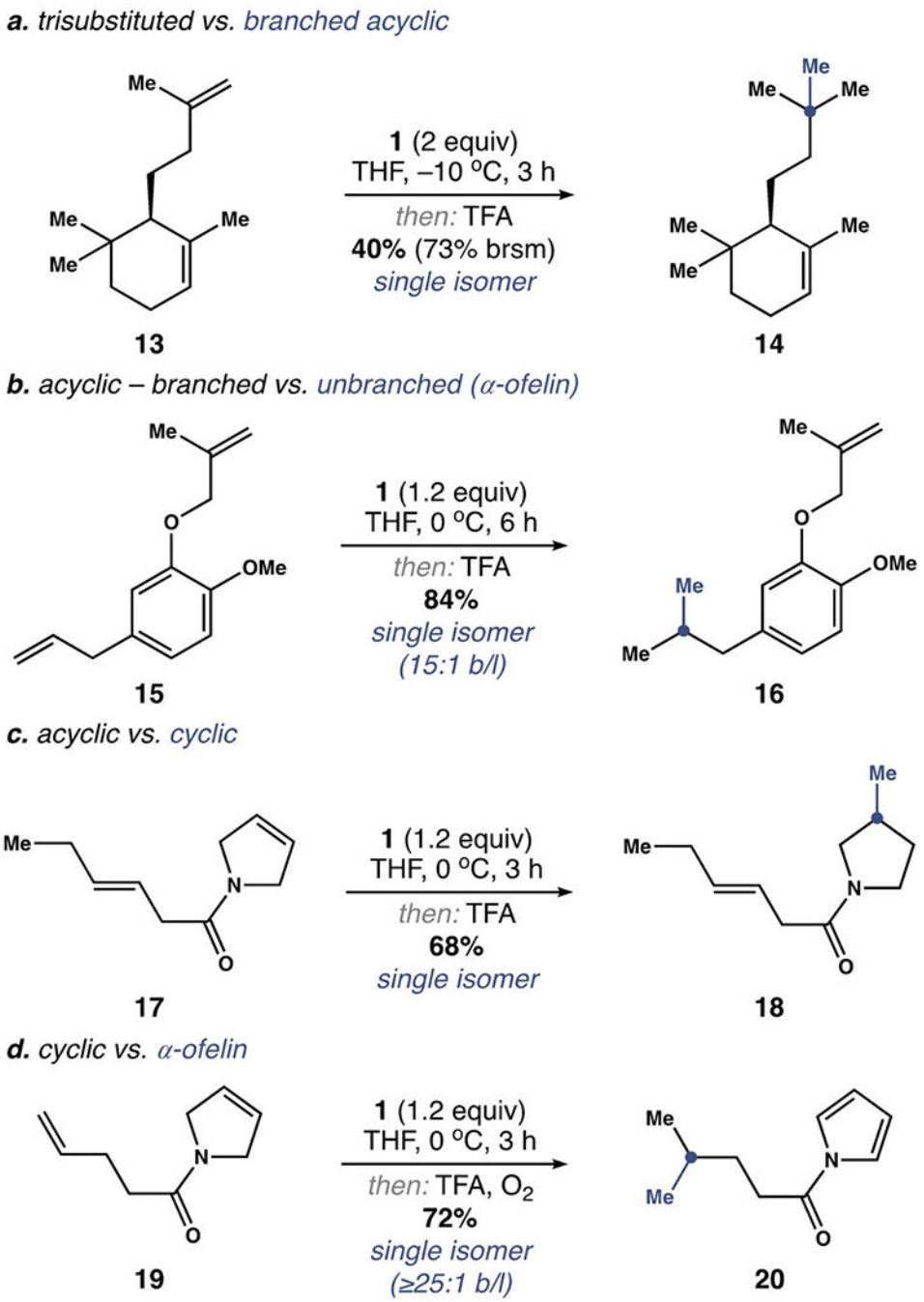


Scheme 2.
Regioselective hydromethylation of α-olefins.



Scheme 3.

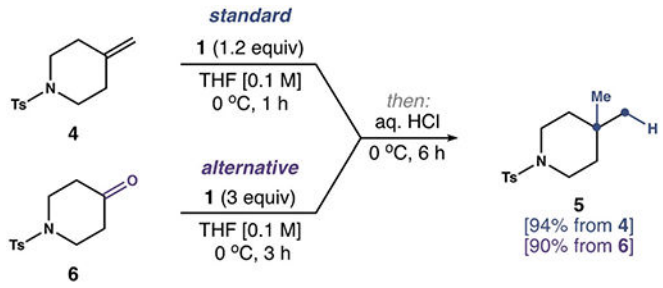
Scope and limitations of the titanium-mediated hydromethylation of alkenes.[a] [a] Yields are based on isolated **12**. [b] Conditions: 1.2 equiv **1**, 1 h; 3M aq HCl, 0°C, 6 h. [c] Conversion of **11** into **12** as judged by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [d] Unreacted **11** was removed by treating the mixture of **11** and **12** with Meta-chloroperoxybenzoic acid (*m*-CPBA).[25] [e] Conditions: 1.2 equiv **1**, 3 h; TFA, −78°C→rt, 6 h. [f] SiO_2 in EtOAc used in place of TFA. [g] Conditions: 2 equiv **1**, THF (0.1 M), −10°C, 3 h; TFA, −78°C→rt, 6 h.



Scheme 4.
Site-specific hydromethylation.

Table 1:

Summary of reaction optimization.[a–c]



Entry	Deviation from standard procedure	*t* [h]	Yield 5 [%]
1	PhMe, 1 equiv DMAP	6	16[d]
2	PhMe	6	0
3	PhMe/THF (2:1)	2	80
4	none	1	94
5	TFA as proton source[e]	1	92
6	none, gram scale	1	89
7	commercial solution of **1**[f]	6	70[d]

[a] Yields are based on isolated **5**.

[b] Reactions were carried out on a 0.2 mmol scale.

[c] Reagent **1** was prepared directly before use.[25]

[d] Reflects conversion of **4** into **5** as judged by ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture.

[e] The reaction was treated with TFA at −78°C and warmed to rt.

[f] Commercial **1** at 0.52 M (in PhMe) was used as received.