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Diverse Reactivity of Diazatitanacyclohexenes: Coupling Reactions of 2*H*-Azirines Mediated by Titanium(II)

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Abstract

2*H*-Azirines are versatile coupling partners for the synthesis of N-heterocycles. Herein, we present our studies on the reactivity of Cp₂Ti(BTMSA) (**1**; BTMSA = bis(trimethylsilyl)acetylene) with a variety of azirines. In all the cases examined, the initial organometallic products formed are diazatitanacyclohexenes, presumably formed via oxidative addition of Ti(II) into the C–N bond of the azirine to form an azatitanacyclobutene intermediate, followed by C=N insertion of a second equivalent of azirine into the Ti–C bond to form the observed products. Diazatitanacyclohexene **3**, bearing phenyl substituents and derived from 2,3-diphenyl-2*H*-azirine, fragments to form an azabutadiene and nitrile, which is shown to be catalytic in the presence of excess 2,3-diphenyl-2*H*-azirine. H-substituted complex **8**, derived from 3-phenyl-2*H*-azirine, decomposes via protonolysis of the Cp ligands. In contrast, the methyl-substituted diazatitanacyclohexene **10**, derived from 2-methyl-3-phenyl-2*H*-azirine, is thermally robust. Attempts to trap the putative azatitanacyclobutene intermediate with an alkyne were unsuccessful, resulting instead in the formation of titanacyclopentadiene (**12**) from coupling of alkyne with BTMSA. Initial reactivity studies found that **10** could be protonolyzed with AcOH to form mixtures of pyrrole and aziridine products, whereas reacting **10** with MeOH results solely in the formation of 2,4-dimethyl-3,5-diphenyl-1*H*-pyrrole.

Graphical Abstract

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Supporting Information

CCDC 1857649–1857650 contains the supplementary crystallographic data for this paper. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00522.

Details of syntheses, characterization data of all new compounds, and X-ray crystallographic data (PDF)

Accession Codes

CCDC 1857649–1857650 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Due to their high strain energy and structural diversity, 2*H*-azirines are attractive coupling partners for the synthesis of larger N-heterocyclic rings.¹ For example, Lu and Xiao have demonstrated the coupling of azirines and electron-deficient alkynes in the presence of a photocatalyst to form highly functionalized pyrroles (Figure 1).² Notably, azirine addition to the alkyne in this instance occurs through cleavage of the C–C bond of the azirine. Historically, transition-metal catalysts have been commonly utilized for coupling reactions of azirines through C–N bond cleavage.^{3,4} Alper and co-workers have shown that the C–N bond of azirines is susceptible to oxidative addition with low-valent palladium to form azaallyl intermediates.⁵ Subsequent carbonylation with CO and attack by a second equivalent of azaallylpalladium results in the formation of β -lactams.

Many of the coupling reactions involving azirines are facilitated by late transition metals, including rhodium,^{6–8} nickel,⁹ and silver.¹⁰ In contrast, examples of azirine functionalization using early metals are much rarer and typically involve group 6 carbonyl complexes as coupling partners.^{11–13} In the sole example using titanium reported to date, Alper and co-workers demonstrated that TiCl₄ can coordinate azirines, activating them to nucleophilic attack from external chloride.¹¹ Motivated by the dearth of reports in the literature on the reactivity of early metals with azirines, we set out to examine the fundamental organometallic reactivity of titanium^{14–17} with these N-heterocycles. Herein, we present our preliminary findings on the reactivity of a family of azirines with a well-defined titanium(II) synthon and their subsequent reactivity to form an array of different products depending on the azirine substituents.

Reaction of equimolar amounts of the Rosenthal complex Cp₂Ti(BTMSA)¹⁸ (**1**; Cp = cyclopentadienyl, BTMSA = bis(trimethylsilyl)acetylene) with 2,3-diphenyl-2*H*-azirine (**2**) in C₆D₆ resulted in an instant color change from golden brown to dark red-purple. ¹H NMR spectroscopic analysis revealed the presence of approximately equimolar amounts of residual **1** and a new organometallic complex (**3**). Addition of a second equivalent of **2** results in full consumption of **1** and the formation of **3** in 66% NMR yield (Figure 2). The ¹H NMR spectrum of **3** displays two singlets in the Cp region (δ 6.02 and 5.93) that each integrate to five protons, indicating that the complex is asymmetric. In addition, resonances at δ 5.00 and 3.71 (both singlets integrating to 1) demonstrate that the two incorporated azirine moieties are in distinct environments. Although we were unable to grow crystals of **3** for X-ray diffraction studies, we assigned the structure as the diazatitanacyclohexene shown in Figure 2, where the titanium is bound by imidyl and aziridinyl ligands. We propose that **3** is formed by oxidative addition of titanium(II) into the C–N single bond of **2** to form the azatitanacyclobutene intermediate **4**, which then undergoes rapid insertion of the C=N bond of another equivalent of **2** into the Ti–C bond to form **3**. Complex **3** is formed as a single diastereomer, which was assigned by 2D NOESY spectroscopy (vide infra).

Complex **3** is unstable in solution, decomposing overnight at room temperature to form (relative to **3**) the products of formal 2*H*-azirine disproportionation: the azabutadiene *N*-(1,2-diphenylvinyl)-1-phenylmethanimine (**5**)¹⁹ in 87% yield and benzonitrile (**6**) in 77% yield (Figure 3). While **6** could clearly be seen by GC/MS and GC/FID analysis, we observed only broadened resonances for it in the ¹H NMR spectrum of the crude reaction mixtures. This is likely the result of a dynamic equilibrium process with Ti in solution. There is only

one other example of this type of formal azirine disproportionation in the literature, catalyzed by Ni^0 .²⁰ In this previous study, the authors propose that the nitrile is formed via retro [2 + 2] cycloreversion of an azanickelacyclobutene. If the titanium system described here is operating by the same mechanism, it would require that the insertion of the second equivalent of 2*H*-azirine into **4** to form **3** be reversible. Preliminary mechanistic experiments of the decomposition of **3** indicate that the rate of decomposition of **3** is relatively unaffected by the presence of excess **2**. This argues against reversible elimination of **2** from **3** followed by [2 + 2] cycloreversion from **4**. Instead, direct ejection of the observed products from **3** via a more complicated electrocyclic mechanism appears to be more plausible. Notably, we do not detect any products of nitrile coupling in these reactions, which has recently been reported for group 4 metallocenes.^{17,21}

Given that release of the azabutadiene fragment **5** should formally regenerate titanium(II), we sought to probe whether this disproportionation could be rendered catalytic. Addition of 10 mol % of **1** to a solution of **2** in C_6D_6 resulted in an immediate color change to dark brown-red. The solution was stirred at room temperature for 16 h before being analyzed by ^1H NMR and GC-FID, revealing the formation of **5** (27% yield) and **6** (33% yield). Although these yields are not ideal, they demonstrate that catalytic turnover is feasible within this system. More broadly, these preliminary results show that titanium(II) is competent for the catalytic functionalization of 2*H*-azirines, a process which has not been reported to date.

We then sought to explore the 2*H*-azirine coupling scope, hypothesizing that bulkier 2*H*-azirine substituents may hinder the insertion of a second equivalent of azirine into the putative azatitanacyclobutene **4**. Unfortunately, reactions of **1** with 2,2-dialkyl-3-phenylazirines ultimately resulted in mixtures of decomposition products (see ESI). In contrast, reaction of **1** with 3-phenyl-2*H*-azirine (**7**) resulted in rapid formation of diazatitanacyclohexene **8**, which was characterized in solution by a variety of NMR spectroscopic methods (Figure 4). Complex **8** decomposed on standing at room temperature over several hours and was thus unisolable in our hands. Interestingly, the main observable product of decomposition of **8** was not an azabutadiene such as **5** but rather cyclopentadiene (CpH).

Addition of **1** to a solution of 2-methyl-3-phenyl-2*H*-azirine (**9**) resulted in an instant color change from brown to purple. ^1H NMR spectroscopy revealed the clean formation of diazatitanacyclohexene **10**, which was found to be thermally robust (Figure 4). Indeed, in contrast to **3** and **8**, **10** was stable in refluxing C_6D_6 for several days. Cooling a saturated solution of **10** in Et_2O overnight at -35°C allowed for the growth of large red crystals suitable for X-ray diffraction studies, and the solid-state structure of **10** is shown in Figure 5. Notably, both the NMR data and the crystallographic data indicate that **10** is formed as a single diastereomer. Both Ti–N bonds are similar in length. The six-membered titanacycle is remarkably flat, with the second equivalent of azirine inserting such that the methyl group of the aziridinyl moiety is pointing away from the ancillary Cp ligand.

To further probe the reactivity of **10**, we undertook protonolysis experiments with a variety of acids in order to cleave the coupled organic fragment from the metal center (Figure 6).

Washing a benzene solution of **10** with 2 M HCl(aq) resulted in an immediate color change from purple to red-orange. ^1H NMR spectroscopic analysis revealed the formation of Cp_2TiCl_2 as the main organometallic species.²² Using weaker acids with less nucleophilic conjugate bases such as 1 M AcOH(aq) instead resulted in mixtures of pyrrole **13**^{23,24} (26% yield) and aziridine **14** (45% yield), as determined by ^1H NMR spectroscopy. Satisfyingly, dissolving **10** in MeOH resulted solely in the formation of **13** (48% yield by ^1H NMR) from the coupled azirine moieties, along with CpH. These transformations are remarkably selective given the relatively simple metal scaffold utilized here and demonstrate that *2H*-azirines can indeed be useful coupling partners for the selective formation of N–H pyrroles and other N-heterocycles using titanium.

Finally, we then sought to examine whether it would be possible to trap the putative azatitanacyclobutene intermediate with an organic substrate other than azirine. Our initial approach involved premixing *2H*-azirine **9** and various amounts of *p*-tolylacetylene (**11**) before addition to complex **1**. While the resulting NMR spectra showed complicated mixtures of products indicative of *2H*-azirine + acetylene coupling (see the Supporting Information), a major product of the reaction was direct coupling of **1** with **11** to form **12** (Figure 7). Upon scaling up these reactions, we were able to isolate brown crystals of **12** (see Figure 5 for the solid-state structure). The titanacyclopentadiene moiety is clearly shown by the short C1–C2 (1.373(5) Å) and C3–C4 (1.344(4) Å) bonds and the long C2–C3 (1.481(4) Å) bond. Remarkably, the only other reported example of cyclization of an alkyne with **1** uses acetylene as a substrate;²⁵ typically, BTMSA is considered as an innocent spectator in reductive coupling reactions.^{26,27} Other efforts to use CO and isocyanides as trapping agents for the azatitanacyclobutene intermediate have so far been unsuccessful.

In conclusion, we have demonstrated that titanium(II) is viable for the rapid coupling of *2H*-azirines to form diazatitanacyclohexenes, which display a wide range of stabilities and reactivities depending on the substituents including *2H*-azirine disproportionation, NH-pyrrole synthesis, and other *2H*-azirine coupling reactions. Efforts to extend the reactivity observed here to catalytic reactions of *2H*-azirines are currently ongoing in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Examples of coupling reactions of azirines.

Figure 2.
 (top) Synthesis of diazatitanacyclohexene **3**, with the ¹H NMR yield given in parentheses.
 (bottom) Partial ¹H NMR spectrum (400 MHz, C₆D₆, 25 °C) of **3**.

Decomposition of **3** via 2H-azirine disproportionation:

Catalytic 2H-azirine disproportionation:

Figure 3.

(top) Decomposition of **3** into **5** and **6**. (bottom) Catalytic 2H-azirine disproportionation.

Legend: (a) ^1H NMR yield; (b) GC-FID yield.

Figure 4. Synthesis of **8** and **10**, with the ¹H NMR yield given in parentheses. Legend: (a) 52% isolated yield.

Figure 5.

Thermal ellipsoid diagrams of **10** (left) and **12** (right) (50% probability ellipsoids). Most H atoms are omitted for clarity. Relevant bond distances (Å): for **10**, Ti1–N1 1.944(1), N1–C1 1.268(2), Ti1–N2 1.975(1), N2–C3 1.479(2); for **12**, Ti1–C1 2.185(4), C1–C2 1.373(5), C2–C3 1.481(4), C3–C4 1.344(4), Ti1–C4 2.145(3).

Figure 6.
Reactivity of **10** with acids, with ¹H NMR yields given in parentheses.

Figure 7.
Synthesis of **12** from **1** and **11**, with the isolated yield given in parentheses.