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Ruthenium Metathesis: A Key Step To Access a New Cyclic Tetrasubstituted Olefin Platform

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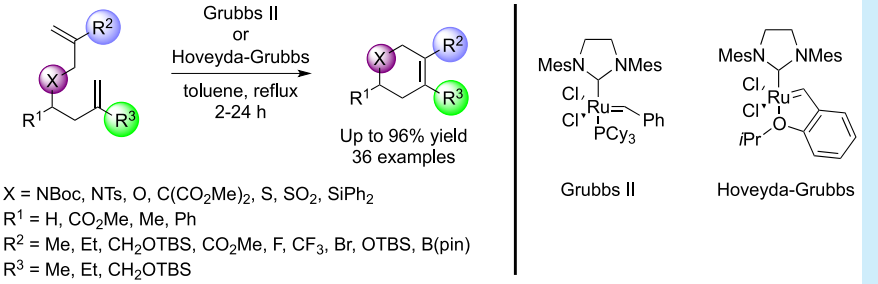

ABSTRACT: An rapid and mild synthetic route for the preparation of cyclic tetrasubstituted platforms via ruthenium-catalyzed ring-closing metathesis (RCM) has been developed. This process tolerates a wide range of functionalities such as nitrogen, oxygen, sulfur, silicon, and carbon tethered groups, as well as very challenging fluorine and boron atoms (36 derivatives, up to 96%). This diversity-oriented method was further demonstrated by the postfunctionalization reactions, such as Pd-couplings, *N*-substitution, and reductive amination introducing a morpholine moiety.

Through the past decades, ruthenium catalysis has emerged as a powerful tool to construct complex structures.[1] Among them, Ring Closing Metathesis (RCM) has been recognized as a versatile and powerful tool in organic chemistry to synthesize small, medium, or large rings.[2] The synthesis of cyclic polysubstituted olefins can be achieved using Grubbs, Hoveyda−Grubbs, or tailormade catalysts, depending on the substitution pattern of the alkene.[3] Whereas several studies have been published on di- and trisubstituted alkenes, relatively few studies have been done on cyclic tetrasubstituted olefins.[1e,4,5] Considering our interest for diversity-oriented synthesis (DOS)[6] and atom-economical metal-catalyzed reactions[7] as well as tetrahydropyridine cores as key building blocks for medicinal chemistry[8] (Figure 1), we anticipated that readily available and functionalized diene derivatives may be suitable substrates for Ru-catalyzed metathesis. We wish, therefore, to report therein our preliminary results on the general, rapid, and unprecedented synthesis of an original and functionalized tetrasubstituted cyclic olefin platform bearing other substituents than the *vic*-dimethyl moiety. Some preliminary postfunctionalization transformations are also presented.

To examine the possibilities of access to tetrahydropyridine and other oxygen, carbon, sulfur, and silicon cores via-Ru-catalyzed metathesis, a wide range of dienes **1** (36 derivatives) were prepared as summarized in Figure 2. A simple two-step synthesis of substrates **1** bearing R^1 = CO_2Me has been developed, starting from commercially available methyl *N*-(diphenylmethylene)glycinate and methylallyl bromide (see

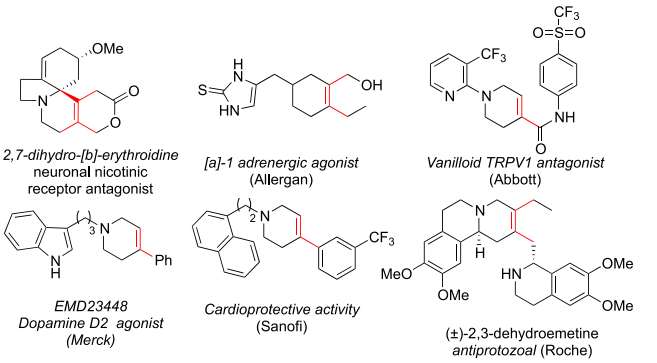

Figure 1. Tetrahydropyridine and cyclohexene cores in bioactive compounds.

Supporting Information).[9] For phenyl- and methyl-substituted derivatives in the R^1 position of **1**, an alkylation of sulfones, readily accessible from the corresponding aldehydes, by methylallyl magnesium chloride yielded the corresponding carbamates,[10] which were submitted in an *N*-alkylation

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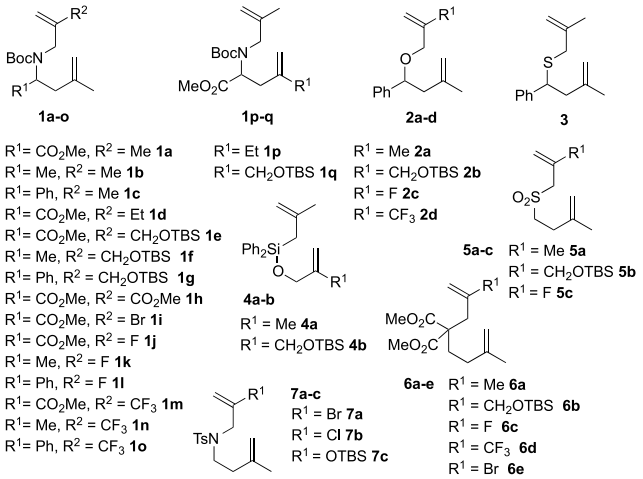
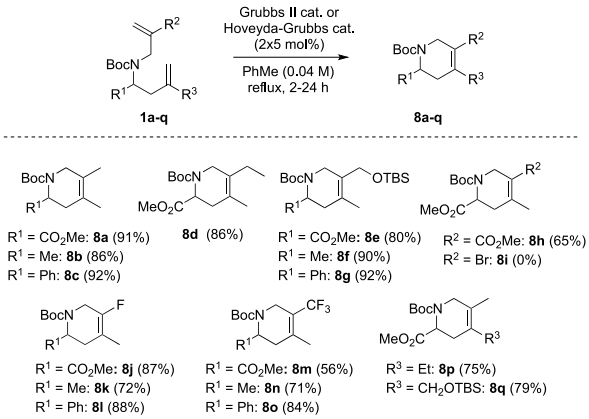


Figure 2. General structures of dienes.

reaction.[11] We gained interest to functionalize the olefin by introducing several heteroatoms. Over the years, it has become clear that fluorine substituents could display a positive effect on pharmacokinetic and pharmacodynamic properties of potential drugs due to their specific chemical, biological, and physical properties.[12] In spite of their interesting features, to date, only scarce examples have been disclosed on metathesis reactions on fluoroalkene derivatives limited mainly to the synthesis of trisubstituted fluoro-olefins.[3u,13] We therefore prepared **1k**–**1o**, bearing a fluoride or trifluoromethyl group, according to nucleophilic substitution with the corresponding allylic bromide derivatives. We also turned our attention to the reactivity of a wide series of heteroatom-tethered dienes **2**–**5**, which were synthesized according to known methodologies (see Supporting Information).[11] Methylmalonate derivatives **6** were also easily prepared, as well as sulfonamide derivatives **7**.

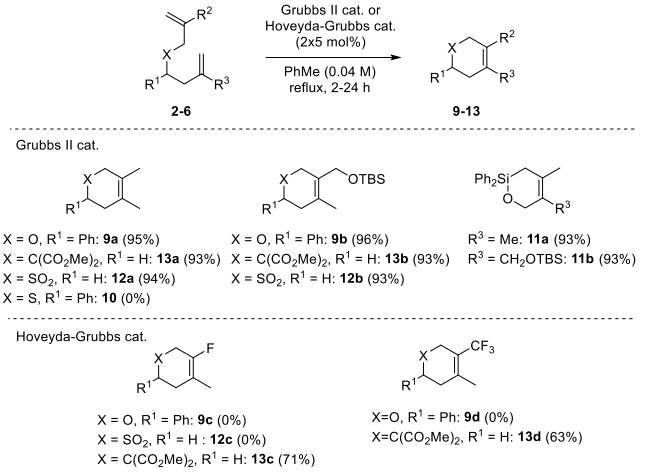
Having in hand a wide range of functionalized dienes (36 congeners), we further utilized them in ring closing metathesis cyclizations (Schemes 1, 2, and 3). Nitrogen-tethered dienes

Scheme 1. Synthesis of Tetrahydropyridines 8a–q

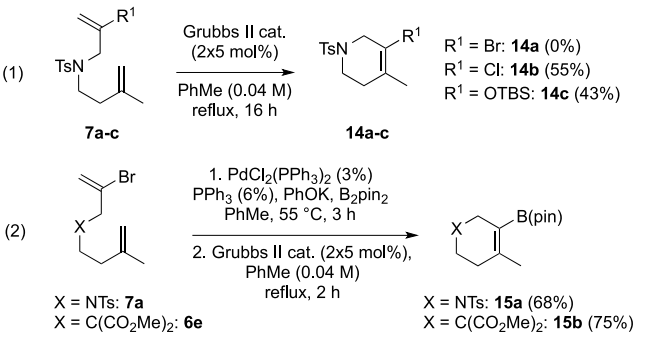


1a–**g** have been successfully cyclized in toluene (0.04 M) using 2 × 5 mol % of Grubbs II catalyst, which allowed the formation of new tetrahydropyridines with good to excellent yields (Scheme 1). A bulky group, such as a TBS-hydroxymethyl group, was tolerated (**8e**–**g**). The RCM reaction was also feasible starting from an acrylate **1h** with 65% even if this reaction took a longer time (24 h).

Scheme 2. Synthesis of Heteroatomic-Core Tetrasubstituted Cyclic Olefins



Scheme 3. RCM of Compounds 7a–c and Pinacol Boranes Derived from 7a and 6e



The use of vinyl bromide derivative **1i** led to no observable conversion with either Grubbs II and Hoveyda–Grubbs catalysts, in accordance to Dorta and co-workers.[14] To our delight, fluorinated olefins **1j**–**l** underwent a cyclization process with the Hoveyda–Grubbs II catalyst (2 × 5 mol %) affording the fluorinated cyclic olefin **8j**–**l** with good yields (72–88%). Trifluoromethylated tetrahydropyridines **8m**–**o** could be obtained as well (56–84%) using the same conditions, but with longer reaction times (24 h). A significant decrease in yield has been observed with the ester derivative **8m** (56% yield).[15] High yields were also observed for tetrahydropyridines **8p**–**q** (75 and 79%).[16]

We then turned our attention to oxygen-, silicon-, sulfur-, and carbon-tethered dienes and were pleased to see that the Ru-catalyzed metathesis reactions of these derivatives were also feasible (Scheme 2). The *vic*-dimethyl cyclic olefin arising from ethers **2a**, sulfones **5a**, silyl **4a**, and malonate derivatives **6a** could be obtained with excellent yields (93–95%), comparable to those obtained with NBoc protected tetrahydropyridines **1a**–**c** (86–92%). Sulfide **3** did not cyclize under these conditions.[17] Interestingly, the TBS-hydroxymethyl group was still tolerated, giving access to heterocycles **9b**[16] and **12b**–**13b** with good yield (93–96%), comparably to those obtained for tetrahydropyridines **1e**–**g** (80–92%).

When the olefin was functionalized by a fluorine or a trifluoromethyl group, malonate-tethered dienes were tolerated and the cyclohexenes **13c** and **13d** were isolated in 71% and 63% yields, respectively. Sulfone **5c** and ethers **2c**–**d** were

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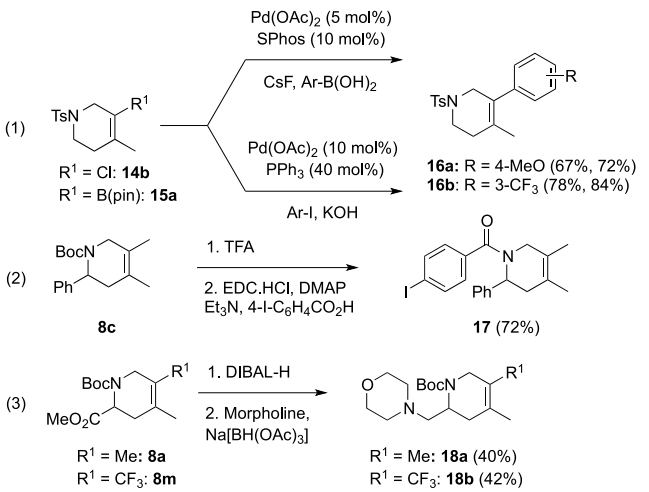
found unreactive under these conditions (Scheme 2). Considering the nonreactivity of **1i**, we turned our attention to the reaction of chloro and bromo sulfonamides **7a–b** (Scheme 3, eq 1).[18] Pleasingly, whereas the bromo derivative **7a** was unreactive, the chloro derivative **7b** reacted nicely, leading to the cyclic derivative **14b** in moderate 55% yield.[19a] Vinyl enol ether **7c** was also subsequently engaged in an RCM reaction,[20] leading remarkably to the corresponding tetrahydropyridine **14c** with 43% yield.[19b] In the pursuit of our effort to gain more diversity, a pinacol borane derivative was considered.[21] We chose to start from vinyl bromide **7a** or **6e** by a classical Miyaura borylation reaction.[22] But all our attempts to isolate pinacol boranes were found to be unsuccessful. So we decided to perform a tandem borylation/RCM reaction, which was able to afford the desired stable pinacol borane **15a** with a fair yield of 68% over two steps. This methodology was also applied to the malonate derivative **6e** forming the pinacol borane **15b** in 75% yield (Scheme 3, eq 2).

Finally, to further illustrate the synthetic utility of such a platform, we chose to perform some post-transformations of the corresponding cyclic aminocyclohexene derivatives (Scheme 4). Palladium-catalyzed Suzuki cross-couplings have

Scheme 4. Postfunctionalization Reactions



been achieved, starting from vinyl chloride **14b**[22] or pinacol borane **15a**,[23] giving access to product **16a–b**. We illustrated the complementarity of having the halogen- or boron-functionalized derivative, giving rise to similar isolated yields for both methods employed (Scheme 4, eq 1). An acidic deprotection on **8c** could be followed by a classical peptidic coupling, leading to amide **17** in 72% isolated yield (Scheme 4, eq 2). A tandem DIBAL reduction/reductive amination could afford pharmacophores **18a–b** in 40–42% yields for the two-step synthesis (Scheme 4, eq 3).

In conclusion, we have therefore extended the methodology of the ruthenium-catalyzed metathesis reactions by studying its applications and opportunities to prepare tetrasubstituted dienes. A practical route for the preparation of cyclic tetrasubstituted olefins was proposed in the presence of Grubbs II or Hoveyda–Grubbs II catalysts giving rise to a rapid access to functionalized platforms. Various carbon- and heteroatom-tethered dienes were tolerated such as oxygen, sulfone, silane, or malonate derivatives, and this protocol also allowed the formation of fluoro- or trifluoromethyl derivatives. We have also carried out various preliminary postfunctionalization reactions over the tetrahydropyridine scaffolds, leading to interesting building blocks. Further studies will focus on practical and industrial applications of this straightforward and diversity-oriented process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01344.

Experimental procedure and analytical data (PDF)
^{1}H and ^{13}C spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(15) Hoveyda−Grubbs II catalyst did not show any activities toward the formation of tetrasubstituted cyclic fluoro- or trifluoromethylated olefins.

(16) Analysis of residual ruthenium level showed a low amount of ruthenium (4.1−5.3 ppm) for **8q** and **9b** (see Supporting Information).

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