Organoytterbium Ate Complexes Extend the Value of Cyclobutenediones as Isoprene Equivalents**

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In memory of Margaret Harrowven

3-Methyl-4-methoxycyclobut-1,2-dione (1a) has long been recognized as a valuable isoprene equivalent in natural products total synthesis, particularly for the preparation of hydroquinones, quinones, and their benzannulated analogues (e.g. Scheme 1).[1,2a] It is readily introduced to a substrate as the electrophilic component in organolithium or Grignard addition reactions, for example, 1a → 2. Here, the differential reactivity of the C1 and C2 carbonyl groups in 1a adds to its value as a synthon by providing a reliable and predictable means of achieving the ubiquitous head to tail connectivity of isoprene units.[1,2a]

Though regiocontrol in the addition of Grignard and organolithium reagents to 1a is of critical importance, it also imposes a severe limitation. As evidenced by the example in Scheme 1, while the method is convenient for the synthesis of benzohydroquinones such as 3, it proves cumbersome when targeting the regiosomer series 7. In this case addition of a carbon nucleophile to the vinylogous ester carbonyl (C2) of 1a is required to achieve the desired outcome. Consequently, a protecting group strategy must be invoked to mask the more reactive C1 carbonyl (e.g. 1a → 4).[2] Addition of the Grignard or organolithium reagent to C1 is then followed by deprotection (e.g. 5 → 6), which can be difficult to achieve efficiently because of the presence of the acid sensitive tertiary alcohol and enol ether functions.

Herein we report an expedient solution to that long-standing problem and reveal some hitherto unknown facets of organoytterbium reactivity. In essence, while organolithium and Grignard reagents favor addition to the C1 carbonyl of cyclobutenedione (1a), the corresponding organoytterbium reagents give exclusive addition to the C2 carbonyl of 1b (Scheme 2).[3]

The discovery was made during an optimization study aimed at reducing side reactions resulting from deprotonation of the C3 methyl substituent in 1a. In the addition of PhLi, for example (Scheme 3), these appeared to limit the yield of the

Scheme 1. Use of 1a as an isoprene equivalent in the synthesis of benzohydroquinones.

Scheme 2. Dichotomous regioselectivity in the addition of organolithium and organoytterbium reagents to cyclobutenediones. TF = trifluoromethanesulfonyl.

Scheme 3. Regioselectivity in the additions of various phenyl organometallics to 1a and 1b. THF = tetrahydrofuran.
adduct 2a to approximately 70–80% when employing standard protocols (e.g., THF at \(-78^\circ\text{C}\)).\[^4\] Inspired by reports from the groups of Molander and Procter on the efficient addition of organoytterbium reagents to carbonyl compounds,\[^5\] we decided to examine the addition of phenyl ytterbium triflate to 1a.\[^2\] The result we attained was quite unexpected, as the reaction led to the formation of both C1 and C2 adducts, 2a and 11a, respectively, in the corresponding yields of 50% and 41% (Scheme 3). Having noted similar anomalies in the additions of PhLi and PhMgBr to 1b, we were delighted to find that the addition of phenyl ytterbium triflate to 1b resulted in a complete reversal of the normal regiochemical course, thus giving the C2 adduct 12a in a remarkable 92% yield upon isolation.\[^5,6\]

To demonstrate the value of the method, a series of aryl ytterbium reagents were prepared and reacted with 1b. These included ortho,\[^7\] meta,\[^7\] and para-substituted aromatics with a variety of substituents (+I, –I, and +M), and a heteroaromatic example (see Scheme 4 and the Supporting Information). In each case the C2 adducts 12 were formed in excellent yield. This result was in stark contrast to the corresponding organolithium additions to 1a where the major product 2 resulted from addition to the C1 carbonyl.\[^7\] For completeness, all adducts were subjected to thermolysis and aerial oxidation, thus leading to the complementary series of benzoquinones 15 and 16.

The complementary reactivity extended to vinyllithium and vinylytterbium additions to 1a and 1b as demonstrated by the syntheses of the hydroquinones 23–25 and 27 (Scheme 5).\[^1\] Notably, vinylytterbium triflate derived from vinylmagnesium bromide displayed the same regiochemical preference as those derived from vinyllithium intermediates. Interestingly, the addition of the vinyllithium 18 to 1a proved unusual in that it gave 27 directly after a bicarbonate quench at \(-78^\circ\text{C}\) and warming to ambient temperature. The minor product of the reaction was the C2 adduct 21b,\[^5\] rather than the corresponding hydroquinone.

The addition of methyl ytterbium triflate to 1b also proved facile (Scheme 6). In contrast, the analogous sequence with nBuLi required a 2:1 equivalence with ytterbium(III) triflate to achieve a high yield of the C2 adduct 28b.\[^8\] The photochemical rearrangement of the adduct 28a into the furanone 29,\[^9\] and the facile generation of the diorganyl cyclobutenediones 30 by exposure of these adducts to acid, provide further illustrations of the method’s utility.

For completeness, the addition of phenylalkynyl ytterbium triflate to 1b was examined (Scheme 7). The reaction proved sluggish (9 h at \(-78^\circ\text{C}\)) in comparison with other additions and regioselectivity was attenuated, with the formation of cyclobutenones 34 and 33 in 69% and 15% yield, respectively. In contrast, the addition of the organolithium 31 to 1a gave the cyclobutene 32 as the sole isolated product.
Thermolyses of the adducts 32 and 34 exposed a further anomaly, with the former giving a 5:4 mixture of the quinone 35 and cyclopentenedione (E)-36, while the latter gave only the cyclopentenedione (Z)-37.

To gain insights into the mechanistic course of organoytterbium addition reactions we decided to initiate a computational study of the reaction of PhYb(OTf)2 with 1b. However, these investigations proved fruitless, with DFT calculations predicting a preference for reaction at the ketonic C1 carbonyl (i.e., \( \Delta G^\ddagger_{C1} > \Delta G^\ddagger_{C2} \)). The results led us to question the nature of the organometallic reagent. Based on limited literature precedent,[11] we had assumed that the reaction of PhLi with Yb(OTf)3 would first give the ate complex PhYb(OTf)3Li, which in turn would collapse to PhYb(OTf)2 and LiOTf. When this premise was tested computationally, our calculations indicated that loss of a triflate ligand from the ate complex would cost approximately 25 kcal mol\(^{-1} \) at \( 78^\circ C \). Moreover, when the reactivity of [PhYb(OTf)3]− towards 1b was examined, the predicted outcome mirrored our experimental findings by revealing a kinetic preference for phenyl addition to the C2 carbonyl (i.e., \( \Delta G^\ddagger_{C2} < \Delta G^\ddagger_{C1} \)).

The modeling also exposed some seminal facets of organoytterbium reactivity (Figure 1). In particular, the pre-reaction complexes of [PhYb(OTf)3]−-1b (F and G) each showed single ytterbium–carbonyl interactions leading to trapezoidal transition states. The strength of those interactions was a key factor in determining the regiochemical course of addition, with \( \Delta G \) less than \( \Delta G^\ddagger \) by about 2.5 kcal mol\(^{-1} \). Additionally, steric interactions in the addition phase play an important role, as evidenced by 1) the need to rotate the \( \beta \)Bu ether during C1 addition (F→E, Figure 1) at a cost of about 2.6 kcal mol\(^{-1} \)[12] and 2) the low selectivity observed for addition of [PhYb(OTf)3]− to 1a compared to that for 1b (Scheme 3).

Finally, to demonstrate the method's potential in terpenoid synthesis we decided to target mansonone B, a natural product whose identity has yet to be determined with rigor but seemed likely to be as depicted in 43.[13] Our synthesis began with (−)-menthone (39, Scheme 8), which was readily transformed into the required vinyl lithium reagent 41 by means of a Shapiro reaction.[14] Transmetallation with ytterbium triflate, and subsequent addition of the resulting vinylytterbium intermediate to 1b, gave a 7:3 diastereomeric mixture of the C2 adduct 42 in 94% yield. Thermolysis of that mixture under continuous flow at 110 °C with concomitant aerial oxidation, gave the quinone 44, from which our target 43 was readily derived. Pleasingly, the physical and spectral characteristics displayed by our synthetic sample (−)-43 matched those reported for mansonone B in its isolation paper,[13a] thus confirming the regiochemical and relative stereochemical identity of the natural product. Its absolute configuration remains uncertain because of a lack of available optical rotation data for comparison.

In conclusion, we have shown that organoytterbium additions to 1b are easy to effect, proceeded in excellent
yield, and follow a complementary regiochemical course to related organolithium additions to 1a. Alkyl, aryl, hetaryl, vinyl, and alkynyl ytterbium reagents participate in the reaction, greatly extending the utility of cyclobutene rearrangements by providing a predictable means of introducing this isoprene unit in a regioselective manner. High-level computational studies have provided seminal insights into the nature of organoytterbium intermediates and their reactivity. Of particular note is the realization that reactions proceed via ytterbium ate complexes.

Keywords: density functional calculations - flow chemistry - natural products - rearrangement - ytterbium

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[7] Additions of ortho-, meta-, and hetero-aryl ytterbium reagents to 1b are detailed in the Supporting Information along with further examples of organolithium additions to 1a and 1b and the thermal rearrangements of 21b and 33.

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