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Regioselective C−H Activation and Sequential C−C and C−O Bond Formation Reactions of Aryl Ketones Promoted by an Yttrium Carbene

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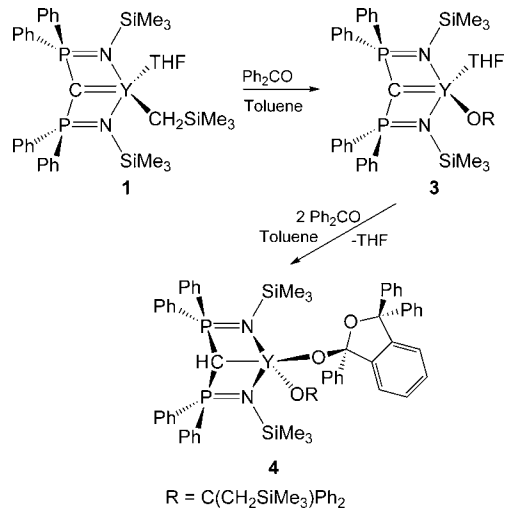
Abstract: Rare earth carbenes exclusively exhibit Wittig-type reactivity with carbonyl compounds to afford alkenes. Here, we report that yttrium carbenes can effect regioselective *ortho*-C−H activation and sequential C−C and C−O bond formation reactions of aryl ketones to give *iso*-benzofurans and hydroxymethylbenzophenones. With MeCOPh, cyclotetramerization occurs giving a substituted cyclohexene. This demonstrates new rare earth carbene reactivity which complements existing Wittig-type reactivity.

Transition metal carbenes are important due to their synthetic applications which are legion.[1] In contrast, rare earth carbenes that do not derive from stable free carbenes are comparatively sparse.[2] This is rationalized on the basis that while novel reactivities are promised due to highly polar bonding, this polarity renders their stabilization a challenge.[3] Consequently, little is known of the intrinsic scope of reactivity of rare earth carbenes.[4]

Following the postulation of rare earth carbenes by Schumann,[5] Cavell structurally evidenced the samarium carbene compound [Sm(L^{PhTMS})(NCy_2)(THF)] [L^{PhTMS} = $C(PPh_2NSiMe_3)_2$; Cy = cyclohexyl],[6] but reactivity studies were not reported. Recently, rare earth carbenes have been characterized in frozen matrices,[7] probed theoretically,[8] isolated using $\{C(PPh_2S)_2\}^{2-}$,[9] and developed by us, e.g. [Y(L^{PhTMS})(R)$(THF)_n$] [R = CH_2SiMe_3, n = 1 (**1**); R = I, n = 2 (**2**)].[10] Without stabilizing phosphorus substituents, polymetallic methylidene clusters result where the carbene is stabilized by coordination to more than one metal.[11] Where rare earth carbene reactivity toward carbonyl compounds has been reported, Wittig-type reactivity to give alkenes has been the exclusive mode of reactivity.[9−13] Herein, we report that yttrium carbenes can effect regioselective C−H activation and sequential C−C and C−O bond formation reactions of aryl ketones to afford substituted *iso*-benzofurans and/or hydroxymethylbenzophenones. When MeCOPh is used, cyclotetramerization occurs to give a substituted cyclohexene. This provides new types of reactivity for rare earth carbenes that are complementary to existing Wittig-type and C_{ketyl}−C_{ketyl}/−H coupling reactivities.[14]

To examine the carbene-based reactivity of **1** toward benzophenone we first converted it to the alkoxide-carbene [Y(L^{PhTMS})-{$OC(CH_2SiMe_3)Ph_2$}(THF)] (**3**), Scheme 1, as DFT calculations suggested that insertion reactivity of the Y−C_{alkyl} bond of **1** would occur before carbene reactivity.[10c] Complex **3** was isolated in 31% crystalline yield and has been fully characterized (Figure 1a).[15] Addition of toluene to a mixture of colorless **3** and 2 equiv of colorless benzophenone resulted in a dark red solution. After a 7 day stir and workup, colorless [Y(L^{PhTMS}H){$OC(CH_2SiMe_3)Ph_2$}O-{$(CPh_2)(OCPh)C_6H_4$}] (**4**) was isolated in 51% yield, Scheme 1. Figure 1b shows the molecular structure of **4**, as determined by X-ray diffraction, which is consistent with the characterization data[15] and confirms the structure.

Scheme 1. Synthesis of **3** and **4**



Substituted *iso*-benzofurans exist in tautomeric equilibria with their hydroxymethylbenzophenone forms.[16] Reasoning that an oxymethylbenzophenone could be a precursor to **4**, we attempted to trap this species using **2**, as in **2** the yttrium center is rendered more electrophilic than in **3** as a consequence of the presence of an iodide rather than an alkoxide coligand, respectively.[10] Thus it

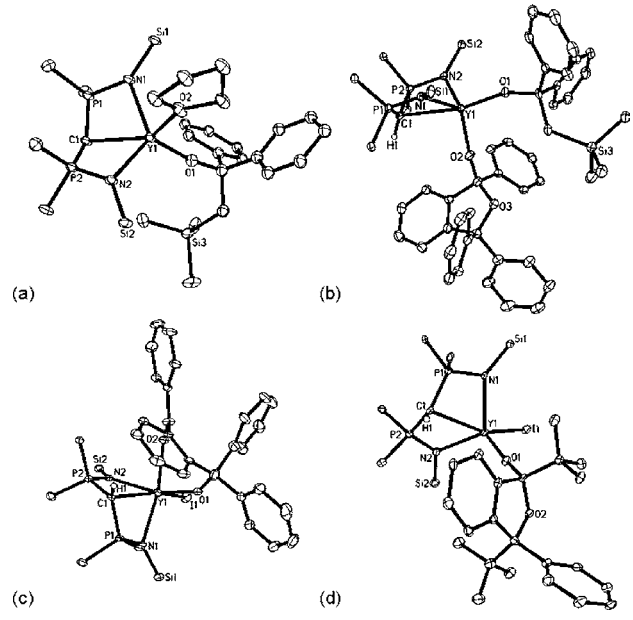
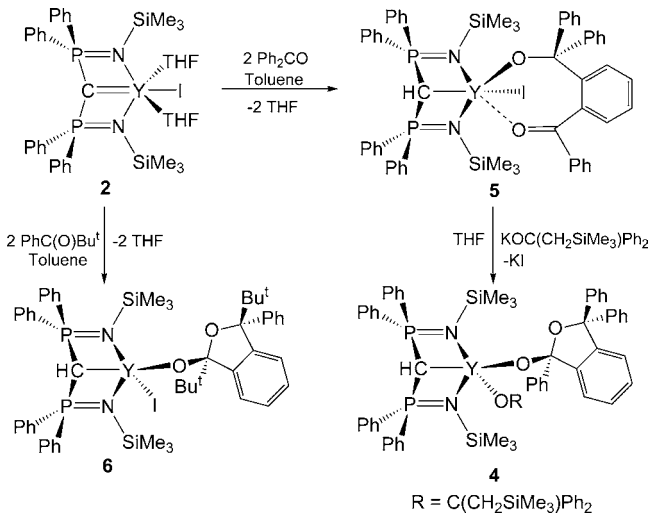


Figure 1. Molecular structures of (a) **3**; (b) **4**; (c) **5**; (d) **6**. Displacement ellipsoids set at 30% probability; peripheral L^{PhTMS} non-*ipso* carbon and nonmethanide hydrogen atoms omitted for clarity.

Scheme 2. Synthesis of **5**, **4** from **5**, and **6**



was anticipated that using **2** would give an yttrium center that would resist the Y−O bond rupture step required for valence tautomerization of the oxymethylbenzophenone.

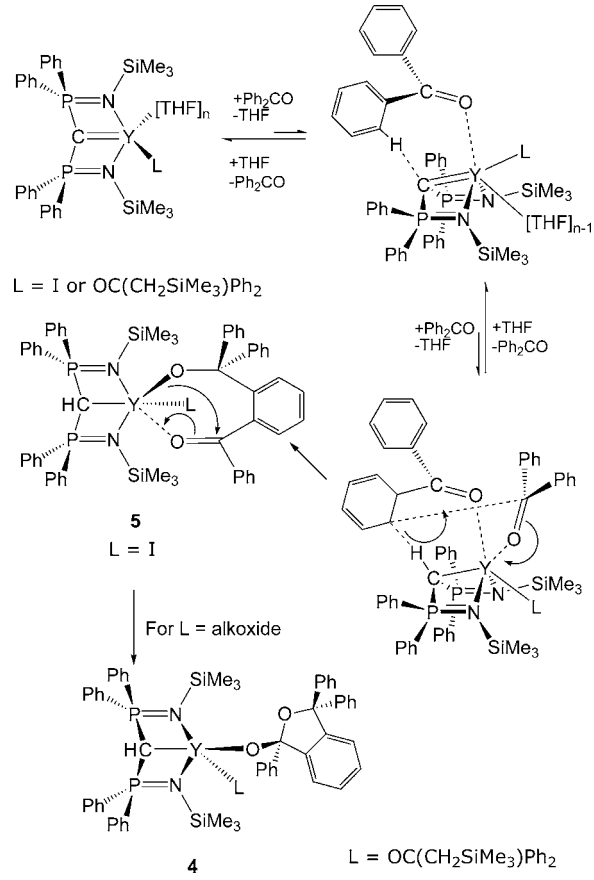
Gratifyingly, treatment of **2** with 2 equiv of benzophenone in toluene resulted in a dark red solution which after workup gave [Y(L^{PhTMS}H){OCPh(C$_6$H$_4$)-2-C(O)Ph$_2$}] (**5**) in 88% yield as a colorless powder, Scheme 2. Figure 1c shows the molecular structure of **5** as determined by X-ray crystallography, which confirmed entrapment of the oxymethylbenzophenone and protonation of the carbene to give a methanide.[15]

To extend this reactivity to diastereomeric products, **2** was treated with 2 equiv of PhCOBu^t to afford [Y(L^{PhTMS}H)(I){O(CPhBu^t)-(OCBu^t)C$_6$H$_4$}] (**6**) in 31% yield as an almost colorless powder, Scheme 2.[15] The crystal structure of **6** was determined, Figure 1d, revealing formation of a diastereomeric *iso*-benzofuran. Whereas the oxymethylbenzophenone tautomer could be trapped with benzophenone, PhCOBu^t gives the *iso*-benzofuran, which we attribute to the Thorpe−Ingold effect.[17]

The intense red color obtained on mixing benzophenone with **2** or **3** in toluene suggests the formation of charge transfer (CT) benzophenone adducts.[15,18] The individual electronic absorption spectra (400−800 nm) of **2** and benzophenone in toluene are featureless. Mixing these solutions gives an absorption $\lambda_{max} = 460$ nm ($\epsilon = 153$ mol^{-1} dm^3 cm^{-1}). This extinction coefficient is low for CT, but only a small proportion of the CT species will be present, as, to coordinate, benzophenone must displace the stronger ligand THF. Germane to this point, solutions of **2** and benzophenone in THF remain colorless and no reaction occurs.

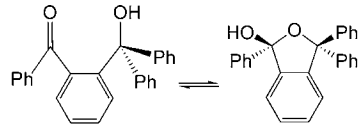
The conversion of **2** to **5**, monitored by ^{31}P NMR spectroscopy, was fitted to second-order kinetics overall (first-order with respect to **2** and Ph$_2$CO) with $k = (2.16 \times 10^{-2}) \pm (0.1 \times 10^{-2})$ mol^{-1} dm^3 s^{-1} (298 K). Eyring and Arrhenius analyses yielded $\Delta H^{\ddagger} = +74.6 \pm 3.0$ kJ mol^{-1} and $\Delta S^{\ddagger} = -44.9 \pm 9.0$ J mol^{-1} K^{-1}, affording $\Delta G^{\ddagger} = +87.9 \pm 3.0$ kJ mol^{-1} (298 K) and $E_a = +77.2 \pm 3.0$ kJ mol^{-1}, which is consonant with the reaction time, which can be decreased to 2 h by conducting the reaction at 50 °C. The relatively low value of $\Delta H^{\ddagger}$ implies a concerted process where bonds are cleaved and formed in a cyclic transition state,[19] which is in line with observations that the concentration of **2** decreases proportionately to the increase in the concentration of **5**. The low, negative $\Delta S^{\ddagger}$ is consistent with closure of the chelate ring in **5** and possibly the loss of THF. Treatment of **2** with 2 equiv of [D$_{10}$]-Ph$_2$CO gave [D$_{20}$]-**5** with deuteration at the carbene confirming the methanide hydrogen in **5** originates from benzophenone. A primary deuterium kinetic isotope effect of $k_H/k_D = 8.7$ was observed which is consistent with the C−H/C−D bond being directly involved in the activation step.[19] Addition of 1 equiv of [K{O(CH$_2$SiMe$_3$)Ph$_2$}] to **5** gave **4** quantitatively which suggests that **5** is the precursor to **4**, Scheme 2.

Scheme 3. Proposed Mechanism for the Yttrium Carbene Promoted Formation of the Oxymethylbenzophenone and Substituted *iso*-Benzofuran Complexes **5** and **4**

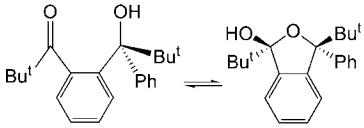


These observations suggest the mechanism illustrated in Scheme 3. Coordination of benzophenone to **3** is followed by *ortho*-C−H aryl activation and protonation of the carbene. This generates an aryl carbanion which attacks a ketyl carbon of another benzophenone molecule to afford the C−C coupled oxymethylbenzophenone in **5**. The thermodynamic data suggest the C−H abstraction and C−C coupling steps are concerted in nature, but we cannot rule out a resting state involving coordination of the carbanion center to yttrium, or indeed the abstracted proton. However, we believe the former is unlikely because through resonance the carbonyl oxygen can acquire substantial alkoxide character, which would render it a better ligand center for the electropositive yttrium than a carbanion. Attempts to isolate the intermediate by treating **3** or **2** with 1 equiv of benzophenone were unsuccessful and, instead, gave 50% conversion to **4** and **5**, respectively. This suggests that the C−H activation step is rate limiting, in line with the observed kinetics, and that the subsequent C−C coupling is rapid, which is consistent with the suggested concerted nature. Finally, rearrangement of the oxymethylbenzophenone to its *iso*-benzofuran form in **4** by C−O bond formation occurs. Whether this latter step occurs depends on the electrophilicity of yttrium, which is modulated by the coligand (iodide or alkoxide), and the steric demands of the ketone substituents. Previous bond activation reactions of ben-

zophenone, subsequently considered to lack acidic hydrogens,[20] were limited to oxidative addition to a silylene[21] or metal-mediated redox couplings,[22] but redox chemistry at d^0 yttrium is unlikely.[23]



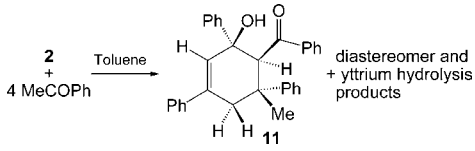
7 **8**



9 **10**

Preliminary attempts to liberate the organic products from **4**−**6** gave empirically pure pale yellow oils identified as mixtures of each tautomer pair (**7**/**8**; **9**/**10**) in yields of 49% and 32%. These tautomers are easily interconverted[16] and represent valuable, easy to prepare synthons to a range of chiral pyrrolidines and furans.[24] Optimization of product yields and extension of this new reactivity to afford dihydrofurans and furanones could potentially provide key precursors to a large number of biologically active compounds, e.g. phthalides,[25] in a straightforward one-pot method at modest cost in comparison to efficient but expensive precious metal catalysts.

Scheme 4. Synthesis of **7**



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When the enolizable ketone MeCOPh is reacted with **2**,[26] C−H activation at the α-methyl group occurs in preference to *ortho*-C−H activation, and cyclotetramerization/dehydration occurs to give the substituted cyclohexene dypnopinacol **11** in 25% crystalline yield after workup, Scheme 4.[15] This is in contrast to the reactivity of [Ta(CHBu^t)(CH$_2$Bu^t)$_3$], which reacts with enolizable carbonyls to give Wittig alkene products,[27] and to the best of our knowledge no rare earth carbene reactivity with enolizable carbonyls has been reported. The reaction eliminates 2 mol equiv of water, which precluded further mechanistic study. Although the reaction is stoichiometric, the cyclotetramerization is achieved in one pot whereas previous preparations of dypnopinacol are multistep.[28]

To conclude, new modes of reactivity for rare earth carbenes are reported. This reactivity is regioselective and incorporates C−H activation and C−C and C−O bond formation in one-pot reactions to selectively give products that represent precursors to a range of potentially valuable organic derivatives. The *ortho*-C−H activation reactivity described herein does not yet constitute a catalytic cycle, but we[10b] and Le Floch have demonstrated that the methanide-carbene back-reaction is feasible.[29] Detailed studies aiming to establish catalytic reactivity and broaden the scope of this yttrium carbene reactivity are underway.

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Supporting Information Available: Experimental, X-ray, and mechanistic data for **3**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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