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Oxidative Carbon–Carbon Bond Formation via Silyl Bis-enol Ethers: Controlled Cross-Coupling for the Synthesis of Quaternary Centers

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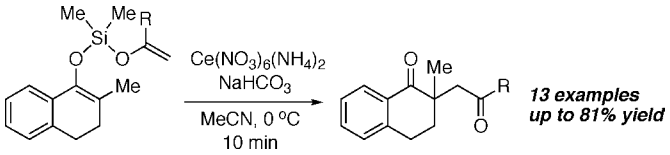
ABSTRACT



Unsymmetrical silyl bis-enol ethers have been developed as effective substrates for synthesizing quaternary centers from tetralone derivatives through oxidative carbon–carbon bond formation. The derived products are shown to be highly versatile intermediates that may be used to generate diverse structures such as cyclopentenones, 2*H*-pyrroles, and spirocyclic pyrrolidines.

The oxidative coupling of enolates, first reported in 1935,[1] provides direct access to highly versatile 1,4-dicarbonyl intermediates.[2] A major limitation of this chemistry lies with the lack of methods that allow for selective and controlled heterocoupling of two different enolates. For many cases a mixture of both homo- and heterocoupled products are obtained (Figure 1, eq 1). Recently, Baran and co-workers demonstrated that a number of selective cross-couplings can be achieved when the oxidation potential between the substrates is significantly different, such as between an amide or ester enolate and a ketone enolate.[3] In the case of silyl enol ethers, cross-coupling can typically only be achieved by using an excess of one enol silane.[4] Narasaka's solution involved the use of enamines, which are preferentially oxidized over enol silanes.[5] MacMillan's recently disclosed catalytic enantioselective oxidative coupling uses enamine catalysis to gain impressive selectivity.[6] To date, no general method for controlled oxidative ketone−ketone cross-coupling has been reported.

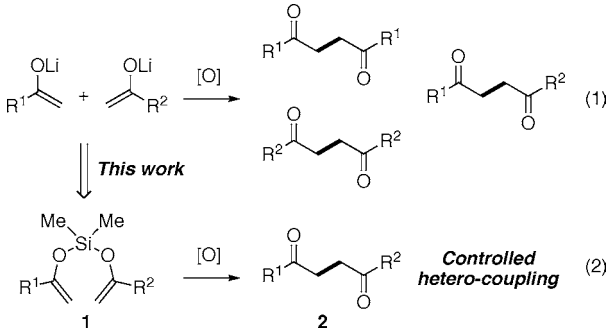


Figure 1. General approach toward controlled oxidative carbon−carbon bond formation.

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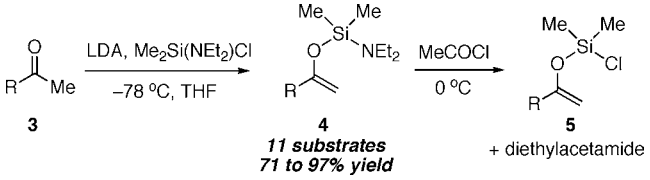
As part of our program directed at synthesizing bioactive polycyclic molecules, we became interested in using silyl bis-enol ethers to generate quaternary centers through intramolecular oxidative bond formation. We were encouraged by a report in 1998 by Schmittel and co-workers who revealed that symmetrical silyl bis-enol ethers will undergo oxidative bond formation to generate 1,4-diketones.[7] Despite the potential utility of this process to generate unsymmetrical 1,4-diketones, it has never been fully developed.[8] We now describe the development of an efficient method for selective ketone−ketone oxidative cross-coupling for the synthesis of quaternary centers, which is based on the use of unsymmetrical silyl bis-enol ethers. The basic concept is outlined in eq 2 of Figure 1.

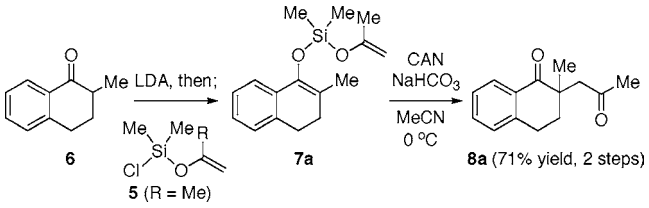
Our initial studies were directed at preparing unsymmetrical silyl bis-enol ethers derived from 2-methyltetralone (**6**) and a variety of methyl ketones. Rathke and Weipert have reported a general method for the synthesis of unsymmetrical silyl bis-enol ethers based on generating chlorosilanes (**5**) in situ from enol silylamines (**4**) and acetyl chloride.[9] Subsequent addition of NaI, triethylamine and the second ketone afforded the desired product in good yield. These conditions, however, led to mixtures of regioisomeric products when ketones with two sets of enolizable positions are used. Therefore, we developed a modified procedure based on Corey's conditions for selective kinetic generation of enol silanes from methyl ketones.[10] Thus, addition of the methyl ketone **3** to a mixture of both LDA and chloro-*N*,*N*-diethylamino-dimethylsilane at −78 °C affords excellent regioselectivity for the desired enol ethers (i.e., **4**). Evaporation of the solvent, trituration with pentanes to remove LiCl, and subsequent distillation provides good to excellent yields for a range of enol silylamines **4** (Scheme 1).[11]

Scheme 1. Regioselective Synthesis of Enol Silylamines



The addition of acetyl chloride to a solution of **4** (R = Me) resulted in rapid formation (<10 min) of the corresponding chlorosilane **5** (R = Me) and diethylacetamide as indicated by ^{1}H NMR spectroscopy. Enolization of 2-methyltetralone (**6**) with LDA, followed the addition of the chlorosilane **5** (R = Me) generated from **4** (R = Me), resulted in clean formation of the desired unsymmetrical silyl bis-enol ether **7a** (Scheme 2). While purification of the silyl bis-enol ether by flash chromatography may be achieved, we found this to be unnecessary due to the effectiveness of the synthesis. Only 1.1 equiv of enol silane **4** (R = Me) was used in relation to 2-methyltetralone **(6)**. This stoichiometry will have important consequences for the use of this chemistry in carrying out complex fragment couplings in the context of total synthesis.

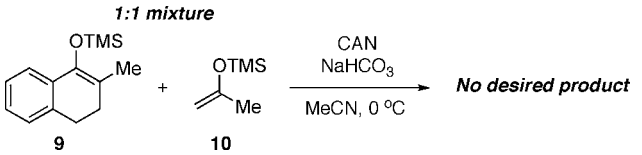
Scheme 2. Conditions for Oxidative C−C Bond Formation



Our initial exploration of potential oxidants utilized enol silane **7a**. Cu(OTf)$_2$[2g] has been reported to be a good oxidant for TMS-enol ether coupling but in our hands gave <10% of the desired adduct **8a**. Cerium(IV) ammonium nitrate (CAN)/NaHCO$_3$[4a] was quickly found to be the oxidant of choice, providing diketone **8a** in an overall yield of 71% from 2-methyltetralone (Scheme 2).

As a control experiment, a 1:1 mixture of the TMS-enol silanes derived from 2-methyltetralone (i.e., **9**) and acetone (i.e., **10**) was exposed to the reaction conditions. The complex reaction mixture that resulted contained little or none of the desired adduct **8a** (Scheme 3).

Scheme 3. Control Experiment



The scope of the methyl ketone component was explored next and was general for a variety of substrates (Table 1). Aliphatic substrates are well tolerated, providing moderate to good yields of the 1,4-diketone products (entries 1−7). As can be seen, increasing steric hindrance led to a decrease in overall reaction efficiency. While β-substitution on the methyl ketone fragment was well tolerated, providing **8e** in 61% overall yield (Table 1, entry 5), α-substitution resulted in lower yields. Isopropyl and tertiary butyl substituents afforded the corresponding products in 50% and 41% yield, respectively (Table 1, entries 6 and 7). Aryl substituents

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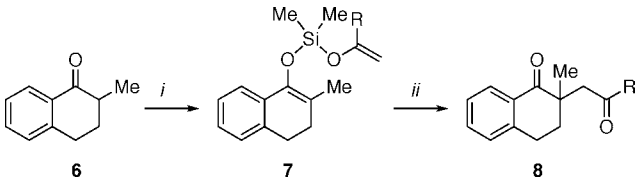
(11) For R = Me and R = *t*-Bu, enol silylamines prepared according to ref. 9.

Table 1. Substrate Scope for 2-Methyltetralone Derived Compounds[a]

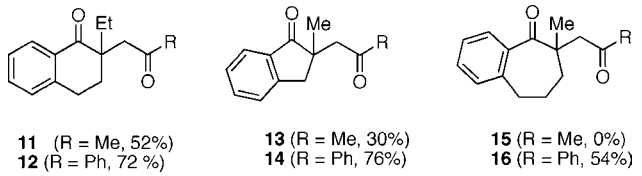


entry	R	overall yield **8** (%)[b]
1	Me (**7a**)	71 (**8a**)
2	Et (**7b**)	62 (**8b**)
3	*n*-Pr (**7c**)	61 (**8c**)
4	CH_2CH_2Ph (**7d**)	51 (**8d**)
5	*i*-Bu (**7e**)	61 (**8e**)
6	*i*-Pr (**7f**)	50 (**8f**)
7	*t*-Bu (**7g**)	41 (**8g**)
8	Ph (**7h**)	81 (**8h**)
9	4-Cl−Ph (**7i**)	72 (**8i**)
10	4-OMe−Ph (**7j**)	73 (**8j**)
11	4-Me−Ph (**7k**)	73 (**8k**)
12	CH=CHPh (**7l**)	75 (**8l**)
13	C≡C−Ph (**7m**)	54 (**8m**)

[a] Reagents and conditions: (i) 1.5 mmol **6**, LDA (1.1 equiv), −78 °C to 0 °C; then **4** (1.1 equiv)/MeCOCl (1.0 equiv); (ii) CAN (2.0 equiv), $NaHCO_3$ (4.0 equiv), MeCN, 0 °C. [b] Isolated yield.

provided good yields, with both electron-rich and electron-poor systems behaving similarly (entries 8−11). Cross-conjugated enol silanes derived from α,β-unsaturated ketones (i.e., **7l** and **7m**) were also suitable compounds (Table 1, entries 12 and 13).

Having established the methodology as useful for 2-methyltetralone substrates, we investigated the use of other cyclic aryl ketones (Figure 2). 2-Ethyltetralone was an effective



11 (R = Me, 52%)
12 (R = Ph, 72 %)

13 (R = Me, 30%)
14 (R = Ph, 76%)

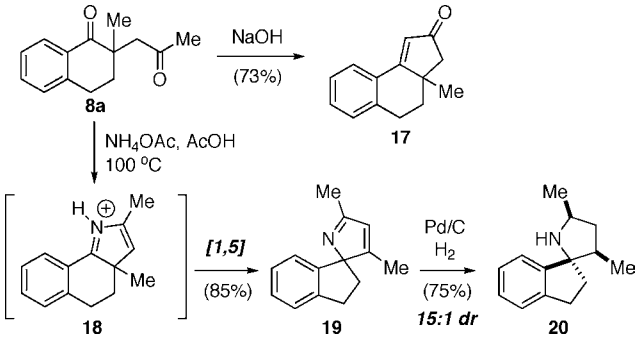
15 (R = Me, 0%)
16 (R = Ph, 54%)

Figure 2. Variation of substituted enolate component.

reaction partner with both acetone and acetophenone derived systems (**11** and **12**, respectively). 2-Methylindanone provided only 30% of dione **13** (R = Me), whereas dione **14** (R = Ph) was obtained in 76% yield. Such dramatic differences in yield were also observed when 2-methylbenzosuberone was used as a substrate. To date, 2-methylcyclohexanone has not proven to be a synthetically useful reaction partner (<10% yield with acetophenone). We are currently engaged in solving this issue in order to fully expand the scope of this methodology.

We were also interested in utilizing the versatility of the 1,4-diketone products by using straightforward reactions to create a diverse array of structures (Scheme 4).

Scheme 4. Substrate Diversity from Dione **8a**



Cyclopentenone **17**[12] was accessed from **8a** by NaOH-mediated aldol condensation (73% yield). Thus, the three-step procedure from 2-methyltetralone (**6**) represents an efficient strategy for cyclopentenone annulation.[13] Condensation of **8a** with ammonium acetate in acetic acid at 100 °C afforded the corresponding 2*H*-pyrrole **19**. We had initially hoped to isolate the 3*H*-pyrrole, but under the acidic reaction conditions a ring contraction of protonated 3*H*-pyrrole **18** ensued to generate the spirocycle **19**. This interesting transformation presumably proceeds through a selective [1,5]-sigmatropic alkyl shift.[14] 2*H*-Pyrrole **19** was selectively reduced (15:1 dr) to pyrrolidine **20** upon treatment with Pd/C and H_2. The X-ray crystal structure of the HCl salt of **20** confirmed that hydrogenation occurred anti to the large aromatic ring.[15] We are currently exploring the generality of this ring contraction/hydrogenation sequence in order to prepare stereochemically rich spirocyclic alkaloids

In summary, we have developed unsymmetrical silyl bis-enol ethers as effective substrates for crossed-ketone oxidative coupling reactions of tetralone derivatives. Using these compounds provides a general method for the preparation of quaternary centers in a convergent manner. Current and future research is directed at expanding the scope of silyl bis-enol ether-based transformations and applying this chemistry to the synthesis of bioactive polycyclic natural products.

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Supporting Information Available: Experimental procedures, spectral data, and crystallographic data (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) See Supporting Information for details.