

# Oxidative Carbon–Carbon Bond Formation via Allyldimethylsilyl Enol Ethers

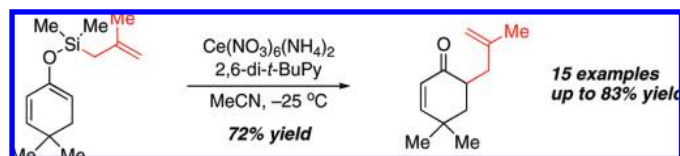
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## ABSTRACT



A method for the oxidative alkylation of ketones through intramolecular allyl-group transfer within preformed allyldimethylsilyl enol ethers is reported. A number of examples are detailed, including a study into the effects of resident stereocenters within cyclic enol ethers.

Ceric ammonium nitrate (CAN) is a powerful single electron oxidant that has significant demonstrated utility in promoting a wide range of useful synthetic transformations.<sup>1</sup> Our interest in CAN as a reagent stemmed from an initial desire to elaborate the synthetic potential of silyl bis-enol ethers, an area we have been actively developing.<sup>2</sup> While the 1,4-diketone adducts derived from silyl bis-enol ether oxidation are of significant value for synthesis, we wished to extend this general reactivity to other species and herein report the development of an intramolecular oxidative allylation from allylsilyl enol ethers.

We were drawn to the work published by the groups of Hwu<sup>3</sup> and Flowers,<sup>4</sup> who have each shown that 1,3-dicarbonyl species undergo effective oxidative allylation with

allyltrimethylsilane in the presence of CAN.<sup>5,6</sup> The scope of these transformations is limited to enolizable 1,3-dicarbonyls since the first step of the reaction pathway is most likely oxidation of the enol tautomer to an intermediate radical cation. We speculated that exposure of an allyldimethylsilyl enol ether (i.e., **1**) to CAN might induce intramolecular bond formation via radical-cation **2**, which would collapse to produce cyclic intermediate **3** (Figure 1). Si–C and Si–O bond cleavage, along with a second single electron oxidation would then produce the desired adduct **4**.<sup>7</sup> Related examples of intermolecular allylation of  $\beta$ -carbonyl imines,<sup>8</sup> and one example of a vinylogous amide<sup>9</sup> have been reported. Moeller and co-workers have shown that intramolecular

(1) For a comprehensive recent review, see: Nair, V.; Deepthi, A. *Chem. Rev.* **2007**, *107*, 1862–1891.

(2) (a) Clift, M. D.; Taylor, C. N.; Thomson, R. J. *Org. Lett.* **2007**, *9*, 4667–4669. (b) Avetta, C. T.; Konkol, L. C.; Taylor, C. N.; Dugan, K. C.; Stern, C. L.; Thomson, R. J. *Org. Lett.* **2008**, *10*, 5621–5624. (c) Clift, M. D.; Thomson, R. J. *J. Am. Chem. Soc.* **2009**, *131*, 14579–14583. See, also: (d) Schmitt, M.; Burghart, A.; Malisch, W.; Reising, J.; Sollner, R. *J. Org. Chem.* **1998**, *63*, 396–400. (e) Schmitt, M.; Haeuseler, A. *J. Organomet. Chem.* **2002**, *661*, 169–179.

(3) Hwu, J. R.; Chen, C. N.; Shiao, S.-S. *J. Org. Chem.* **2002**, *60*, 856–862.

(4) (a) Zhang, Y.; Raines, A. J.; Flowers, R. A. *Org. Lett.* **2003**, *5*, 2363–2365. (b) Devery, J. J., III; Mohanta, P. K.; Casey, B. M.; Flowers, R. A., II *Synlett* **2009**, 2009, 1490–1494.

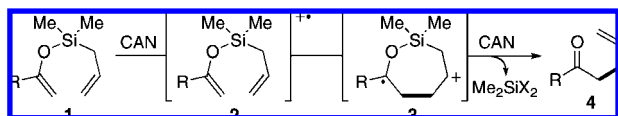
(5) Phenols have been shown to undergo a related oxidative allylation, see: Sabot, C.; Commare, B.; Duceppe, M.-A.; Nahi, S.; Guérard, K. C.; Canesi, S. *Synlett* **2008**, 2008, 3226–3230.

(6) Hirao and coworkers have reported that oxidative allylation of 1,3-dicarbonyl compounds with allylsilanes can be achieved using  $\text{VO}(\text{OEt})\text{Cl}_2$  as the oxidant, see: Hirao, T.; Sakaguchi, M.; Ishikawa, T.; Ikeda, I. *Synth. Commun.* **1995**, *25*, 2579–2585.

(7) The exact timing of the process from intermediate **3** onwards is unclear. It seems likely that cleavage of the Si–C bond precedes the second oxidation and Si–O bond cleavage. X in Figure 1 is most likely nitrate, although it is known that cleavage of Si–C bonds in radical cations is accelerated by nucleophilic solvents such as acetonitrile, see: Dinnocenzo, J. P.; Farid, S.; Goodman, J. L.; Gould, I. R.; Mattes, S. L.; Todd, W. P. *J. Am. Chem. Soc.* **2002**, *124*, 8973–8975.

(8) Zhang, Y.; Raines, A. J.; Flowers, R. A., II *J. Org. Chem.* **2004**, *69*, 6267–6272.

allylation of enol ethers with allylsilanes is possible when the silane is part of the ketone (i.e., linked through the carbon backbone rather than the enol oxygen such as in our system).<sup>10</sup> MacMillan and co-workers have elegantly demonstrated the power of their SOMO activation strategy by developing an enantioselective allylation of aldehydes using organocatalysis.<sup>11</sup> Against this background, the method for intramolecular allylation of unactivated ketones (i.e., not 1,3 dicarbonyls) that we report herein expands the scope of compounds that may be accessed through oxidative coupling.

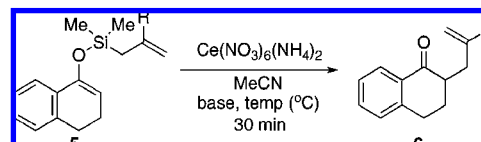


**Figure 1.** Proposed intramolecular oxidative allylation.

We began our study by preparing the allyldimethylsilyl ether derived from tetralone (i.e., **5a**, R = H), since such ketones had proved exceptional in our prior work on silyl bis-enol ether oxidative coupling. Preparation of the substrate was trivial and involved the addition of commercially available chloro allyldimethylsilane to the lithium enolate of tetralone.<sup>12</sup> Exposure of **5a** (R = H) to the standard set of conditions known to promote oxidative coupling of enol silanes led to formation of the desired material in 51% yield (Table 1, entry 1). Conducting the reaction at a lower temperature (−30 °C) increased the yield to 57% (Table 1, entry 2), while use of 2,6-di-*t*-butylpyridine (DTBP) afforded a 46% yield of **6a** (R = H). The addition of a base is required in these reactions to minimize decomposition of the acid-sensitive enol ether; exposure of **5a** (R = H) to CAN in the absence of a base gave exclusively tetralone (Table 1, entry 4). We investigated the use of other oxidants known to promote enol silane coupling, such as Ag<sub>2</sub>O and Cu(OTf)<sub>2</sub>/Cu<sub>2</sub>O, but these provided none of the desired product. At this juncture, we prepared the allyldimethylsilyl enol ethers of several other ketones, but were disappointed to obtain generally low yields. We speculated that the general lack of scope might be due to the poor nucleophilicity of the allyl group. If intramolecular C–C bond formation from the initial radical-cation (akin to **2** → **3** in Figure 1) is slow, then unproductive Si–O bond cleavage may compete and lead to diminished yields. Allylsilanes possessing electron-releasing substituents at C2 are known to be more nucleophilic than unsubstituted systems,<sup>13</sup> so we investigated the methallylsilyl enol ether **5b** (R = Me).<sup>11</sup> Exposure of **5b** to CAN/

NaHCO<sub>3</sub> at −30 °C provided only 39% yield of **6b** (Table 1, entry 5), but when conducted at −40 °C gave an enhanced 52% yield (Table 1, entry 6). Unlike for the simple allyl system (i.e., **5a**), replacing NaHCO<sub>3</sub> with 2,6-di-*t*-butylpyridine led to a further improvement in yield to 83% (Table 1, entry 7). Under these conditions the benzyloxy substituted silyl ether **5c** (R = CH<sub>2</sub>OBn)<sup>9</sup> gave 62% yield of the desired allylated ketone **6c** (R = CH<sub>2</sub>OBn), indicating that functionalized allyl fragments may be employed with this chemistry.

**Table 1.** Initial Development of the Oxidative Allylation<sup>a</sup>



entry	R	base	temp (°C)	yield (%) <sup>b</sup>
1	H ( <b>5a</b> )	NaHCO <sub>3</sub>	0	51
2	H ( <b>5a</b> )	NaHCO <sub>3</sub>	−30	57
3	H ( <b>5a</b> )	2,6-di- <i>t</i> -BuPy	−30	46
4	H ( <b>5a</b> )	none	−30	0
5	Me ( <b>5b</b> )	NaHCO <sub>3</sub>	−30	47
6	Me ( <b>5b</b> )	NaHCO <sub>3</sub>	−40	52
7	Me ( <b>5b</b> )	2,6-di- <i>t</i> -BuPy	−40	83
8	CH <sub>2</sub> OBn ( <b>5c</b> )	2,6-di- <i>t</i> -BuPy	−40	62

<sup>a</sup> **5** (1.0 mmol), 0.1 M MeCN. <sup>b</sup> Isolated yield after chromatography.

Given the limited results obtained with the simple allyldimethylsilyl enol ether when we attempted to use ketones other than tetralone, we wished to conduct an analysis of ketone scope for the 2-substituted allylsilanes (Table 2, prepared in 59–99% yield from the corresponding ketones, see Supporting Information). In general, the 2-substituted allylsilanes gave good yields of the allylated material on exposure to CAN/DTBP (Table 2, entries 1 and 2). When 2-methyltetralone was used as the ketone substrate, the oxidative allylation procedure led to smooth generation of a quaternary stereocenter in good yield (Table 2, entry 3). Acyclic α-aryl substituted ketones also proved to be suitable substrates for the reaction. For example, the allylsilanes (R = Me or CH<sub>2</sub>OBn) derived from propiophenone, gave 81% and 59% yields of the respective allylated adduct (Table 2, entry 4). The 2-acetylfuran derived system also performed well in the reaction (Table 2, entry 5).

Surprisingly, the oxidative allylation of carvone afforded low levels of diastereoselectivity, which stood in contrast to what we have observed in our ketone–ketone cross-coupling.<sup>2b</sup> The locked bicyclic enol silane derived from trans-decalone, however, produced a 3:1 mixture favoring of the axial product **8j** (43% isolated yield of single

(9) Chandra, A.; Pigza, J. A.; Han, J.-S.; Mutnick, D.; Johnston, J. N. *J. Am. Chem. Soc.* **2009**, *131*, 3470–3471. Narasaka and coworkers reported two examples of an alkene adding to a vinylogous amide under the action of CAN, see: Narasaka, K.; Okauchi, T.; Tanaka, K.; Murakami, M. *Chem. Lett.* **1992**, 2099–2102.

(10) Hudson, C. M.; Marzabadi, M. R.; Moeller, K. D.; New, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 7372–7385.

(11) Beeson, T. D.; Mastracchio, A.; Hong, J. B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582–585.

(12) See Supporting Information for full experimental details.

(13) For a systematic analysis and discussion of such relative nucleophilicities, see: Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500–9512.

**Table 2.** Ketone Scope of the Oxidative Allylation<sup>a</sup>

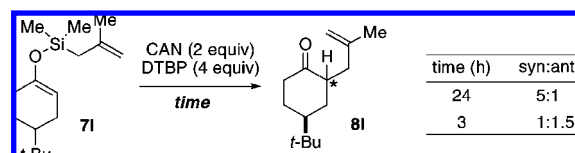
entry	ketone (7)	R	product (8)	R	yield [%] <sup>b</sup> (dr) <sup>c</sup>
1		Me (7a)		Me (8a)	72
		CH <sub>2</sub> OBn (7b)		CH <sub>2</sub> OBn (8b)	51
2		Me (7c)		Me (8c)	56 (1:1)
		CH <sub>2</sub> OBn (7d)		CH <sub>2</sub> OBn (8d)	67 (1:1)
3		Me (7e)		Me (8e)	73
		CH <sub>2</sub> OBn (7f)		CH <sub>2</sub> OBn (8f)	61
4		Me (7g)		Me (8g)	81
		CH <sub>2</sub> OBn (7h)		CH <sub>2</sub> OBn (8h)	59
5		Me (7i)		Me (8i)	73
6		Me (7j)		Me (8j)	43 <sup>d</sup> (3:1)
7		Me (7k)		Me (8k)	76 (20:1)
8		Me (7l)		Me (8l)	52 (5:1)

<sup>a</sup> Standard conditions for oxidative allylation: **7**, CAN (2.0 equiv), 2,6-di-*t*-BuPy (4.0 equiv), 0.1 M MeCN, −25 °C, 0.5–24 h. <sup>b</sup> Isolated yield after chromatography. <sup>c</sup> Determined by <sup>1</sup>H NMR spectroscopy. <sup>d</sup> Isolated yield of single isomer.

diastereomer, Table 2, entry 6). We also wished to determine the effect a more remote stereocenter at C4 would have on the facial selectivity. To probe this issue, the enol allylsilanes of 4-*t*-Bu-cyclohexenone and of 4-*t*-Bu-cyclohexanone were prepared and exposed to conditions for effecting oxidative bond formation. Allylation of the cyclohexenone derivative proceeded in 76% yield as a 20:1 mixture of diastereomers, favoring the 1,3-anti isomer **8k** (Table 2, entry 6). The corresponding saturated derivative gave a slightly diminished yield (52%), but favored the syn isomer **8l** (5:1 syn to anti).

At first glance the preferential formation of the 1,3-syn isomer **8l** from *t*-Bu-cyclohexanone derivative **7l** (Table 2, entry 7) was surprising, given the results for **7k** (Table 2, entry 6) and the well documented preference for axial alkylation in similar systems.<sup>14</sup> We suspected that under the mildly basic reaction conditions, the less stable 1,3-anti isomer would undergo epimerization to the thermodynamically

favoured 1,3-syn isomer. Independent synthesis of the 1,3-anti isomer,<sup>15</sup> and its subsequent exposure to the reaction conditions confirmed that significant isomerization was occurring (9:1 anti:syn → 1:5 anti:syn after 24 h at −25 °C). In light of this result, we assessed the diastereoselectivity as a function of reaction time (Figure 3). Typical reaction times for the oxidative allylation of **7l** were about 24 h and afforded a 5:1 ratio of syn to anti isomers. Quenching the reaction after just 3 h, however, revealed a modest preference for the anti diastereomer indicating that kinetic axial alkylation was occurring to a significant extent, but the extended reaction times required for all the starting material to be consumed allowed for significant product isomerization. In light of these details, the poor diastereoselectivity of the carvone-derived allyl silanes (**7c** and **7d**) may be attributed to an internal competition between axial addition leading to the syn isomer and allylation anti to the isopropenyl substituent. In this instance there appears to be no bias for one stereochemical course over the other.<sup>16</sup>

**Figure 3.** Product stereochemistry with respect to reaction time.

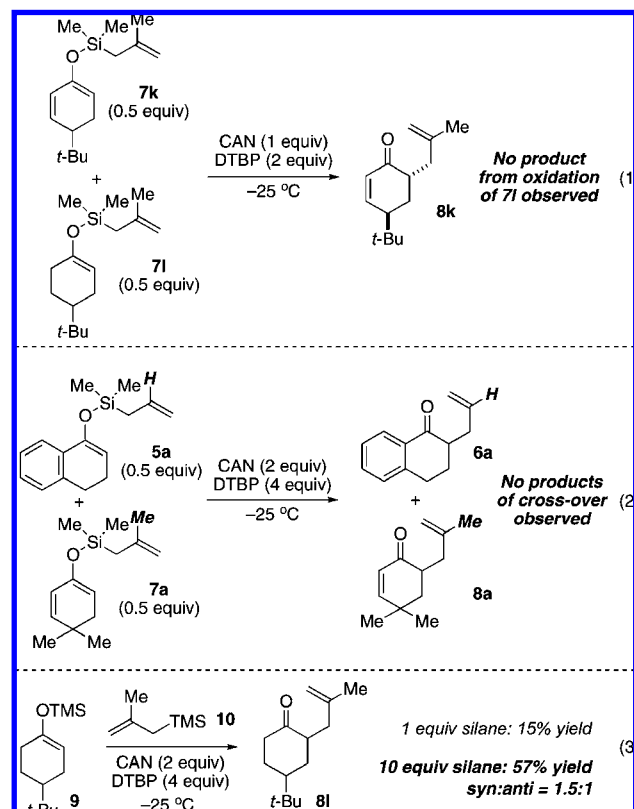
The diminished yields for saturated systems (i.e., entries 6 and 8, Table 2) relative to aryl and unsaturated derivative systems, is most likely a consequence of slower oxidation of the less electron-rich nonconjugated  $\pi$ -system and subsequent generation of a less stable initially formed radical-cation intermediate. We probed this issue by conducting an experiment where an equimolar ratio of **7k** and **7l** were exposed to only enough CAN to oxidize one substrate completely. Our hypothesis regarding the different reactivity proved correct: only the unsaturated derivative **7k** underwent oxidative allylation to form **8k**, and the corresponding adduct of the saturated derivative **7l** was not observed (eq 1, Figure 4).

Crossover experiments were conducted to determine whether the reaction was proceeding solely through intramolecular delivery of the allyl fragment (Figure 4). Accordingly, a 1:1 mixture of the allylsilanes **5a** and **7a**, each of which performed well on their own, was exposed to the oxidation conditions and the product mixture analyzed (eq 2, Figure 4). Only the products of intramolecular delivery were

(14) (a) Corey, E. J.; Sreen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6269–6278. (b) Velluz, L.; Valls, J.; Nominé, G. *Angew. Chem., Int. Ed.* **1965**, *4*, 181–200. (c) Evans, D. A. In *Asymmetric Synthesis*, Vol 3; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; p 2.

(15) Prepared by a modification of the procedure for axial alkylation reported by: Lightner, D. A.; Bouman, T. D.; Vincent Crist, B.; Rodgers, S. L.; Knobloch, M. A.; Jones, A. M. *J. Am. Chem. Soc.* **1987**, *109*, 6248–6259.

(16) Resubjection of the 1:1 mixture of diastereomers of **8c** to the reaction conditions led to equilibration to the favored anti isomer.



**Figure 4.** Experiments to gain insight into the reaction process.

observed. We also investigated whether intermolecular oxidative allylation could be achieved when using an external

nucleophile. In the event, exposure of the TMS-enol ether of 4-*t*-Bu-cyclohexanone (i.e., **9**) to CAN/DTBP in the presence of one equivalent of allylsilane **10** gave little of the desired adduct **8l**. By increasing the amount of allylsilane used to ten equivalents, a chemically efficient allylation could be achieved (57% yield), albeit as a 1.5:1 mixture of diastereomers. The necessary use of excess silane negates this alternative as a possible fragment coupling for advanced precursors, and serves to highlight the utility of the intramolecular allylation in the context of complex molecule synthesis.

To summarize, we have successfully expanded the scope of silicon-tethered oxidative carbon–carbon bond formation to allow for allylation of ketones. The reaction was shown to be compatible with aryl ketones, enones, and saturated systems. This new method for allylation offers an additional synthetic tool for chemists for cases where direct enolate alkylation, Claisen rearrangement or palladium-catalyzed methods are insufficient to achieve construction of the desired molecule.

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**Supporting Information Available:** Experimental procedures and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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