

Diastereoselective Oxidative Carbon–Carbon Bond Formation via Silyl Bis-enol Ethers

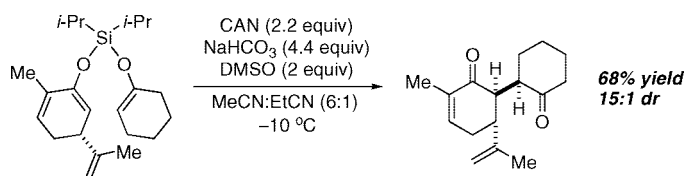
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Received October 30, 2008

ABSTRACT



Diisopropylsilyl bis-enol ethers are shown to be powerful intermediates for the diastereoselective dimerization and cross-coupling of cyclic ketones. The trends observed for the oxidative coupling of a range of different dialkylsilyl bis-enol ethers derived from cyclohexanone are rationalized by invoking a stereochemical model based on a Thorpe–Ingold effect.

Reliable bond-forming reactions that produce multiple stereocenters are of significant strategic value for the synthesis of complex natural products since retrosynthetic application of such transformations allows for rapid clearance of stereocenters while simultaneously enforcing a convergent synthesis plan.¹ As part of our program directed toward synthesizing bioactive polycyclic molecules, we sought to develop methods to effect the stereocontrolled oxidative coupling of cyclic ketones and thus provide a convergent route to linked bicyclic ring systems prevalent in numerous natural products, such as the lomaiviticins.² The oxidative

coupling of enolates has been known for over 70 years,³ but it is only in relatively recent times that synthetically useful procedures for cross-coupling have emerged.⁴ Recently, we demonstrated the utility of silyl bis-enol ethers for controlled cross-coupling and quaternary stereocenter generation.⁵ Despite these advances, it is still difficult to conduct the cross-coupling of substrates with similar oxidation potentials, and diastereoselective cross-coupling remains largely undeveloped.

Previous literature reports have shown that the dimerization of lithium enolates or trimethylsilyl enol ethers derived from cyclohexanone produce the 1,4-diketone in modest yield and with low levels of diastereocontrol.⁶ Schmittel and co-workers have shown that silicon-tethered enol silanes may be used to prepare the dimer of propiophenone with good

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

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(7) (a) Schmittel, M.; Burghart, A.; Malisch, W.; Reising, J.; Sollner, R. *J. Org. Chem.* **1998**, *63*, 396–400. (b) Schmittel, M.; Haueseler, A. *J. Organomet. Chem.* **2002**, *661*, 169–179.

stereoselectivity,^{7a,8} and they have reported a single example of a diastereoselective cross-coupling between propiophenone and 1-*p*-tolylpropan-1-one.^{7b} Given the synthetic potential of these silyl bis-enol ethers, it is somewhat surprising that these are the only diastereoselective examples reported in the literature. Our interest in preparing complex linked bicyclic structures led us to explore the generality of silyl bis-enol ethers for preparing synthetically useful intermediates beyond the acyclic aryl ketones explored by Schmittl and co-workers. We now report general conditions to enable oxidative dimerization and cross-coupling of cyclic ketones in good yield and with high diastereoselectivities.

Table 1. Influence of Silicon Substituents on Stereoselectivity

entry	R ₂ Si	dr (2:3) ^a	yield 2 (%) ^b
1	Me ₂ Si (1a)	2.4:1	29
2	Et ₂ Si (1b)	5:1	47
3	<i>i</i> -Pr ₂ Si (1c)	10:1	57
4	Ph ₂ Si (1d)	5:1	29
5	 n=1 (1e)	3:1	31
6	 n=2 (1f)	6:1	56

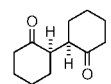
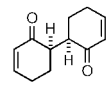
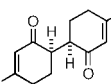
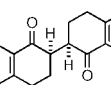
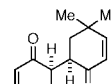
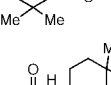
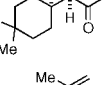
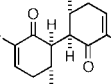
^a Diastereomeric ratio determined by ¹H NMR spectroscopy on unpurified reaction mixture. ^b Isolated yield of **2** after chromatography.

We initiated our research by preparing the dimethylsilyl bis-enol ether derived from cyclohexanone (i.e., **1a**)⁹ and conducted the oxidative coupling using a mixture of cerium(IV) ammonium nitrate (CAN) and NaHCO₃. Under these conditions, we obtained a low yield and modest stereoselectivity for the chiral isomer **2** over the *meso*-isomer **3** (Table 1, entry 1). While we were encouraged by the modest stereoselectivity, we were disappointed with the low yield obtained. Consequently, we elected to investigate a number of variables that might influence both the yield and stereoselectivity of this bond-forming process. We found that the size of the silicon substituents had a dramatic effect on both of these variables. While diethylsilyl ether **1b** afforded dione **2** as a 5:1 mixture of diastereomers and with an improved yield (Table 1, entry 2), the bulkier diisopropylsilyl ether **1c** gave **2** as a 10:1 mixture in 57% yield (Table 1, entry 3). The diphenyl and cyclic silyl ethers (Table 1, entries 4–6)

(8) A number of diastereoselective dimerizations of chiral carboxylate derivatives have been reported. For a review summarizing this area of research, see: Csáky, A. G.; Plumet, J. *Chem. Soc. Rev.* **2001**, *30*, 313–320.

(9) Prepared according to: Rathke, M. W.; Weipert, P. D. *Synth. Commun.* **1991**, *21*, 1337–1351. See the Supporting Information for further details of bis-enol ether synthesis.

Table 2. Diastereoselective Dimerization of *i*-Pr₂Si-enol Ethers

entry	1,4-diketone	yield (%) ^a	dr ^b	
1		2	67	14:1
2		4	71	3:1
3		5	82	2:1
4		6	77	20:1
5		7	77	13:1
6		8	55	10:1
7		9	84	20:1
8		10 (n = 1) 11 (n = 3)	45 50	7:1 14:1

^a Isolated yield. ^b Determined by ¹H NMR spectroscopy on the unpurified reaction mixture.

all provided lower levels of stereocontrol than diisopropylsilyl ether **1c**, so this system was selected for further development.¹⁰

During the course of optimizing the formation of dione **2** from **1c**, we found that a 6:1 mixture of acetonitrile to propionitrile in the presence of DMSO (2.0 equiv) enhanced substrate solubility and provided improved stereoselectivity (67% yield, 14:1 dr) (Table 2). The results for a number of ketone dimerizations via diisopropylsilyl bis-enol ethers are displayed below; in all cases investigated, the major diastereomer was that shown.¹¹

Unsaturation was tolerated on the substrates, although the absence of significant steric hindrance resulted in lower levels of stereoinduction (i.e., **4** and **5**). Tetralone dimer **6** was

(10) We were unable to prepare the di-*t*-Bu bis-enol ether.

(11) See the Supporting Information for details related to stereochemical proofs.

(12) Mazzega, M.; Fabris, F.; Cossu, S.; De Lucchi, O.; Lucchini, V.; Valle, G. *Tetrahedron* **1999**, *55*, 4427–4440.

formed in good yield and with high levels of stereocontrol (77% yield, 20:1 dr). Geminal substitution was tolerated; diones **7** and **8** were produced with 10:1 selectivity. The dimerization of (*R*)-carvone to afford dimer **9**¹² proceeded in good yield and with 20:1 diastereoselection. The high selectivity of this reaction establishes that both the ring substituents and the effect of the silicon tether are mutually reinforcing. Lastly, cyclopentanone gave dione **10**^{6d} in 57% yield and with moderate selectivity (7:1), while cycloheptanone provided the corresponding dimer **11**^{6d} in 50% yield as a 14:1 mixture of diastereomers.

Table 3. Stereoselective Cross-Coupling of *i*-Pr₂Si-enol Ethers

entry	1,4-diketone	yield (%) ^a	dr ^b
1		82	20:1
2		50	20:1 ^c
3		42 67	15:1 20:1
4		53 68	16:1 15:1
5		74	6:1
6		61	5:1 ^d

^a Isolated yield. ^b Determined by ¹H NMR spectroscopy on unpurified reaction mixture. ^c Stereochemistry assigned by analogy. ^d Refers to the ratio of the major isomer to the mixture of minor isomers.

The establishment of stereocontrolled oxidative dimerization of ketones is an important goal since it may enable access to bioactive dimeric natural products.¹³ Diastereoselective oxidative cross-coupling is a more challenging goal,

(13) Shair and co-workers reported a stereoselective oxidative enolate dimerization en route to the core of lomaiviticin A; see: Krygowski, E. S.; Murphy-Beninato, K.; Shair, M. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1680–1684.

(14) See the Supporting Information for procedures regarding substrate synthesis.

(15) Schmittl and co-workers postulated similar conformations for the substrates they investigated; see ref 7.

however. To extend this diastereoselective process and thus enable such cross-coupling, we prepared a number of unsymmetrical silyl bis-enol ethers.¹⁴ Exposure of the unsymmetrical substrates to our previously developed conditions afforded the cross-coupled products with variable yields and selectivities (Table 3).¹¹ For a number of substrates, the yields and diastereoselectivities were high. The cross-coupled products derived from carvone (i.e., **16**, **17**, **18**, and *rac*-**19**) demonstrate the potential power of this chemistry to generate contiguous stereoarrays. Interestingly, the coupling of the *meso*-silyl bis-enol ether derived from (*R*)- and (*S*)-carvone furnished the racemic product **19** in preference to the two possible *meso*-isomers (61% yield, 5:1 ratio of *rac*-**19** to other isomers).

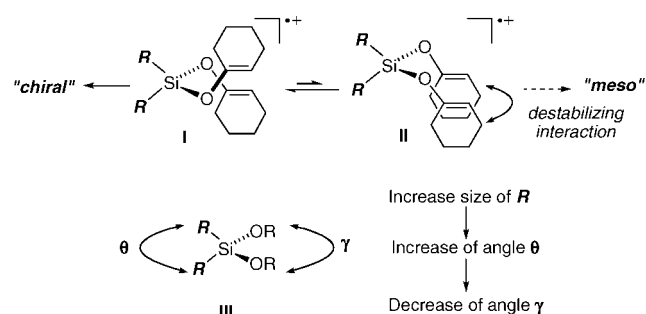


Figure 1. Model for stereoselectivity.

We have rationalized the inherent selectivity for the observed stereochemistry by considering the two possible conformations of the intermediate radical–cations that would lead to the diastereomeric products (**I** and **II** in Figure 1).¹⁵

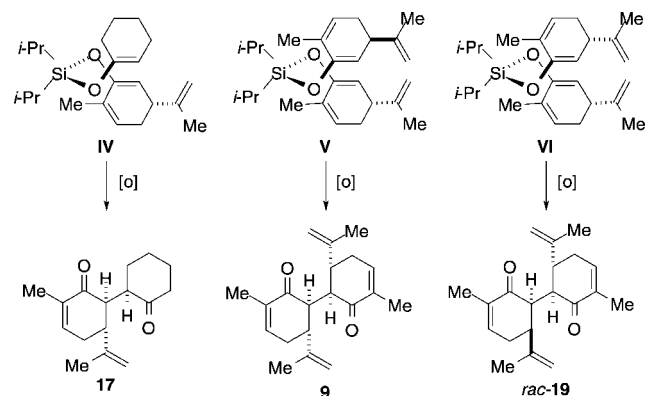


Figure 2. Models for the impact of resident stereocenters.

Reactions proceeding through conformation **I** avoid destabilizing interactions between the two rings that are present in conformation **II**. The enhanced selectivity observed with larger silicon substituents may be due to a Thorpe–Ingold effect (see **III**).¹⁶ Here, the larger diisopropyl groups cause an increase in the angle θ and a corresponding compression

of angle γ , which ultimately increases the destabilization of **II**. These bond angle differences are seen in the X-ray crystal structures of $\text{Et}_2\text{Si}(\text{OH})_2$ ($\text{O}-\text{Si}-\text{O} = 109.8^\circ$)^{17a} and $i\text{-Pr}_2\text{Si}(\text{OH})_2$ ($\text{O}-\text{Si}-\text{O} = 106.6^\circ$).^{17b} We speculate that the effect of the DMSO additive might be due to the intermediacy of hypervalent silicon species¹⁸ and are actively investigating this possibility.

The substrates derived from carvone enable the impact of resident stereocenters on the stereochemical outcome to be determined. Three situations were investigated (Figure 2): the cross-coupling of (*R*)-carvone with achiral ketones (via bis-enol **IV**), the dimerization of (*R*)-carvone (via bis-enol **V**), and the coupling of (*R*)- and (*S*)-carvone (via **VI**). In all instances, the stereochemistry of the newly formed centers reflects that the reaction most likely proceeded through a conformation akin to **I** in Figure 1. For the reaction of bis-enol **IV**, the isopropenyl group effectively blocks one face of the substrate so that the newly formed bond is generated opposite the β -substituent (15:1 dr with cyclohexanone). For the (*R,R*)-carvone dimer **9**, bond formation most likely occurs through conformer **V**, where both substituents are positioned away from the forming bond. In the (*R,S*)-carvone system (i.e., *rac*-**19**), bond formation proceeds through conformer **VI**, but syn to one isopropenyl group and anti to the other.¹⁹ From this last example, we conclude that the effects of ring

substituents are subordinate to the conformational bias imparted by the silicon tether.

The diastereomeric ratios we observed for these cross-coupling reactions (up to 20:1 dr) are, to the best of our knowledge, the highest reported to date. As a point of comparison, the conditions developed by Baran and co-workers^{4d,g} for enolate cross-coupling afforded a maximum diastereomeric ratio of 2.8:1.

Future research in our group will further probe the impact that resident stereocenters have on the stereochemical outcome of these couplings, particularly when the two substituents are different (i.e., not both isopropenyl groups). Application of silyl bis-enol ethers to the construction of complex polycyclic molecules should enable convergent and concise syntheses, while investigations into Lewis base effects during oxidative coupling might open avenues for asymmetric induction.

Acknowledgment. This work was supported by Northwestern University (NU) and the NU Intergrated Molecular Structure and Education Research Center (NSF Grant Nos. DMR0114235 and CHE9871268). K.D. acknowledges the award of a Northwestern Undergraduate Research Grant. We thank Prof. K. A. Scheidt (NU) and Mr. M. D. Clift (NU) for helpful discussions.

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

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(16) For a review, see: Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–176.

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(18) For a recent review of synthetic processes involving hypervalent silicon species, see: Rendler, S.; Oestreich, M. *Synthesis* **2005**, 1727–1747.

(19) See the Supporting Information for a more detailed discussion.