

# SYNLETT Spotlight 465

## Silyl Ketene Imines

Compiled by Fausto Daniel dos Santos Queda



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Fausto Daniel dos Santos Queda was born in 1990 in Barreiro, Portugal. He received his B.Sc. in biochemistry from the Universidade Nova de Lisboa, Portugal in 2012. Presently, he is carrying out research under the supervision of Professor M. Manuel B. Marques at the Faculdade de Ciências e Tecnologia of the Universidade Nova de Lisboa. His research focuses on the synthesis of functionalized chitoooligosaccharides.

REQUIMTE, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, 2829-516 Caparica, Lisboa, Portugal  
E-mail: f.queda@campus.fct.unl.pt

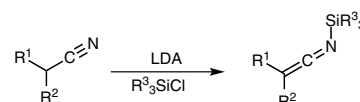
Silyl ketene imines (SKIs) are a wide variety of nucleophiles possessing a pair of orthogonal substituents within a cumulene group and can have other functional groups, including alkenes, allenes, ketenes, and amines. SKIs can be employed in a wide range of reactions involving C–C bond formation and/or the formation of stereogenic centers.

When combined with an appropriate catalyst and ligand, C–C bond forming reactions with SKIs are highly stereoselective. SKIs can be converted into nitriles which are precursors of many other functional groups including carboxylic acids, amines, and aldehydes.<sup>2</sup> One of the first synthetic applications of SKIs was described in 1987: a Diels–Alder [4+2] cycloaddition stating a versatile meth-

od to obtain anilines and cyclohexanones, leading to a range of aromatic amines in 52–89% yield.<sup>3</sup>

Due to their geometry and the presence of two orthogonal substituents, SKIs have proven to be excellent nucleophiles in order to obtain stereogenic centers.<sup>4</sup>

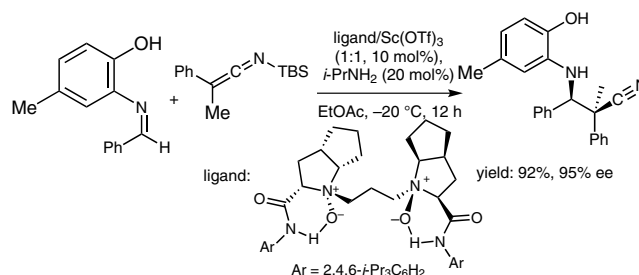
SKIs are not commercially available, but they can be easily prepared from organic nitriles in the presence of a strong base, such as LDA, and of a silylating agent (Scheme 1).<sup>5</sup>



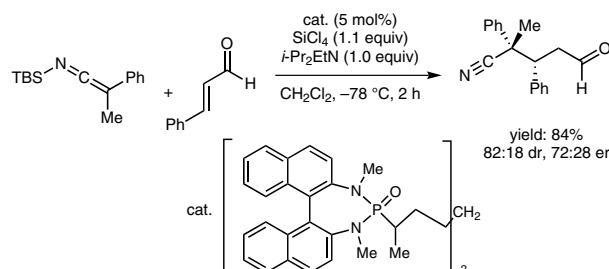
**Scheme 1** General method for the synthesis of silyl ketene imines

### Abstracts

(A)  $\beta$ -Amino nitriles are important precursors in organic synthesis because they are easily converted into  $\beta$ -amino acids. Feng and co-workers reported a three-component, one-pot method in which SKIs were reacted in the presence of a chiral  $N,N'$ -dioxide ligand and scandium(III) to provide  $\beta$ -amino nitriles in high enantiomeric excess (up to 97% ee) and yield (up to 95%).<sup>6</sup>



(B) The Lewis base catalyzed conjugated addition of SKIs to  $\alpha,\beta$ -unsaturated aldehydes and ketones resulted in an improvement of diastereomeric and enantiomeric ratio in these Mukaiyama–Michael reactions. The corresponding adducts were obtained in high regioselectivity (1,4/1,2 = 92:8), yield, diastereomeric ratio, and enantioselectivity.<sup>1</sup>



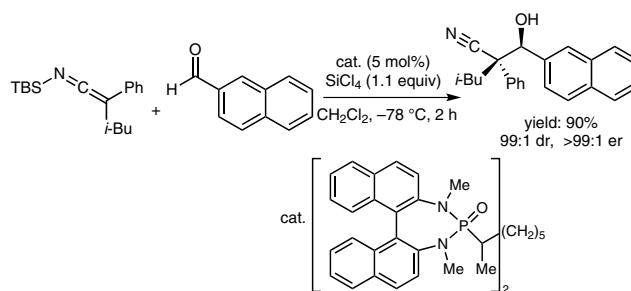
SYNLETT 2014, 25, 0896–0897

Advanced online publication: 21.02.2014

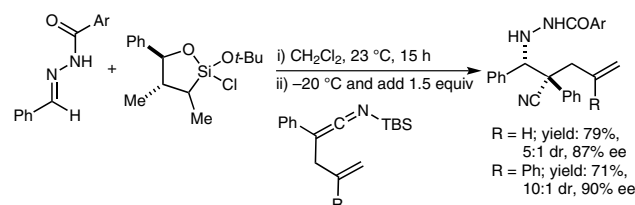
DOI: 10.1055/s-0033-1340855; Art ID: ST-2013-V0472-V

© Georg Thieme Verlag Stuttgart · New York

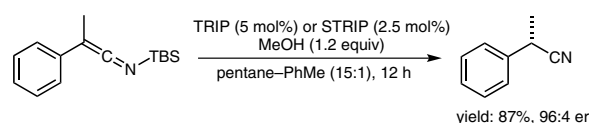
(C) Several SKIs were studied in an aldol-type reaction to generate  $\beta$ -hydroxy nitriles with an  $\alpha$ -quaternary center. This study involved the use of many aromatic aldehydes using a  $\text{SiCl}_4$ -bisphosphoramide catalyst system for this new Lewis base catalyzed aldol reaction.<sup>7</sup> SKIs have also been reported as substrates for aldol-type reactions to prepare  $\beta,\gamma$ -dihydroxy nitriles.<sup>8</sup>



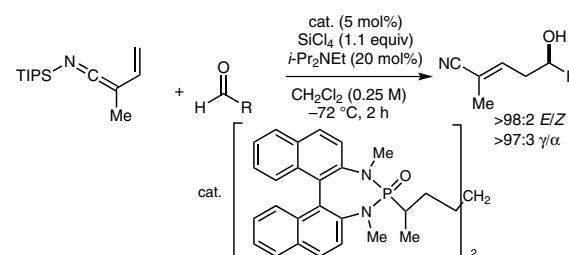
(D) The addition of SKIs to acyl hydrazines in the presence of a chiral silane Lewis acid has been reported as an easy and enantioselective strategy for Mannich-type reactions. Depending of the *R*-substituent in the SKI, the diastereomeric and enantiomeric ratios are affected. This strategy led to a new way of obtaining a wide range of nitrogen heterocycles.<sup>9</sup> The authors have also reported the use of  $\alpha$ -aryl silyl ketene acetals and imines in highly enantioselective Mannich reactions.<sup>10</sup>



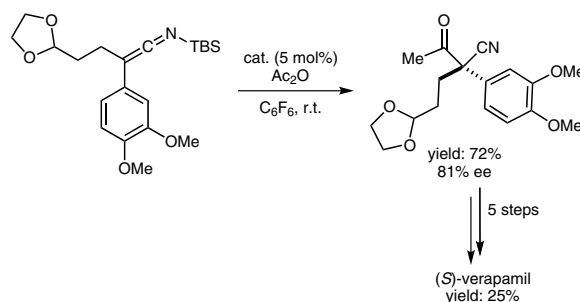
(E) Catalytic asymmetric protonation of SKIs is an important route to access  $\alpha$ -nitrile stereogenic centers. Due to the versatility of the nitrile group as a precursor to other functional groups, this route highlights the importance of SKIs. Many catalysts were studied, and the chiral phosphoric acids TRIP and STRIP provided the best enantiomeric ratios and yields.<sup>11</sup>



(F) Through vinylogous addition of SKIs the attack at the  $\gamma$ -position is possible, leading to  $\alpha,\beta$ -unsaturated nitriles with a stereogenic center in the  $\gamma$ -position. In this study, it was shown that olefinic and aromatic aldehydes react much faster than aliphatic aldehydes. This method provides unsaturated nitriles containing a trisubstituted double bond.<sup>12</sup>



(G) The intermolecular acylation of SKIs leads to the formation of a new carbon-carbon bond. At room temperature and in the absence of a catalyst, SKIs are inert to a variety of acylating agents, but in the presence of a chiral catalyst, such as a 4-(pyrrolidino)piperine derivative, the acylation products are obtained with high enantioselectivity (81–82% ee) under anhydrous conditions. The first catalytic asymmetric synthesis of verapamil using an enantioselective acylation of SKIs was described; with a 25% total yield.<sup>13</sup>



## References

- (1) Denmark, S. E.; Wilson, T. W. *Synlett* **2010**, 1723.
- (2) Denmark, S. E.; Wilson, T. W. *Nature Chem.* **2010**, *2*, 937.
- (3) Differding, E.; Vandavelde, O.; Roekens, B.; Van T, T.; Ghosez, L. *Tetrahedron Lett.* **1987**, *28*, 397.
- (4) Denmark, S. E.; Wilson, T. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 9980.
- (5) Watt, D. S. *J. Org. Chem.* **1974**, *39*, 27990.
- (6) Zhao, J.; Liu, X.; Luo, W.; Xie, M.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2013**, *52*, 3473.
- (7) Denmark, S. E.; Wilson, T. W.; Burk, M. T.; Heemstra, J. R. *J. Am. Chem. Soc.* **2007**, *129*, 14864.
- (8) Long, S.; Panunzio, M.; Qin, W.; Bongini, A.; Monari, M. *Eur. J. Org. Chem.* **2013**, 5127.
- (9) Vu, J. M. B.; Leighton, J. L. *Org. Lett.* **2011**, *13*, 4056.
- (10) Notte, G. T.; Vu, J. M. B.; Leighton, J. L. *Org. Lett.* **2011**, *13*, 816.
- (11) Guin, J.; Varseev, G.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 2100.
- (12) Denmark, S. E.; Wilson, T. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 3236.
- (13) Mermerian, A. H.; Fu, G. C. *Angew. Chem. Int. Ed.* **2005**, *44*, 949.