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Diastereoselective synthesis of 2-isoxazolines via silaketal tethered 1,3-dipolar cycloadditions

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Abstract

The use of silaketals derived from allylic alcohols and 1-substituted nitroethanols for the stereocontrolled synthesis of 3,4,5-trisubstituted 2-isoxazolines via intramolecular 1,3-dipolar cycloaddition is demonstrated. High levels of stereoselectivity (70–92% *de*) were obtained from the reaction involving nitrile oxides with dipolarophiles having a stereocenter located at the allylic position. Intramolecular cycloaddition of precursors having only a stereocenter in α-position to the nitrile oxide moiety, produced 2-isoxazolines with moderate diastereoselectivities. The use of silyl nitronates increased the level of selectivity, albeit at the expense of conversion yields. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: cycloadditions; diastereo selection; isoxazolines; 4,5-dihydroisoxazoles; nitrile oxides; silyl nitronates.

In view of their potent and varied biological activity,[1a] 2-isoxazolines continue to be of interest to researchers.[1] Furthermore, they are often regarded as useful synthons for non-heterocyclic compounds because they can be selectively transformed into 1,3-amino alcohols or β-hydroxy ketones through reductive N–O bond cleavage.[2] This transformation stands as a very interesting alternative to asymmetric aldol condensation.[2c,d] Their use as versatile intermediates in organic synthesis is hampered by several synthetic difficulties. Indeed, the use of nitrile oxides, which are the most useful 1,3-dipoles for the rapid assembly of these heterocycles, often results in low yield and/or poor regio- or stereoselectivity especially when unsymmetrical 1,2-disubstituted alkenes are used as dipolarophiles.[1,3] Thus, studies aimed at improving the level of the regioselectivity as well as the understanding of the origin of the stereochemical outcome are fully justified.[4] For instance, Kanemasa and Ukaji have reported superior regio- and stereoselectivity in the 1,3-dipolar cycloaddition between magnesium crotyl alcoholate[5a] as well as allylic alcohols,[5b] including α-silylated allylic alcohols[5c] and benzonitrile oxides as a consequence of the coordination of both reactants with Mg[5a,c] or Zn ions.[5b] Another approach to overcome these limitations has been the use of intramolecular nitrile oxide cycloaddition methodology, in

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which the linking arm is part of the final molecule.[1b,d] Indeed, intramolecularity is a general strategy for imposing regio- and stereoselectivity. Removable tethers allow reactions to be rendered intramolecular, provided the substrates have points of attachment for the tether. For example, the use of silicon-based tethers in intramolecular 1,3-dipolar cycloadditions has been reported.[6] The advantage is that, following cycloaddition, the temporary linkage can be removed providing access to open chain derivatives.

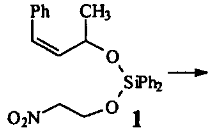
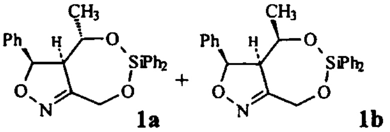
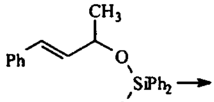
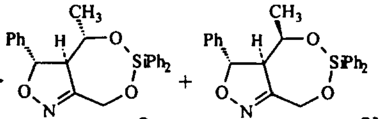
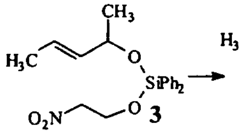
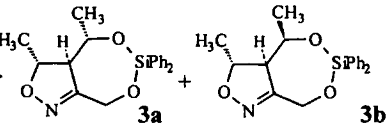
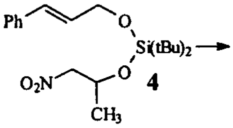
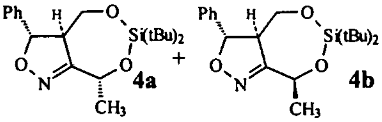
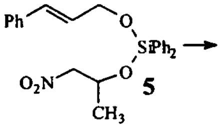
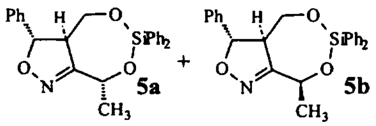
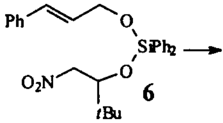
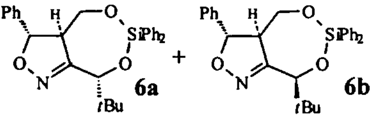
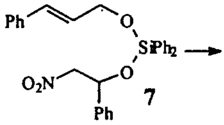
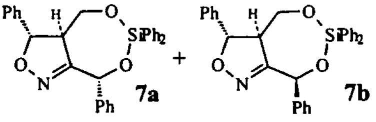
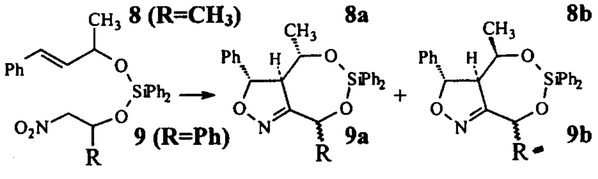
In order to fully exploit the use of 2-isoxazolines as precursors of open chain multifunctional molecules, their enantioselective synthesis must involve readily available reagents or catalysts in both enantiomeric forms and we need to be able to predict the absolute stereochemistry of the newly generated stereocenters. In all of the above intramolecular processes, the study of the stereochemistry involved cycloadducts containing 5–5 and 5–6 ring systems.[1b] We are interested in the study of longer tethering arms leading to cycloadducts containing 5–7 ring systems, since this procedure will allow for the use of chiral allyl alcohols and 1-substituted 2-nitroethanols, which are readily synthesized in both optically active forms.[7] In this context, we have reported the use of disposable silicon tethers in the regio- and stereocontrolled synthesis of 2-isoxazolines.[8] We now wish to report on the level of asymmetric transfer and the factors which control the stereoselectivity in cycloadditions involving silaketals.

Racemic silaketals **1** to **9** were prepared from the corresponding alcohols[9] and dichlorodialkylsilane in a one-pot synthesis according to a procedure we have previously reported.[8] The nitrile oxides were generated by various methods, and the cycloadditions were followed by NMR.[10] The diastereomeric products were isolated in pure form by chromatography and the results obtained are summarized in Table 1. The stereochemistry of all compounds was determined by NOE experiments.[11]

Method of activation: The Mukaiyama conditions for the dehydration of the nitro group to generate the nitrile oxide (method A)[12a] required the use of a large excess of phenyl isocyanate over a long period of time. The crude reaction mixtures thus obtained were difficult to purify due to the formation of the by-product, diphenyl urea. Method B,[12b] which involves the use of $(BOC)_2O$ and a catalytic amount of base for the generation of nitrile oxide, gave higher conversion yields in a shorter reaction time (i.e. 2–3 days). The crude reaction mixtures consisted essentially of diastereomers, in ratios identical to those obtained by the Mukaiyama procedure (entries 1, 5–9). The low conversion yields observed in some cases are due to partial hydrolysis of the diphenylsilaketal tether during chromatography (entries 1 and 3). The use of a more robust silaketal tether yielded better results (entry 4).[13] All substrates reacted at room temperature using methods A and B. In contrast, reactions involving silyl nitronate (condition C; formed by treating the substrate with TMSCl and Et_3N)[12c] did not take place below 80°C. The harsher conditions required for the cycloaddition using method C gave consistently lower yields of adducts (entries 5 and 7).

Stereoselectivity: Taking into account the complete relay of the *cis*- and *trans*-alkene geometries into the heterobicycles, we observed a good level of stereoselectivity (i.e. 70–92% *de* in favor of **1a**, **2a** and **3a**) for silaketals substituted at the allylic position (entries 1–3), with the highest level occurring when the alkene has a *cis* geometry. A significantly lower level of stereoselectivity (i.e. 20–40% *de* in favor of **4b**–**7b**) was noted for silaketals having only a stereocenter in α-position to the nitrile oxide moiety (entry 4–7). The stereochemistry was reversed in favor of the epimers **5a** and **7a**, with up to 80% *de*, by using silyl nitronates as the dipole (entries 5 and 7). Diastereoselective cycloadditions with good levels of stereocontrol also took place with more highly functionalized substrates (i.e. asymmetric centers at both the allylic and the nitroether positions). In this case, the favored diastereomers, **8a** and **9a**, were produced with up to 80% *de*.[11] The reaction pathways presented below suggest a rationale for the observed difference in stereocontrol. Transition state (TS) **I** is consistent with higher levels of selectivity observed with substrates that bear an allylic asymmetric center (e.g, **1a**–**3a**); the $A^{1,3}$ strain that destabilizes **II** is expected to be more pronounced in the presence of a *cis*-alkene. These results are in line with those reported for a five-membered ring tether.[14] The near-linear geometry of nitrile oxides

Table 1
Diastereoselective intramolecular cycloadditions of compounds **1–9**

Entry	Substrate	Cycloadducts **a** + **b**	Conditions[1]	Time (Days)	Selectivity[2] a : b	Yield[3] (%)
1	 **1**	 **1a** **1b**	A B	11 5	96 : 4* 96 : 4*	36 45
2	 **2**	 **2a** **2b**	B	2	88 : 12*	58
3	 **3**	 **3a** **3b**	A	13	86 : 14*	28
4	 **4**	 **4a** **4b**	B	3	30 : 70	88
5	 **5**	 **5a** **5b**	A B C	12 3 12	40 : 60 40 : 60 70 : 30	57 72 45
6	 **6**	 **6a** **6b**	A B	11 2	30 : 70 30 : 70	52 66
7	 **7**	 **7a** **7b**	B C	3 13	30 : 70 90 : 10	58 23
8 9	 **8** (R=CH$_3$) **9** (R=Ph)	**8a** **8b** **9a** **9b**	A B A B	14 2 13 2	90 : 10* 90 : 10* 90 : 10* 90 : 10*	35 59 61 90

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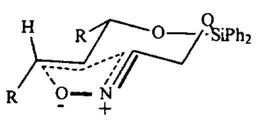
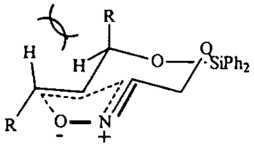
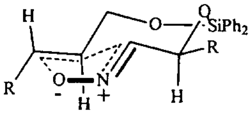
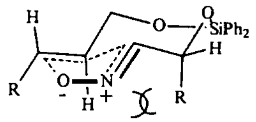
[1] Conditions: (A) Per day: 2 eq of PhNCO, 2 eq of Et_3N, C_6H_6 room temperature.[12a] (B) Per day: 1.5 eq BOC_2O, 0.1 eq DMAP, THF, room temperature.[12b] (C) Per day: 2 eq of TMSCl, 2 eq of Et_3N, C_6H_6 reflux.[12c]
[2] Determined by 300 MHz ^1H NMR analysis of the crude reaction mixture. [3] Isolated yields after silica gel chromatography. *These isomers could not be isolated in pure form.

(**III** and **IV**) precludes any such stereodifferentiation when the stereocenter is α to it. Therefore, the weak steric interaction present in structure **IV** slightly favors **III** leading to **4b** to **7b** with low levels of discrimination.

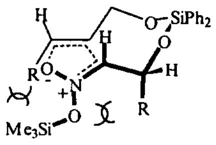

Transition state I leading to Cycloadducts 1a-3a

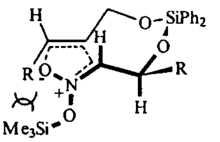

Transition state II leading to Cycloadducts 1b-3b

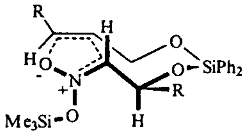

Transition state III leading to Cycloadducts 4b-7b


Transition state IV leading to Cycloadducts 4a-7a

When both asymmetric centers are present, and nitrile oxides are involved, stereodifferentiating control is dictated by the allylic stereocenter, via TS **I**, to afford **8a** and **9a** in comparable ratios to those found for compounds **2a** and **3a**. The enhanced selectivity in reactions of silyl nitronates (favoring the intermediacy of isoxazolidines **VII**) is due to the $A^{1,3}$ strain involving the appropriate N–OTMS bonds in **V** and steric repulsion in **VI**; such unfavorable interactions are minimized in **VII**. This TS is analogous to nitrone cycloadditions.[1d,15]


Transition state V leading to Cycloadducts 5a, 7a


Transition state VI leading to Cycloadducts 5b, 7b


Transition state VII leading to Cycloadducts 5a, 7a

These experiments thus reveal that it is possible to achieve good levels of diastereoface selectivity in intramolecular 1,3-dipolar cycloaddition reactions with longer tethers, as long as an allylic asymmetric center is present within the intervening bridge. This is in contrast to studies carried out on the cycloaddition of nitrile oxides and silyl nitronates with simple olefins in which an increase in the tether length by one methylene unit, led to 5–5 and 5–6 ring systems with lower diastereoselectivity, from 99:1 to 1:2.6.[1d] Future studies, including the optimization of silyl nitronates to induce cyclization and the employment of the corresponding aminoalcohols in the synthesis of natural products are currently under way.

Acknowledgements

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9. Those allylic alcohols not commercially available were prepared by the addition of Grignard reagents to the corresponding unsaturated aldehydes. Nitroalcohols were prepared from the condensation of nitromethane with the corresponding aldehydes.
10. The reaction was quenched when the ^{1}H NMR analysis of a sample of the reaction mixture showed a complete disappearance of the resonances attributed to the alkene function accompanied by the appearance of those attributed to the 2-isoxazoline product.
11. All new compounds gave the correct elemental analysis and suitable spectroscopic data (IR, ^{1}H, ^{13}C NMR). The assignment of all resonances was supported by COSY and HMQC cross peak correlations. Stereochemistry was established on the basis of NOE experiments. Because each silaketal is derived from racemic alcohols, both diastereomers **8a** and **9a** are obtained as a mixture of epimers at C-2 in equal proportions.
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