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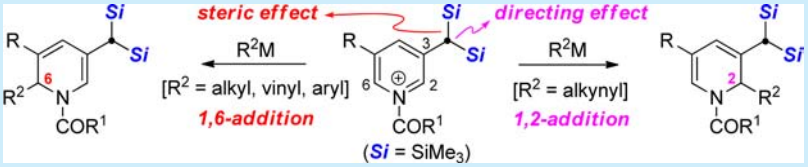
Regioselective Nucleophilic Addition of Organometallic Reagents to 3-Geminal Bis(silyl) *N*-Acyl Pyridinium

Ya Wu,[†] Linjie Li,[†] Hongze Li,[†] Lu Gao,[†] Hengmu Xie,[†] Zhigao Zhang,[†] Zhishan Su,[§] Changwei Hu,*[,§] and Zhenlei Song*[,†,‡]

[†]Key Laboratory of Drug-Targeting of Education Ministry and Department of Medicinal Chemistry, West China School of Pharmacy, [‡]State Key Laboratory of Biotherapy, West China Hospital, [§]Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610041, P. R. China

Supporting Information

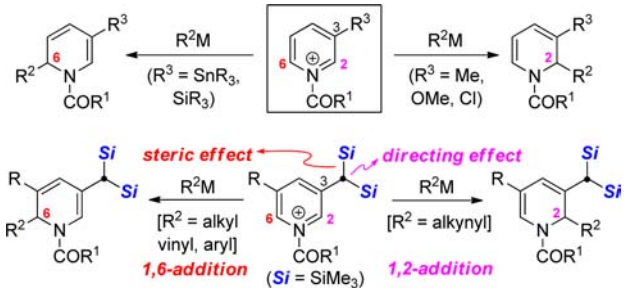


ABSTRACT: A regioselective nucleophilic addition to 3-geminal bis(silyl) *N*-acyl pyridinium has been described. Geminal bis(silane) shows contrasting roles that lead to different regioselectivities for the addition of different nucleophiles: its steric effect dominates to favor 1,6-addition of alkyl, vinyl, and aryl organometallic reagents; its directing effect dominates to favor 1,2-addition of less sterically demanding alkynyl Grignard reagents.

Nucleophilic addition of organometallic reagents to *N*-acyl pyridinium species[1] is one of the most widely used protocols to functionalize pyridine. The dihydropyridines so generated can be transformed by reduction into tetrahydropyridines and piperidines or by oxidation into substituted pyridines.[2] All these heterocycles are important building blocks in the synthesis of biologically active molecules.[3]

When *N*-acyl pyridinium contains a 3-substituent, the addition of hard nucleophiles such as Grignard reagents generally proceeds through either a 1,2- or 1,6-pathway (Scheme 1, top). The regioselectivity usually depends on the nature of the 3-substituent. Methyl, methoxy, or halogen groups at the 3-position favor 1,2-addition as a result of the so-called "*directing effect*".[4] Charette recently reported that such a 1,2-regioselectivity can be even enhanced by utilizing an imidate as the *N*-activating group to provide an extra "*directing effect*".[5] On the other hand, trialkyltin and trialkylsilyl groups at the 3-position effectively block both C-2 and C-4, and this so-called "*steric effect*" favors 1,6-addition, as Comins elegantly showed.[6]

Scheme 1. General Description of 1,2- and 1,6-Addition to 3-Substituted *N*-Acyl Pyridinium (Top); Geminal Bis(silane)-Controlled Addition with Divergent Regioselectivity (Bottom)



We recently embarked on a series of investigations into geminal bis(silanes),[7] in which two silyl groups are attached to one carbon center. In the course of this work, we discovered that geminal bis(silane) in the 3-position of *N*-acyl pyridinium exerted contrasting effects on the regioselectivity of nucleophilic addition (Scheme 1, bottom). In additions involving alkyl, vinyl, and aryl Grignard reagents, the bulkiness of the geminal bis(silyl) group imposes a strong steric effect that shields both C-2 and C-4, selectively promoting 1,6-addition. In additions involving less sterically demanding alkynyl Grignard reagents, geminal bis(silane) exerts a directing effect that favors 1,2-addition. Donohoe recently observed a contrasting regioselectivity in the addition of Grignard reagents to 4-methoxy methyl picolinate-derived *N*-alkyl pyridinium. The discrepancy was rationalized by the hard/soft acid/base (HSAB) model based on the different charge distribution at the C-2 and C-6 centers.[8] Here we describe detailed studies of our reaction.

First we examined the reaction using geminal bis(trimethylsilyl)-substituted pyridine **1** as a model scaffold, which was prepared in 80% yield via Kumada coupling of $(SiMe_3)_2CHMgCl$ and 3-bromopyridine. Acylation of **1** with *i*-PrCOCl in THF at −78 °C generated the corresponding pyridinium. Subsequent addition by EtMgBr afforded 1,6-adduct **2a** in 45% yield as a major regioisomer, which was

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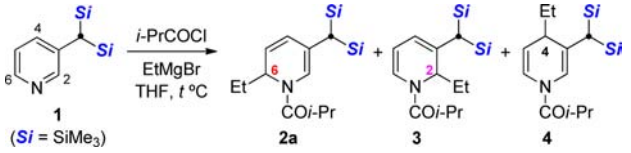
contaminated with 1,2- and 1,4-adducts in a ratio of 82:8:10 (Table 1, entry 1). We attributed the moderate yield to incomplete conversion of **1** under these reaction conditions. Consistent with this idea, a higher yield of 72% was obtained by increasing the loading of both *i*-PrCOCl and EtMgBr to 4.0 equiv (entry 3),[9] although this also decreased regioselectivity slightly to 78:7:15. The reaction temperature strongly affected regioselectivity, with higher temperatures leading to lower 1,6-regioselectivity (entries 3−5).

This approach proved applicable to a range of alkyl, vinyl, and aryl Grignard reagents; the desired 1,6-adducts **2b**−**2h** were obtained in good yields with high regioselectivity. While no 1,2-adducts were observed, 1,4-adducts were detected in some cases (Table 2, entries 1−4). In general, the ratio of 1,6- to 1,4-addition increased as the nucleophiles became bulkier (entries 1−5). The ratio of 1,6- to 1,4-addition also increased when switching from alkyl Grignard reagents (entries 1−3) to harder vinyl and aryl ones (entries 4−7). Nevertheless, (*E*)-zinc enolate derived from 3-pentanone, which is softer than organomagnesium, underwent predominantly 1,6-addition (1,6-/1,4- = 90:10) to give **2i** in 80% yield as a single *syn*-isomer.[10] However, addition of the even softer $(n\text{-Bu})_2$CuLi favored the 1,4-pathway to afford **2j** in 35% yield.

This addition also proved applicable to pyridiniums derived from **1** using various activating reagents, including unbranched alkyl acyl chloride substituted with olefin and halides (Table 3, entries 1−3), bulky pivaloyl chloride (entry 4), and ethyl chloroformate (entry 5). Complete 1,6-regioselectivity was observed in all these cases. The adducts **2k** and **2l** possess the potential for subsequent intramolecular transformations, such as a Diels−Alder reaction of **2k** and radical cyclization of **2l**.

Next we tested the addition of EtMgBr to 5-methyl-substituted geminal bis(silyl) pyridine **5**. Surprisingly, the addition gave **6** in 63% yield with an even higher ratio of 1,6- to 1,2-adduct (90:0) than the addition using compound **1** without a 5-substituent (78:7), even though the C-6 of **5** is more crowded (Scheme 2). NOE experiments of **1** revealed an approximately 1:3 equilibrium of conformers **1-Con-A** and **1-Con-B**.[11] While both conformers favor 1,6-addition, it seems reasonable that **1-Con-B** would undergo 1,2-addition to some extent because the geminal bis(silane) shields the C-2 less effectively than it does in **1-Con-A**. NOE analysis of **5** showed an approximately 1:1 equilibrium of **5-Con- A** and **5-Con-B**.[12]

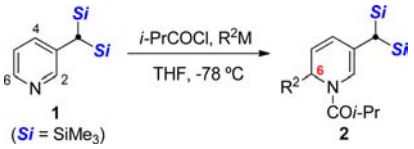
Table 1. Screening of Reaction Conditions[a]

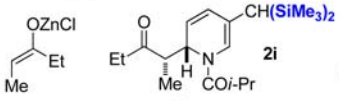


entry	*i*-PrCOCl (equiv)	EtMgBr (equiv)	*t* (°C)	yield[b] (2a)	2a/3/4[c]
1	1.3	1.3	−78	45%	82:8:10
2	2.0	2.0	−78	51%	80:8:12
3[a]	**4.0**	**4.0**	**−78**	**72%**	**78:7:15**
4	4.0	4.0	−40	65%	72:9:19
5	4.0	4.0	0	57%	68:11:21

[a]Reaction conditions: 0.21 mmol of **1** and 0.84 mmol of *i*-PrCOCl in 0.8 mL of THF at −78 °C; then 0.84 mmol of EtMgBr for 30 min. [b]Isolated yields after purification by silica gel column chromatography. [c]Ratios were determined by ^{1}H NMR spectroscopy.

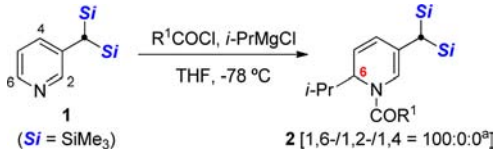
Table 2. Scope of Organometallic Reagents for 1,6-Addition



entry	R^2M	product	yield (2)[a]	1,6-/1,2-/1,4[b]
1	*i*-PrMgCl	**2b**	90%	93:0:7
2	CyMgBr	**2c**	70%	95:0:5
3	Me_3SiCH_2MgCl	**2d**	88%	98:0:2
4	CH_2=CHMgBr	**2e**	89%	98:0:2
5	CH_2=C($SiMe_3$)MgBr	**2f**	88%	100:0:0
6	PhMgBr	**2g**	95%	100:0:0
7	2-ThienylMgBr	**2h**	92%	100:0:0
8		**2i**	80% [*dr* ≥ 95:5]	90:0:10
9	$(n\text{-Bu})_2$CuLi	 **2j**	35%	22:0:78

[a]Isolated yields after purification by silica gel column chromatography. [b]Ratios were determined by ^{1}H NMR spectroscopy.

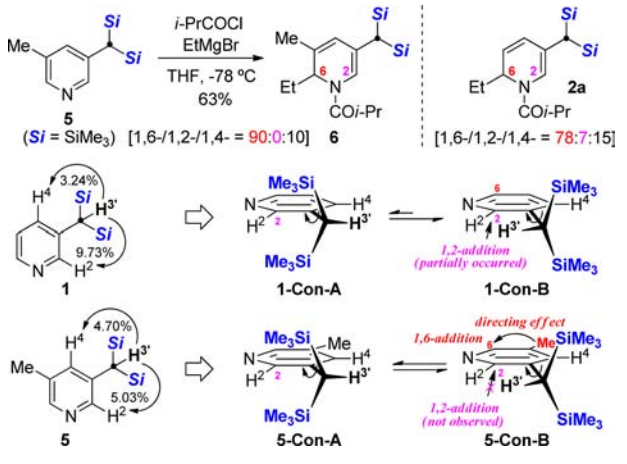
Table 3. Scope of Activating Reagents for 1,6-Addition



entry	R^1COCl	product	yield[b]
1	CH_2=$CH(CH_2)_2$COCl	**2k**	45%
2	$Br(CH_2)_2$COCl	**2l**	51%
3	$ClCH_2$COCl	**2m**	72%
4	PivCOCl	**2n**	65%
5	EtOCOCl	**2o**	57%

[a]Ratios were determined by ^{1}H NMR spectroscopy. [b]Isolated yields after purification by silica gel column chromatography.

Scheme 2. Comparing the 1,6-Regioselectivity in the Formation of 6 and 2a



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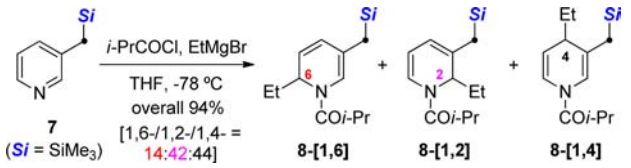
The 1,2-pathway of addition should be even more unfavorable for **5-Con-B** than for **1-Con-B**, since the directing effect from 5-Me should provide extra driving force favoring 1,6-addition.

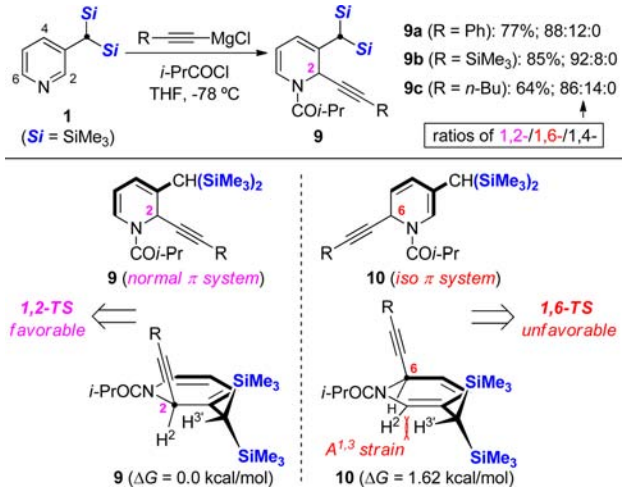
When mono-$SiMe_3$-substituted pyridine **7** was reacted with *i*-PrCOCl and EtMgBr, **8**-[**1,6**], **8**-[**1,2**], and **8**-[**1,4**] were obtained in an overall yield of 94% and in a ratio of 14:42:44 (Scheme 3). This contrasts with the ratio of 78:7:15 in the formation of **2a**. Such a large difference in regioselectivity suggests that the unique steric effect of geminal bis(silane) is a crucial driver in the preference for 1,6-addition to **1**.

Scheme 3. Reaction of Mono-$SiMe_3$-Substituted Pyridine 7



We were surprised to find that using harder and less sterically demanding alkynyl Grignard reagents switched the regioselectivity of addition from the 1,6- to 1,2-pathway (Scheme 4).

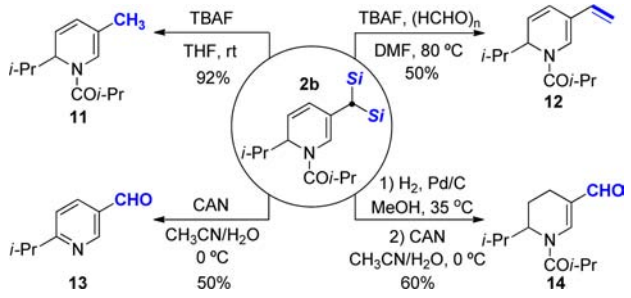
Scheme 4. 1,2-Addition of Alkynyl Grignard Reagents to 1



In these reactions, the 3-geminal bis(silane) behaves more like a methyl group than a bulky silyl group. In other words, the silyl group's directing effect becomes more dominant than its steric effect, favoring addition to the more crowded C-2. We rationalize this directing effect according to Sundberg's proposal that transition states in the addition of small nucleophiles possess a product-like character that reflects the stability of the products.[13] The 1,2-adduct **9** should be more stable than the 1,6-adduct **10** because **9** features a diene containing a terminal-substituted geminal bis(silane). This bis(silane) acts as a donor substituent due to the double hyperconjugation effect between the two C−Si bonds and the C−C double bond.[14] Such a normal π-system should be more stable than the iso π-system embedded in **10**.[15] A second line of reasoning similarly suggests that **9** should be more stable: **10** probably suffers 1,3-allylic strain between H^2 and $H^{3'}$, while such an interaction does not exist in **9** because the H^2 is oriented pseudoequatorially. Therefore both arguments predict the 1,2-adduct to be more stable than the 1,6-adduct, implying by extension that the 1,2-transition state is more favorable than the 1,6-transition state, which would explain the observed preference for 1,2-addition. The hypothesis was further supported by the results from DFT calculation at the B3LYP/6-311++G**(PCM, THF) //B3LYP/6-311G** level, which shows that 1,2-adduct **9** is energetically more stable than 1,6-adduct **10** by 1.62 kcal/mol.

The geminal bis(silyl) group in **2b** was subjected to transformations into other useful functionalities (Scheme 5).

Scheme 5. Functionalization of 2b



Removing two silyl groups with TBAF provided 3-methyl dihydropyridine **11** in 92% yield, while desilylation and Peterson olefination with formaldehyde afforded **12** containing a 3-vinyl group in 50% yield. Double oxidation[16] of the dihydropyridine and geminal bis(silane) with CAN generated **13** in 50% yield. Partially hydrogenating **2b** to generate tetrahydropyridine and then oxidizing it with CAN gave **14** in an overall yield of 60%.

In summary, we have described a regioselective nucleophilic addition of organometallic reagents to 3-geminal bis(silyl) *N*-acyl pyridinium. While the steric effect of geminal bis(silane) favors 1,6-addition of alkyl, vinyl, and aryl organomagnesiums, the directing effect favors 1,2-addition of alkynyl Grignard reagents. Further applications of this methodology are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: changweihu@scu.educn.
*E-mail: zhenleisong@scu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(10) The *syn*-stereochemistry was assigned based on Comins' studies on diastereoselective addition to 3-substituted *N*-acyl pyridinium, in which various acylic and cyclic (*E*)-zinc enolates reliably provided the *syn*-stereochemical outcome. For the related reference, see: Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J. *J. Am. Chem. Soc.* **1999**, *121*, 2651.
(11) We propose that the equilibrium still exists at −78 °C and that **1-Con-B** is favored even more at this reduced temperature because of the more restricted C3−C3′ bond rotation. At the same time, we remain unsure whether the ratio of **1-Con-A** to **1-Con-B** is related to the ratio of the 1,6- to 1,2-adduct, based on the Curtin−Hammett principle.
(12) It is unclear how the methyl group in the 5-positon of **5** influences the rotation of the C3−C3′ bond, giving the different ratio of two conformers from that of **1**. See Supporting Information for more detailed computational results and discussions.
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(14) For reviews, see: (a) Panek, J. S. Silicon Stabilization. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. *1*, p 579. (b) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.
(15) One more resonance structure can be drawn for **9** than **10**; this structure is stabilized by the hyperconjugation effect of geminal bis(silane).
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