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Synthetic Methods

Concise Synthesis of Multisubstituted Isoquinolines from Pyridines by Regioselective Diels–Alder Reactions of 2-Silyl-3,4-pyridynes

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Abstract: A four-step regioselective synthesis of multisubstituted isoquinoline derivatives from 3-bromopyridines was developed by the Diels–Alder (DA) reactions of 2-silyl-3,4-pyridynes with furans, followed by functional-group transformations. In particular, the silyl group at the C2-position of the 3,4-pyridynes played two important roles: firstly, it functioned as the directing group for the DA reaction, and secondly, it served to introduce diverse substituents at the C1-position of the isoquinolines by electrophilic *ipso*-substitution.

Introduction

Isoquinolines are abundant in biologically active natural and non-natural compounds,[1,2] many of which are currently used as therapeutic agents, such as antibiotics,[2a] antineoplastics,[2b] and antispasmodics.[2c] Therefore, the synthesis of isoquinolines has attracted considerable attention from both synthetic and biological perspectives. Although diverse synthetic methods for isoquinolines have been reported,[3–6] most of them are based on the construction of a pyridine ring on benzene;[4,5a,c–i] for example, the ring closure at the C1-position of isoquinoline, in the Pictet–Spengler[4] and Bischler–Napieralski reactions,[4] and at the C4-position, in the Pomeranz–Fritsch reaction[4] (Figure 1). In contrast, the "reverse approach", the construction of a benzene ring on pyridine, has not been investigated in detail.[5b,6] Therefore, the development of an effective methodology for this reverse approach is important to synthesize structurally diverse substituted isoquinolines.

The Diels–Alder (DA) reaction of 3,4-pyridynes[6–8] with dienes, such as furans, is classified as the reverse approach and may be a powerful tool for the synthesis of isoquinolines; however, this reaction suffers from severe regioselectivity problems (Figure 1).[6] To the best of our knowledge, only two research groups have reported a total of three regioselective DA reactions. Guitián and co-workers developed a Cl-atom-directed regioselective DA reaction for the total synthesis of ellipticine.[6d,f] Recently, Goetz and Garg reported that a OSO_2NMe_2 moiety and a Br atom on 3,4-pyridyne could be used as directing groups for DA reactions with furan.[6i] These electron-withdrawing directing groups were transformed into other substituents, such as amino and aryl, and H groups by transition-metal-catalyzed reactions. However, the regioselectivity of the products and the number of substituents accessed from them were not sufficient, and the generality of these reactions has not been investigated in detail. Therefore, to make the reverse approach more practical, a new methodology, which utilizes another powerful and versatile directing group, is required.

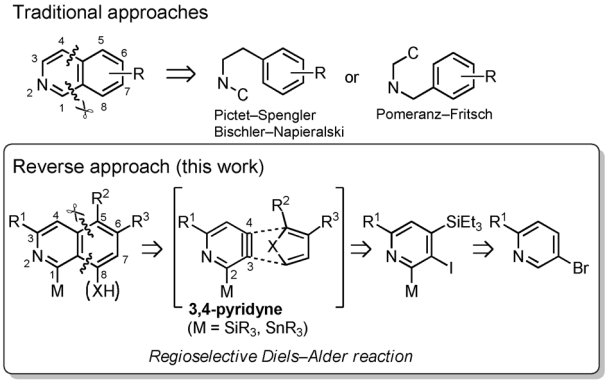

Figure 1. Comparison between traditional approaches and this work for the syntheses of isoquinolines.

Herein, we demonstrate that inductively electron-donating groups (M) such as silyl[9] and stannyl, can be used as directing groups for the first time and the DA reactions of such 3,4-pyridynes can be achieved with moderate-to-excellent regioselec-

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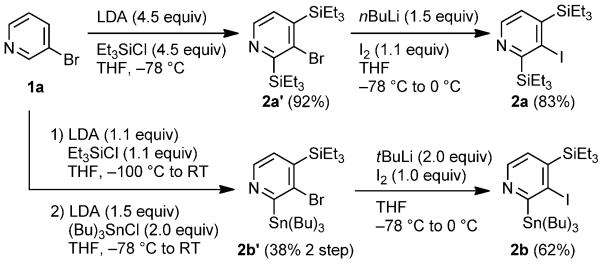
tivity (Figure 1). Moreover, the silyl groups of the DA adducts worked to introduce diverse substituents (R) at the C1-position of isoquinolines. Thus, the overall process results in the four-step synthesis of diverse multisubstituted isoquinoline derivatives from readily available 3-bromopyridines.

Results and Discussion

We designed new precursors, 3-iodo-2,4-bis(triethylsilyl)pyridine (**2a**)[10] and 3-iodo-2-(tributylstannyl)-4-(triethylsilyl)pyridine (**2b**), to afford 3,4-pyridynes, possessing the directing silyl (**3a**)[9] or stannyl group (**3b**) at the C2-position, by treatment with a fluoride ion. After intensive trials, **2a** and **2b** were synthesized from commercially available 3-bromopyridine **1a** (Scheme 1). Thus, the in situ double triethylsilylation of **1a**

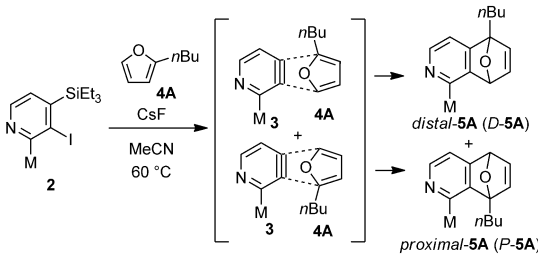


Scheme 1. Synthesis of new precursors, 2,4-bis(triethylsilyl)-3-iodopyridine (**2a**) and 3-iodo-2-(tributylstannyl)-4-(triethylsilyl)pyridine (**2b**).

using excess amounts of lithium diisopropylamide (LDA) and Me_3SiCl afforded 2,4-bis(triethylsilyl)-3-bromopyridine **2a′**.[11] The transformation of **2a′** to **2a** was achieved by a Br/Li exchange followed by I_2 quenching (76% over two steps). On the other hand, the sequential C4-silylation and C2-stannylation afforded **2b′** regioselectively; the iodination of **2b′** afforded **2b** (24% in three steps).[12]

The generation of 3,4-pyridynes **3a–f** from the corresponding pyridines **2a–f**, and the regioselectivity of their DA reactions with 2-butylfuran **4A**, were examined by using CsF in MeCN at 60 °C (Table 1). The reaction of 2-(triethylsilyl)-3,4-pyridyne **3a**,[13] generated from **2a**, preferentially afforded *distal*-**5Aa** (*distal*-**5Aa**/*proximal*-**5Aa** = 2.3:1, Table 1, entry 1). Notably, although precursor **2a** has silyl groups at the C2- and C4-positions, 3,4-pyridyne **3a** was obtained with excellent chemoselectivity.[12] The precursor **2a**, bearing a 3-iodo group, was necessary to achieve a high yield (93% yield, obtained by NMR spectroscopy) of *distal*- and *proximal*-**5Aa**; when the 3-bromo analogue, **2a′**, was used the total yield of **5Aa** slightly decreased (78%, obtained by NMR spectroscopy) owing to the protodesilylation of **2a′** (entry 2). The regioselectivity of 3,4-pyridyne **3c** bearing a bulkier tributylsilyl group at the C2-position (*distal*-**5Ac**/*proximal*-**5Ac** = 2.4:1, entry 3) was similar to that of **3a**, whereas a similar reaction of 2-(tributylstannyl)-3,4-pyridyne **3b** afforded slightly higher regioselectivity (*distal*-**5Ab**/*proximal*-**5Ab** = 2.8:1, entry 4). However, the silyl group is more attractive because of its significantly low toxicity compared to that of the stannyl group.

Table 1. Regioselectivity in the DA reactions of various 3,4-pyridynes **3**, obtained from pyridines **2**, with 2-butylfuran **4A**.[a]



Entry	M	2, 3	Time [h]	*D*-**5A**/*P*-**5A**[b]	**5A**	Yield [%][c]
1	$SiEt_3$	**2a**, **3a**	9	2.3:1	**5Aa**	93 (82)[d]
2[e]	$SiEt_3$	**2a′**, **3a**	6	2.3:1	**5Aa**	78 (77)[d]
3	$Si(Bu)_3$	**2c**, **3c**	25	2.4:1	**5Ac**	77 (70)[d]
4	$Sn(Bu)_3$	**2b**, **3b**	11	2.8:1	**5Ab**	83 (71)[d]
5	H	**2d**, **3d**	9	1.0:1	**5Ad**	48
6	*t*Bu	**2e**, **3e**	8	1.1:1	**5Ae**	92 (77)[d]
7	OMe	**2f**, **3f**	16	1:1.5	**5Af**	61 (56)[d]

[a] Conditions: 1.0 equiv of pyridine **2**, 7.0 equiv of furan **4A**, 1.5 equiv of CsF in MeCN (0.40 M) at 60 °C for 4–24 h. [b] Determined by ^1H NMR spectroscopy. [c] Total NMR yield of *distal*-**5A** and *proximal*-**5A**. [d] Total isolated yield of *distal*-**5A** and *proximal*-**5A**. [e] 2,4-Bis(triethylsilyl)-3-bromopyridine **2a′** was used instead of **2a**.

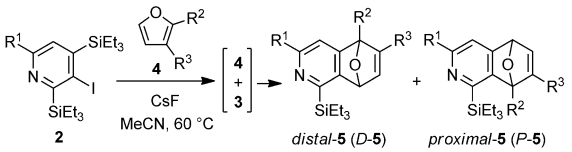
The above-mentioned results are significant because no selectivity was observed for the reactions of unsubstituted **3d** (*distal*-**5Ad**/*proximal*-**5Ad** = 1:1, entry 5) and 2-*tert*-butyl-3,4-pyridyne **3e** (*distal*-**5Ae**/*proximal*-**5Ae** = 1.1:1, entry 6). The reaction of 2-methoxy-3,4-pyridyne **3f** preferentially afforded *proximal*-**5Af** with low selectivity (*distal*-**5Af**/*proximal*-**5Af** = 1:1.5, entry 7). As expected, the electron-donating inductive effects of the silyl and stannyl groups of **3a–c** afforded the *distal* adducts, which is opposite to the case of 2-methoxypyridyne **3f**.

The effects of methoxy (**3g**) and *t*Bu (**3h**) groups at the C6-position of 3,4-pyridyne on the regioselectivity were insignificant (*distal*-**5A**/*proximal*-**5A** = 2.5:1 for **5Ag** and 1.7:1 for **5Ah**) (Table 2, entries 1 and 2).

Next, the substrate scope and limitation of the DA reactions of **3a** with various furans **4** were investigated. The total isolated yields were moderate to excellent (60–92%, Table 2, entries 3–11), and all reactions afforded *distal*-**5a** as the major product. The regioselectivity increased according to the bulkiness of the R^2 and R^3 groups (entries 3–7); the highest regioselectivity was obtained by using 2-stannylfuran **4F** (*distal*-**5Fa**/*proximal*-**5Fa** = 14:1, entry 7). Interestingly, the distal products were preferentially obtained from the reactions with furans (**4G** and **4H**) bearing an electron-withdrawing substituent ($R^2 = CO_2Me$ and COMe) at the C2-position, even though the regioselectivity decreased (entries 8 and 9). In these cases, the protection of the carbonyl groups as an acetal significantly increased the distal selectivity and yield (entries 10 and 11).

The reaction of pyridyne **3a** with C2-substituted pyrrole **4K** afforded *distal*-**5Ka** with high regioselectivity (*distal*-**5Ka**/*proximal*-**5Ka** = 8.8:1, total 87% yield) [Eq. (1)]. This type of cycloaddition product, **5Ka**, containing an azabicyclo[2.2.1]heptane

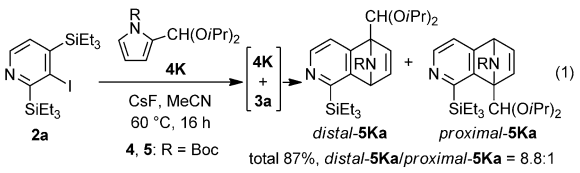
Table 2. Substrate scope and limitation of the regioselective DA reactions of 2-silyl-3,4-pyridynes **3** with various furans **4**.[a]



Entry	R^1	2, 3	R^2	R^3	4	*D*-5/*P*-5[b]	5	Yield [%][c]
1	OMe	**2g**, **3g**	*n*Bu	H	**4A**	2.5:1	**5Ag**	86
2	*t*Bu	**2h**, **3h**	*n*Bu	H	**4A**	1.7:1	**5Ah**	95[b]
3	H	**2a**, **3a**	Me	H	**4B**	2.0:1	**5Ba**	66
4	H	**2a**, **3a**	*t*Bu	H	**4C**	7.8:1	**5Ca**	92[d]
5	H	**2a**, **3a**	Me	Me	**4D**	4.3:1	**5Da**	65
6	H	**2a**, **3a**	$SiMe_3$	H	**4E**	>4.5:1	**5Ea**	88[e]
7[f]	H	**2a**, **3a**	$Sn(Bu)_3$	H	**4F**	14:1	**5Fa**	89
8	H	**2a**, **3a**	CO_2Me	H	**4G**	1.3:1	**5Ga**	60
9	H	**2a**, **3a**	COMe	H	**4H**	1.8:1	**5Ha**	62
10	H	**2a**, **3a**		H	**4I**	9.5:1	**5Ia**	79
11	H	**2a**, **3a**	$CH(OEt)_2$	H	**4J**	4.2:1	**5Ja**	63

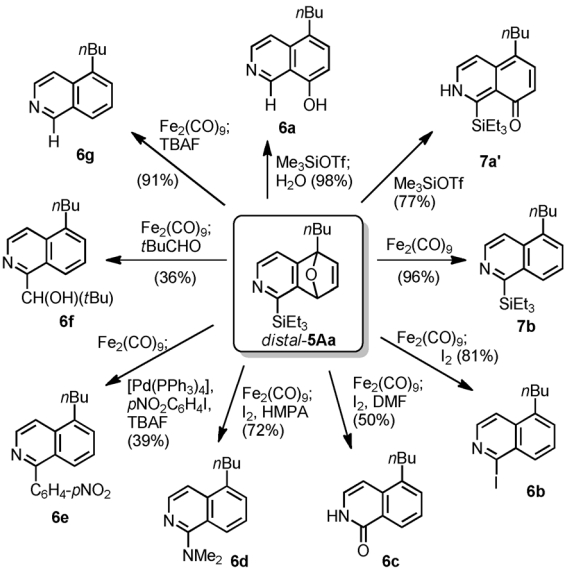
[a] Conditions: 1.0 equiv of **2**, 7.0 equiv of **4**, 1.5 equiv of CsF in MeCN (0.40 M) at 60 °C for 2–24 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Total isolated yield of *distal*-**5** and *proximal*-**5**. [d] Total isolated yield of *distal*-**5Ca** (58%), desilylated *distal*-**5Ca**′ (17%, M = H), and *proximal*-**5Ca**′ (17%, M = H). [e] Total isolated yield of *distal*-**5Ea** (72%), desilylated **5Ea**′ (2.4%, M = H), and **5Ea**″ (14%, R^2 = H). [f] 3.0 equiv of CsF was used.

skeleton can be used for the synthesis of functionalized alkaloids or other analogues.[14]



As a typical example, the DA adduct, *distal*-**5Aa**, was further transformed into various substituted isoquinolines **6a**–**6g**, **7a**′, and **7b** (Scheme 2). The 1,4-epoxide of **5Aa**[15] was opened by treatment with trimethylsilyl triflate (Me_3SiOTf), followed by quenching with H_2O, to afford 8-hydroxyisoquinoline **6a**. In contrast, the same reaction without quenching with H_2O afforded **7a**′. The deoxygenative cleavage[15a] of the 1,4-epoxide by using $Fe_2(CO)_9$ afforded 1-(triethylsilyl)isoquinoline **7b**, the silyl group of which was converted to an iodo (**6b**), oxo (**6c**), amino (**6d**), aryl (**6e**), alkyl (**6f**), or H (**6g**) group.[16] Therefore, the overall process provides a new method for the four-step, regioselective synthesis of various substituted isoquinoline derivatives (**6** and **7**) from 3-bromopyridine **1**.

Finally, the origin of the regioselectivity of the DA reactions of 3,4-pyridynes was analyzed by density-functional-theory (DFT) and natural-bond-orbitals (NBO) calculations (Figure 2).[17] The structures of **3a**, **3f**, and **4B** were optimized by DFT [B3LYP/6-31G(d)], and the electron densities of their reacting orbitals were calculated by NBO 5.0 (for reference, those of **3d** and **3e** are shown in the Supporting Information). The distortion and electronic property strongly indicate that the C3-position of **3a** is more electrophilic than the C4-position, and the C4-position of **4B** is more nucleophilic than the C2-position (for details, see the Supporting Information).[18] Therefore, the delocalization of electrons between the C3-position of **3a** and the C4-position of **4B**, and that between the C4-position of **3a** and the C2-position of **4B**, may be the major driving force for the distal selective DA reaction. In a similar manner, the observed opposite proximal selectivity in the case of **3f** can be explained by the distortion[6i,9f] and electronic properties[18] of **3f** (i.e., the C4-position of **3f** is more electrophilic). The properties of **3a** and **3b** can be attributed to the electron-donating inductive effects of the Si and Sn atoms, respectively, and those of **3f** can be attributed to the electron-withdrawing inductive effect of the O atom (Allred–Rochow electronegativities: O, 3.5; C, 2.5; Si, 1.7; Sn, 1.7).[19]



Scheme 2. Transformations of *distal*-**5Aa** to multisubstituted isoquinolines (**6a**–**6g**, **7a**′, and **7b**). TBAF = tetrabutylammonium fluoride; HMPA = hexamethylphosphoramide.

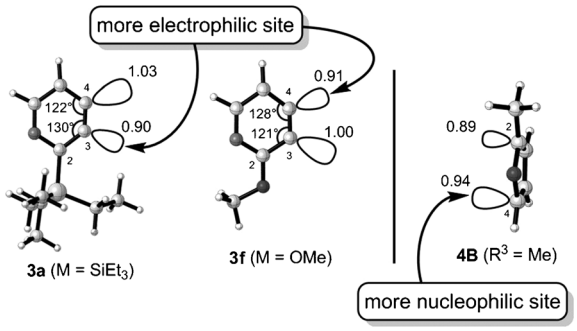


Figure 2. Electron densities and internal angles of 2-substituted pyridynes (**3a** and **3f**) and 2-methylfuran **4B**.[17]

Conclusion

We have demonstrated that various substituted isoquinoline derivatives could be synthesized in four steps starting from commercially available 3-bromopyridines. The silyl group attached at the C2-position of 3,4-pyridynes functions as an effective directing group for the regioselective DA reaction of 3,4-pyridynes with furans and also acts as a versatile functional group for further *ipso*-substitution, affording diverse substituents. The regioselectivity control by the 2-silyl group can be attributed to its electronic effect, as explained by theoretical studies. Further investigations, including the improvement of regioselectivities, the synthetic applications, and detailed mechanistic studies of the DA reactions with furans bearing electron-withdrawing groups are underway.

Experimental Section

Synthesis of 3-iodo-2,4-bis(triethylsilyl)pyridine 2a (Scheme 1)

A flame-dried flask with a stir bar was charged with 3-bromopyridine **1a** (1.0 equiv), capped with a three-way stopcock, and evacuated and back-filled with Ar. Anhydrous THF (0.50 M) was added by a syringe, and the mixture was cooled to −78 °C. A freshly prepared 0.80 M LDA (4.5 equiv) solution of THF was slowly added to the flask through a cannula over 5 min at −78 °C, and the mixture was stirred for 10 min. Et_3SiCl (4.5 equiv) was added at −78 °C, and the reaction mixture was warmed up to RT and stirred for 2 h. H_2O and Et_2O were added to the reaction mixture, and the aqueous phase was extracted three times with Et_2O. The combined organic phase was washed with a saturated aqueous NaCl solution. The organic phase was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 100:1 with 1% Et_3N) to afford 3-bromo-2,4-bis(triethylsilyl)-pyridine **2a′**. Another flame-dried flask with a stir bar was charged with **2a′** (1.0 equiv), capped with a three-way stopcock, and evacuated and back-filled with Ar. Anhydrous THF (0.30 M) was added by a syringe, and the mixture was cooled to −78 °C. A 1.6 M *n*BuLi solution (1.5 equiv) in hexane was slowly added by a syringe over 10 min under stirring, and the reaction mixture was stirred at −78 °C for 10 min. A 1.0 M iodine solution (1.1 equiv) in THF was slowly added to the flask by a syringe over 5 min. The reaction mixture was warmed to RT and stirred for 30 min. 5% $Na_2S_2O_3$ and Et_2O were added to the reaction mixture, and the aqueous phase was extracted three times with Et_2O. The combined organic phase was washed with a saturated aqueous NaCl solution. The organic phase was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 70:1 with 1% Et_3N) to afford precursor **2a**.

General procedure for DA reaction of 3,4-pyridyne 3 with furan 4 (Tables 1 and 2)

CsF (1.5 equiv) was flame-dried under reduced pressure in a reaction flask with a stir bar and a three-way stopcock, and evacuated and back-filled with Ar. A solution of precursor **2** (1.0 equiv) and furan **4** (7.0 equiv) in anhydrous MeCN (0.40 M) was added to the flask through a cannula. The mixture was stirred at 60 °C for the period shown in Tables 1 and 2 and cooled to RT. H_2O and Et_2O were added to the reaction mixture, and the aqueous phase was extracted three times with Et_2O. The combined organic phase was washed with a saturated aqueous NaCl solution. The organic phase was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was subjected to ^1H NMR analysis for calculating the ratio and total yield of the two regioisomers (*distal*- and *proximal*-**5**) using naphthalene as the internal standard. The crude product was purified by flash column chromatography on silica gel (hexane, a mixture of hexane and EtOAc, or CH_2Cl_2) to afford *distal*- and *proximal*-**5**.

Acknowledgements

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Keywords: cycloaddition · furans · isoquinolines · pyridynes · silyl groups

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