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Ring-Fluorinated Isoquinoline and Quinoline Synthesis: Intramolecular Cyclization of *o*-Cyano- and *o*-Isocyano-β,β-difluorostyrenes

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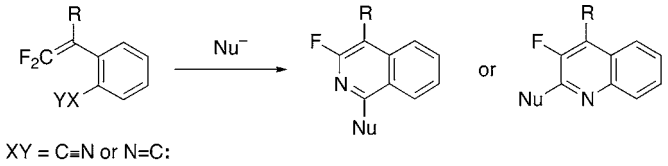
ABSTRACT



***o*-Cyano-β,β-difluorostyrenes react with organolithiums selectively at the cyano carbon to generate the corresponding sp² nitrogen anions, which in turn undergo intramolecular replacement of the vinylic fluorine to afford 3-fluoroisoquinolines. Similarly, the reaction of β,β-difluoro-*o*-isocyanostyrenes with organomagnesiums or -lithiums generates the corresponding sp² carbanions on the isocyano carbon. Subsequent cyclization via substitution of the fluorine leads to 3-fluoroquinolines.**

The quinoline and isoquinoline nuclei are regioisomers of benzene-annulated pyridines (benzo[*b*]pyridine and benzo[*c*]pyridine). They are widespread in the alkaloid family and constitute an important class of compounds in pharmaceuticals, agrochemicals, and dyestuffs.[1] Due to their substantial applicability, the syntheses of quinolines and isoquinolines are extensively studied topics.[2,3] However, despite their common properties and much research on their preparation, a synthetic methodology based on a single concept that can be applied to both ring systems remains to be developed.

In our recent publications, we have reported the construction of five- and six-membered ring-fluorinated heterocyclic compounds such as indoles, benzo[*b*]furans, benzo[*b*]thiophenes, 2-pyrrolines, 2,3-dihydrofurans, 2,3-dihydrothiophenes, isochromenes, and isothiochromenes (Scheme 1a).[4] *gem*-Difluoroalkenes bearing functional groups such as NHTs, OH, and SH undergo nucleophilic 5- and 6-*endo*-*trig* cyclizations via deprotonation of these functional groups that generates sp³ nitrogen, oxygen, and sulfur nucleophiles. The reactions are promoted by the unique reactivity of *gem*-difluoroalkenes toward nucleophilic substitution of their

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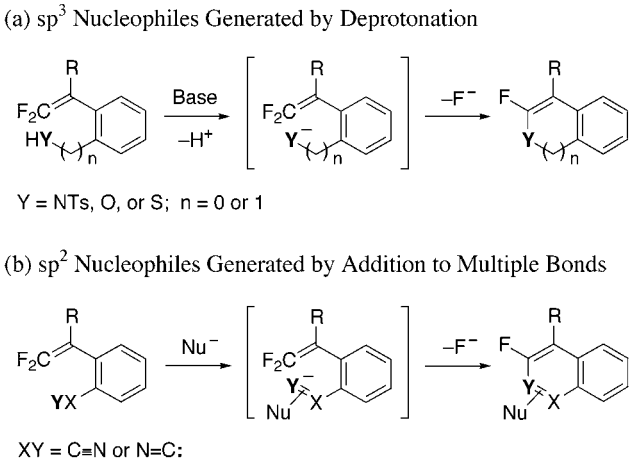
Scheme 1. Intramolecular Substitution of in Situ-Generated Nucleophiles ($\mathbf{Y}^-$)



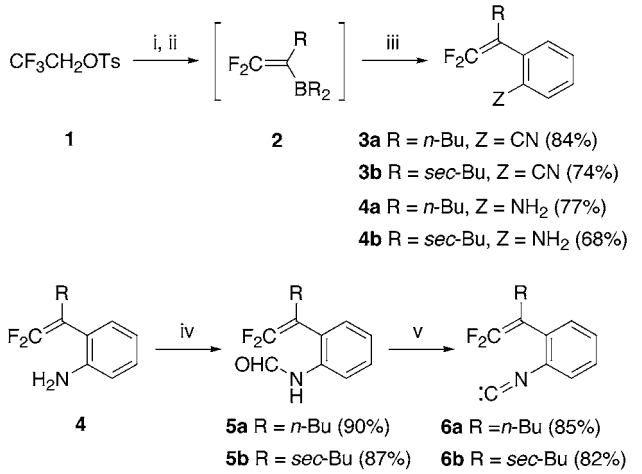
vinylic fluorines via addition−elimination processes.[5] Their reactivity is due to (i) the electrophilic activation of the C−C double bond by the two fluorine atoms, (ii) the stabilization of the intermediary carbanion by the β-anion stabilizing effect of fluorine, and (iii) the leaving-group ability of the fluoride ion. This "intramolecular substitution" concept for ring formation prompted us to explore its application to the construction of quinoline and isoquinoline frameworks.

Herein we wish to report a facile, common methodology for the syntheses of 3-fluorinated isoquinolines and quinolines starting from *ortho*-substituted β,β-difluorostyrenes. Although these selectively ring-fluorinated heterocycles have significant potential as components[6a] and synthetic intermediates[6b] of biologically active substances and advanced materials,[7] their synthetic methods are still quite limited.[8,9] The introduction of fluorine atoms especially onto heterocyclic ring carbons is even more difficult than the fluorine introduction onto the carbons of fused benzene rings.

To accomplish direct construction of six-membered aromatic nuclei, we chose to examine sp^2 nucleophiles for the intramolecular substitution of *gem*-difluoroalkenes. It was expected that addition of external nucleophiles (Nu) to C−N multiple bonds (XY) such as those of cyano and isocyano groups would generate sp^2 nitrogen and carbon nucleophiles, respectively, as shown in Scheme 1b.[10] These in situ-generated nucleophilic groups located at the *ortho* position of β,β-difluorostyrenes would then promote similar cyclizations, leading directly to the construction of ring-fluorinated aromatics, both isoquinolines and quinolines with incorporation of a substituent (Nu) on the heterocyclic rings.[11]

The starting materials were easily prepared as outlined in Scheme 2 by using the one-pot sequence that we have previously developed for the preparation of β,β-difluorostyrenes.[12] The coupling reactions of 2,2-difluorovinylboranes **2** [generated in situ from 2,2,2-trifluoroethyl *p*-toluenesulfonate (**1**)] with *o*-iodobenzonitrile or *N*-butylmagnesio-*o*-iodoaniline (generated from *o*-iodoaniline and dibutylmagnesium) were carried out in the presence of CuI and a palladium catalyst to give *o*-cyano-β,β-difluorostyrenes **3** and *o*-amino-β,β-difluorostyrenes **4**. Aminostyrenes **4** were subjected to formylation of the nitrogen followed by dehydration of the resulting formamides **5**, leading to the desired β,β-difluoro-*o*-isocyanostyrenes **6**.

Scheme 2. Preparation of *Ortho*-Substituted β,β-Difluorostyrenes **3** and **6**[a]



[a] Reagents and conditions: (i) *n*-BuLi (2.1 equiv), THF, −78 °C, 0.5 h; (ii) BR_3 (1.1 equiv), THF, −78 °C, 1 h, and then rt, 3 h; (iii) *o*-IC_6H_4CN or *o*-IC_6H_4NHMgn-Bu (0.9 equiv), CuI (1.0 equiv), $Pd_2(dba)_3$·$CHCl_3$ (0.02 equiv), PPh_3 (0.08 equiv), THF−HMPA (4:1), rt, 1 h; (iv) HCO_2H (1.2 equiv), Ac_2O (1.2 equiv), pyridine, rt, 1 h; (v) $POCl_3$ (1.2 equiv), Et_3N (2.2 equiv), CH_2Cl_2, 0 °C, 0.5 h.

We first attempted the generation of intramolecular nucleophiles in difluorostyrenes **3** by the addition of external

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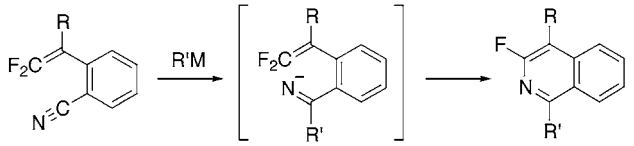
(11) For the synthesis of isoquinolines from aryl cyanides, see: (a) Lysén, M.; Kristensen, J. L.; Vedsø, P.; Begtrup, M. *Org. Lett.* **2002**, *4*, 257. For the synthesis of quinolines from aryl isocyanides, see: (b) Curran, D. P.; Du, W. *Org. Lett.* **2002**, *4*, 3215. (c) Kobayashi, K.; Nakashima, T.; Mano, M.; Morikawa, O.; Konishi, H. *Chem. Lett.* **2001**, 602. (d) Suginome, M.; Fukuda, T.; Ito, Y. *Org. Lett.* **1999**, *1*, 1977 and references therein.

(12) Ichikawa, J. *J. Fluorine Chem.* **2000**, *105*, 257 and references therein.

nucleophiles to the cyano group. In this scheme, the external nucleophile should exclusively attack the cyano carbon without adding to the difluoromethylene carbon. When **3a** was treated with *n*-BuMgCl, its nucleophilic attack took place on the cyano carbon to generate the corresponding imino nitrogen anions, which in turn underwent intramolecular substitution of the fluorine to give the expected 3-fluoroisoquinoline **7a** in 65% yield (Table 1, entry 1). While treatment of **3a** with *n*-BuLi/$CeCl_3$, an effective reagent for 1,2-additon to α,β-unsaturated ketones,[13] afforded **7a** in 62% yield (entry 2), the reaction of **3a** with *n*-BuLi gave an even better result (74% yield, entry 3). Screening of solvents in this reaction revealed that in Et_2O or toluene, the addition of *n*-BuLi occurred regioselectively at the cyano carbon of **3a** to afford **7a** in 86 and 82% yields (entries 4 and 5).

Table 1. Synthesis of 1,4-Disubstituted 3-Fluoroisoquinolines **7** from **3**



3a R = *n*-Bu
3b R = *sec*-Bu

7

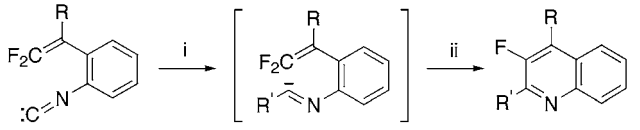
entry	**3**	R′M (equiv)	solvent	temp, time	% yield
1	**3a**	*n*-BuMgCl (4.0)	THF	reflux, 10 h	65 (**7a**)
2	**3a**	*n*-BuLi/$CeCl_3$ (3.0)	THF	−78 °C, 3 h	62 (**7a**)
3	**3a**	*n*-BuLi (1.2)	THF	−78 °C, 4 h	74 (**7a**)
4	**3a**	*n*-BuLi (1.2)	Et_2O	−78 °C, 0.5 h	86 (**7a**)
5	**3a**	*n*-BuLi (1.2)	toluene	−78 °C, 1 h	82 (**7a**)
6	**3b**	*n*-BuLi (1.2)	Et_2O	−78 °C, 7 h	82 (**7b**)
7	**3a**	MeLi (1.2)	toluene	0 °C, 0.5 h	81 (**7c**)
8	**3a**	*t*-BuLi (1.2)	Et_2O	−78 °C, 0.5 h	88 (**7d**)
9	**3a**	PhLi (1.2)	toluene	−78 °C, 1 h	85 (**7e**)
10	**3a**	HA*i*-Bu_2 (1.1)	toluene	90 °C, 7 h	84 (**7f**)

Under the reaction conditions obtained above, we examined the reaction of other nucleophiles such as methyllithium, *tert*-butyllithium, phenyllithium, and diisobutylaluminum hydride. As summarized in Table 1, treatment of **3** with these nucleophiles successfully led to cyclization to afford high yields of 3-fluoroisoquinolines **7a**−**f** bearing a butyl, methyl, *tert*-butyl, or phenyl group or hydrogen at the 1-position and a butyl or *sec*-butyl group at the 4-position (entries 4−10). Thus, this sequence provides a facile entry to 1,4-disubstituted 3-fluoroisoquinolines.

After having accomplished the synthesis of isoquinolines as described above, we next tried to construct the quinoline framework by means of the same strategy with the reversed order of the carbon and nitrogen in the *ortho* substituent. For this purpose, β,β-difluorostyrenes bearing an isocyano group instead of a cyano group should be employed as starting materials. The reaction of *o*-isocyanostyrenes with nucleophiles was expected to proceed in a similar manner via the corresponding sp^2 carbanion, providing 3-fluoroquinolines with a substituent at the 2-position.

Treatment of isocyanostyrene **6a** with *n*-BuLi in THF gave a complex mixture, probably due to its high nucleophilicity. After the reactions of **6a** with a Grignard reagent were conducted in several solvents, the choice of solvent was found to be crucial in controlling the reaction site. When **6a** was treated with *n*-BuMgBr in THF and toluene, *o*-(1-butyl-2,2-difluorovinyl)-*N*-pentylideneaniline was obtained in 10 and 73% yields, respectively. These results indicated that the addition of Grignard reagent in toluene selectively occurred on the isocyano carbon, but subsequent cyclization did not take place. To raise the reactivity of the intermediary carbanion, HMPA was added to the reaction mixture after generation of the carbanion, leading to the desired 3-fluoroquinoline **8a** in 69% yield (Table 2, entry 1). Several other 2,4-disubstituted 3-fluoroquinolines **8b**−**e** were successfully obtained on treatment of **6** with primary, secondary, or tertiary alkylmetals such as *n*-BuMgBr, EtMgBr, *i*-PrMgCl, and *t*-BuLi (entries 2−5).

Table 2. Synthesis of 2,4-Disubstituted 3-Fluoroquinolines **8** from **6**[a]



6a R = *n*-Bu
6b R = *sec*-Bu

8

entry	**6**	R′M (equiv)	% yield
1	**6a**	*n*-BuMgBr (1.2)	69 (**8a**)
2	**6b**	*n*-BuMgBr (1.2)	60 (**8b**)
3	**6a**	EtMgBr (1.2)	59 (**8c**)
4	**6a**	*i*-PrMgCl (1.2)	64 (**8d**)
5[b]	**6a**	*t*-BuLi (1.2)	78 (**8e**)
6[c]	**6a**	Et_3GeLi (1.5)	61 (**8f**)

[a] Reagents and conditions: (i) R′M, toluene, rt, 15 min; (ii) toluene−HMPA (5:1), 0 °C, 1 h, and then rt, 1 h. [b] Conditions: −78 °C, 1 h, and then rt, 1 h. HMPA was not added. [c] Solvent: toluene−THF (6:1). Conditions: −78 °C, 1 h, and then rt, 4 h.

In the attempted synthesis of 2-silylated 3-fluoroquinolines by the reaction of **6a** with triphenylsilyllithium or dimethylphenylsilyllithium as the external nucleophile, 4-butyl-3-fluoroquinoline was obtained instead in 50 or 46% yield, respectively, probably due to the instability of 2-silyl-3-fluoroquinolines. We also examined a similar reaction of **6a** with triethylgermyllithium, prepared in situ from triethylgermanium hydride, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, and *t*-BuLi.[14] The expected addition to the isocyano group and the subsequent cyclization occurred, leading to 3-fluoroquinoline **8f** with a germyl group at the 2-position (entry 6).[15] As shown in Table 2, diverse 2,4-disubstituted 3-fluoroquinolines can be synthesized by this method.

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In conclusion, we have accomplished the efficient construction of ring-fluorinated isoquinoline and quinoline frameworks starting from *ortho*-substituted β,β-difluorostyrenes via (i) the addition of nucleophiles to generate intramolecular sp^2 nucleophiles and (ii) their cyclization by substitution of the vinylic fluorine. Both 3-fluoroisoquinolines and 3-fluoroquinolines with a variety of substituents are readily synthesized by this methodology on the basis of the same concept. Thus, we have disclosed a new aspect of fluorine as a synthetic tool for heteroaromatic ring-forming reactions.

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Supporting Information Available: Experimental procedures and spectroscopic data of compounds **3**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Reaction of **6a** with tributylstannyllithium afforded 4-butyl-3-fluoroquinoline or the corresponding biquinoline, and these results will be reported in detail elsewhere.