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Synthesis of dictyomedins using phosphazene base catalyzed diaryl ether formation

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Abstract—Dictyomedins isolated from dictyostelium cellular slime molds were synthesized by using diaryl ether derivatives as key intermediates for the cyclization to dibenzofuran followed by palladium catalyzed intramolecular biaryl formation.

Dictyomedins A (**1a**) and B (**1b**) from Dictyostelium cellular slime molds were recently discovered by Oshima and co-workers as physiologically active substances, which inhibit their own development.[1a] Although they showed attractive biological activities in a preliminary biological evaluation, the isolated sample amount was not sufficient enough for various biological screening tests. Only a trace amount of dictyomedins can be isolated from a large amount of a dried fruit body extract of Dicyostelium and the synthetic supply of these compounds was strongly desirable from the biological interests. Besides the attractive biological activity, dictyomedins also have the unique structural feature, that is both dictyomedins A and B have a 4-aryldibenzofuran structure. Resembling dibenzofuran natural products kehokorins A–C were isolated from myxomycete and were revealed to possess cytotoxic activity against the HeLa cells.[1b] By taking the characteristic structural feature of dibenzofuran into consideration, a route using the combination of intramolecular biaryl formation and the diaryl ether formation was expected to provide easy access to benzofuran ring construction. From the viewpoint of medicinal chemistry, this synthetic plan is also considered to offer a diverse set of dictyomedin analogs for various biological studies. Thus we chose the halogenated diaryl ether **2** as a key precursor of dictyomedins, and we assembled three different aromatic rings (A, B, and C). We set up our synthetic plan using three sequential coupling reactions, namely, Suzuki–Miyaura coupling reaction for introducing an aryl group on A ring, diaryl ether synthesis, and transition metal catalyzed cyclization for dibenzofuran formation (Fig. 1). Diaryl ether synthesis[2] is considered to be one of the most important reactions in our synthetic plans. Conventionally, copper catalyzed reaction[3] or palladium catalyzed reaction[4] have been used for the biaryl ether synthesis, however we focused our interest on using S_NAr reaction[5] of aryl fluorides.

In connection with our recent studies on phosphazene base promoted reactions,[6] we have already reported S_NAr reaction of aryl fluorides with aryl silylether catalyzed by phosphazene bases to form diaryl ethers under mild reaction conditions, and other groups also reported similar organic base catalyzed diaryl ether synthesis.[7] Recently, we also developed a new system for direct coupling of aryl fluorides with nucleophiles in the presence

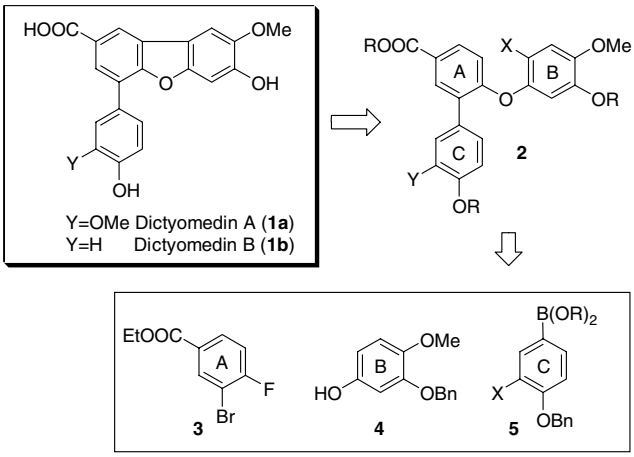

Figure 1. Dictyomedins and synthetic plan.

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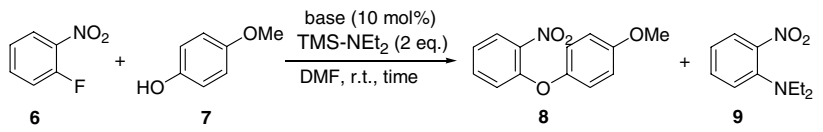
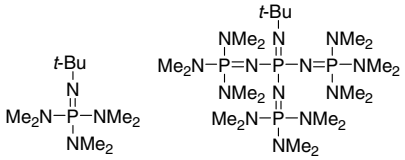
Table 1. S_NAr reaction and *t*-Bu-P4 base



6 7 8 9



t-Bu-P1 *t*-Bu-P4

Entry	Base	Time (h)	Yield of **8** (%)	Ratio of **8**:**9**[b]
1	*t*-Bu-P4	2	98[a]	98:2
2	*t*-Bu-P1	20	—	55:45
3	DBU	20	—	10:90
4	NEt_3	20	—	0:100
5	None	20	—	0:100

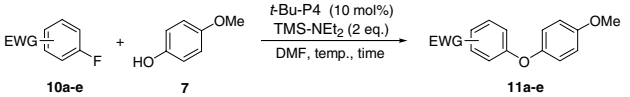
[a] Isolated yield.
[b] Estimated by ^1H NMR analysis.

of Et_3SiH as an additive.[8] However, after various optimization of additives, it was found that the use of TMS-NEt_2 works more effectively for the S_NAr reaction with phenols to shorten the reaction time.

As shown in Table 1, the reaction of fluoronitrobenzene (**6**) with *p*-methoxyphenol (**7**) proceeded smoothly in the presence of 2 equiv of $TMSNEt_2$ as an additive and 10 mol % of *t*-Bu-P4 base to give diaryl ether **8** in 98% yield (entry 1). The choice of base catalyst is crucial and *t*-Bu-P4 base showed the most excellent performance among various organic bases. The use of *t*-Bu-P1 base as a catalyst gave a mixture of the biaryl ether **8** and the undesired nitrodiethylaniline **9** (entry 2). The use of DBU and triethylamine gave **9** predominantly and the absence of base also led to give **9** (entries 3–5). The ratios of products **8** and **9** were estimated by analyzing ^1H NMR of crude reaction material.

We examined further reactions of functionalized fluorobenzenes **10a–e** with methoxyphenol (**7**) using these reaction conditions. The reaction of *m*-fluoronitrobenzene (**10a**) was slow at room temperature and the reaction was carried out at 100 °C for 2 h to give the diaryl ether (**11a**) in 96% yield (Table 2, entry 1). The reaction of *p*-fluoronitrobenzene (**10b**) proceeded smoothly at room temperature and product **11b** was obtained in quantitative yield (Table 2, entry 2). The reaction of *o*-fluorobenzonitrile (**10c**) also proceeded at room temperature to give product **11c** in quantitative yield (Table 2, entry 3). The reaction of ethyl *o*-fluorobenzoate (**10d**) was slow at room temperature and the reaction was conducted at 100 °C for 2 h to give product **11d** in quantitative yield (Table 2, entry 4). The reaction of *o*-bromofluorobenzene **10e** was also carried out at 100 °C to give the bromodiaryl ether **11e** in quantitative yield, but the reaction required 48 h for completion. Based on these results on S_NAr reaction, our interest was focused on the application to the syntheses of dictyomedins.

Table 2. *t*-Bu-P4 catalyzed S_NAr reaction



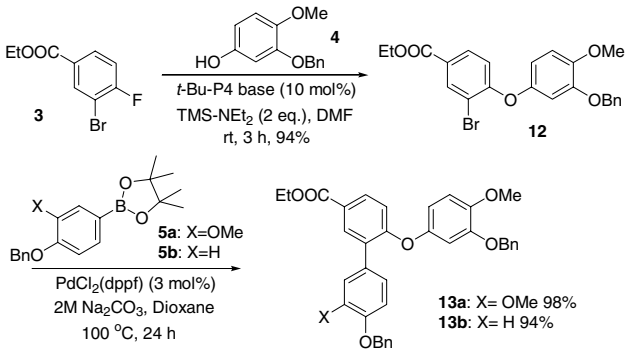
10a-e 7 11a-e

Entry	EWG	Temp (°C)	Time (h)	Yield (%)
1	*m*-NO_2 (**10a**)	100	2	96
2	*p*-NO_2 (**10b**)	rt	2	Quant.
3	*o*-CN (**10c**)	rt	2	Quant.
4	*o*-COOEt (**10d**)	100	2	Quant.
5	*o*-Br (**10e**)	100	48	Quant.

The syntheses of dictyomedins A and B were started with the coupling of ethyl 3-bromo-4-fluorobenzoate (**3**) and 3-benzyloxy-4-methoxyphenol (**4**). Fluorobenzoate **3** was easily prepared from 3-bromo-4-fluorobenzaldehyde and the functionalized phenol **4** was derived from isovanillin (see Supplementary data). The reaction of fluorobenzoate **3** with **4** proceeded smoothly at room temperature in the presence of 2 equiv of $TMSNEt_2$ as an additive and 10 mol % of *t*-Bu-P4 base to give diaryl ether **12** in 94% yield. Subsequently Suzuki–Miyaura coupling[9] of **12** was carried out using two types of boronic acid derivatives.

4-Benzyloxy-3-methoxy phenylboronic acid pinacolate (**5a**) and 4-Benzyloxy phenylboronic acid pinacolate (**5b**) were easily prepared from vanillin or 4-bromophenol, respectively (see Supplementary data). The Suzuki coupling of **12** with boronate **5a** or **5b** was carried out at 100 °C for 24 h using $PdCl_2$(dppf) and the desired arylated products **13a** and **13b** were obtained in 98% and 94% yields, respectively (Scheme 1).

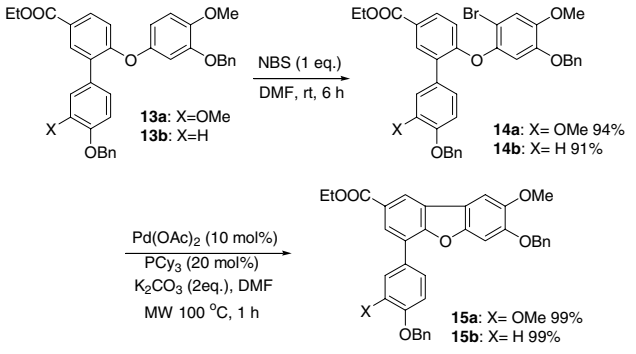
In order to form dibenzofuran ring system from **13a**,**b** using palladium catalyzed cyclization,[10] we first exam-



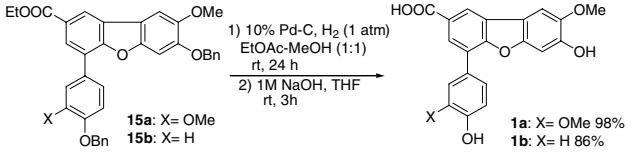
Scheme 1. Biaryl ether synthesis and Suzuki coupling.

ined the halogenation of **13a**,**b**. Judging from the electron density of aromatic ring carbons, the halogenation is expected to proceed at the position adjacent to biaryl ether oxygen at B ring. So the diaryl ethers **13a**,**b** were treated with NBS in DMF at room temperature and the desired mono brominated products **14a**,**b** were obtained in 94%, 91% yields, respectively. Then, palladium catalyzed intramolecular biaryl formation[11] was investigated and **14a**,**b** were treated with $Pd(OAc)_2$ and PCy_3 in the presence of K_2CO_3 at 100 °C for 1 h under microwave irradiation. Conventional oilbath heating gave the product in low yield with the formation of many side products. The use of microwave dramatically accelerated the cyclization and the irradiation was critical to obtain the products in high yields in a shorter reaction time (Scheme 2).

The final deprotection of benzyl groups was carried out by H_2, 10% Pd/C and the consequent hydrolysis of the ethoxycarbonyl group afforded dictyomedins A and B in 98% and 86% yields, respectively. (Scheme 3, **1a** and **1b**). The spectroscopic properties of both synthetic dyctyomedins A and B were identical with



Scheme 2. Dibenzofuran formation.



Scheme 3. Deprotection to dictyomedins.

those reported for naturally occurring dictyomedins A and B.

In conclusion, the first syntheses of dyctyomedins A, B have been accomplished using phosphazene catalyzed diarylether formation and palladium catalyzed intramolecular biaryl formation as key steps and the structures of natural dictyomedins were unambiguously confirmed. Further study for the analog synthesis of dyctyomedins using our methodology for biological evaluation is underway.

Acknowledgments

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Supplementary data

Experimental procedures and spectral data of synthesized compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.031.

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