Synthesis of Functionalized Biaryls Based on a Heck Cross-Coupling–[3+3] Cyclization Strategy

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Abstract: 6-Arylsalicylates were regioselectively prepared by formal [3+3] cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 1-aryl-3-ethoxyprop-2-en-1-ones which are available by Heck reaction of benzoyl chlorides with ethylvinyl ether. In this context, the first [3+3] cyclizations of brominated substrates are reported.

Key words: arenes, cyclizations, regioselectivity, silyl enol ethers

Functionalized biaryls containing a 6-arylsalicylate substructure occur in a variety of pharmacologically relevant natural products. This includes cytotoxic and hepatoprotective glycoside esters (e.g., amaroswerin),[1] cancerostatic benzo[1,2-*c*]phenanthridin-14-ones (e.g., sanguinarinone and oxysanguinarine),[2] dibenzo[*b*,*d*]-pyran-6-ones (e.g., the antitumor-active graphislactones),[3] simple biaryls,[4] complex macrocycles (e.g., sanguine),[5] dibenzoorthoquinones (e.g., murayaquinone),[6] 9,10-dihydrophenanthrenes (e.g., juncunone),[7] and the cynandiones (which show a considerable in vitro activity against hepatocytes, human bladder carcinoma T-24 cells, epidermoid carcinoma KB cells, and human hepatoma PLC/PRF/5 cells).[8]

The most important syntheses of biaryls rely on palladium(0)-catalyzed cross-coupling reactions.[9] Although these methods are broadly applicable, the synthesis of sterically encumbered products can be difficult or not possible at all. In addition, the synthesis of the required starting materials, functionalized arenes, can be a difficult task. An alternative strategy for the synthesis of biaryls relies on the assembly of the benzene moiety by cyclization reactions. Some years ago, Chan et al. developed[10] a convenient approach to salicylates by formal [3+3] cyclizations[11] of 1,3-bis(trimethylsilyloxy)-1,3-butadienes[12] with 3-trimethylsilyloxy-2-en-1-ones. Herein, we report an efficient synthesis of 6-arylsalicylates which is, to the best of our knowledge, the first application of a 'Heck cross-coupling–[3+3] cyclization' strategy. In this context, we also report for the first time the synthesis of brominated arenes by [3+3] cyclization reactions. Noteworthy, the sterically encumbered and functionalized biaryls reported herein are not readily available by other methods.

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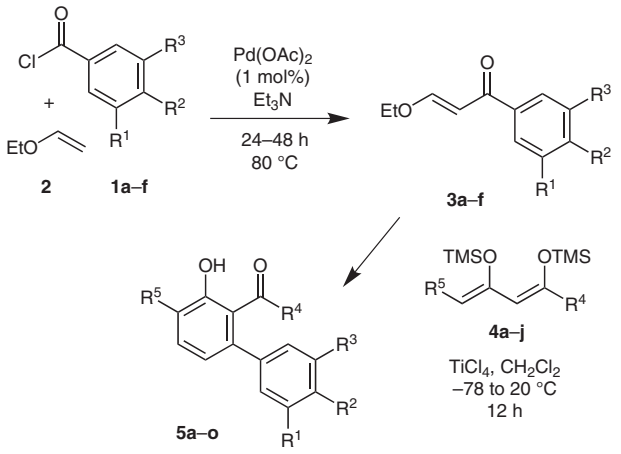
The Heck reaction of benzoyl chlorides **1a–f** with ethylvinyl ether (**2**) afforded the 1-aryl-3-ethoxyprop-2-en-1-ones **3a–f** (Scheme 1, Table 1).[13,14] The $TiCl_4$-mediated cyclization of **3a–f** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **4a–j**, prepared from the corresponding 1,3-dicarbonyl compounds,[10] afforded the 6-arylsalicylates **5a–o**. The best yields of products **5** were generally obtained when the reaction was carried out in a highly concentrated solution using stoichiometric amounts of the starting materials.[15] The low yield of **5o** can be explained by the generally lower reactivity of 1,3-diketone-derived compared to β-ketoester-derived 1,3-bis(silyl enol ethers).



Scheme 1 Synthesis of **5a-o**

The regioselective formation of **5a** (and of all other biaryls **5**) can be explained by $TiCl_4$-mediated conjugate addition of the terminal carbon atom of **4a** onto **3a** (intermediate **A**), cyclization by attack of the central carbon atom of the 1,3-bis(trimethylsilyloxy)-1,3-butadiene onto the carbonyl group (intermediate **B**), and subsequent aromatization upon aqueous workup (Scheme 2).

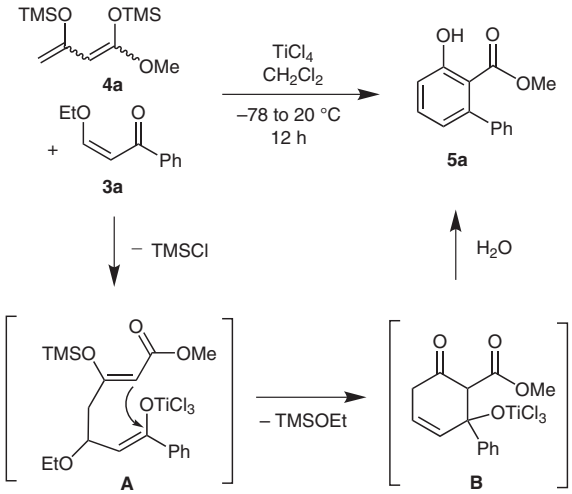
The structure of all products was established by spectroscopic methods. The structure of **5c** was independently confirmed by X-ray crystal structure analysis (Figure 1).[16] In addition, the configuration of biaryl **5a** was confirmed by its conversion into fluorenone (**6**, Scheme 3).

The bromination of **3a** and **3e** afforded **7a** and **7b**, respectively (Scheme 4, Table 2). The $TiCl_4$-mediated cyclization of **7a**,**b** with 1,3-bis(trimethylsilyloxy)-1,3-

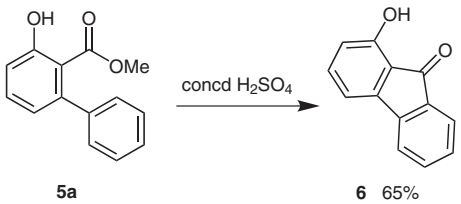
Table 1 Synthesis of **5a–o**

3	4	5	R^1	R^2	R^3	R^4	R^5	Yield of **3** (%)[a]	Yield of **5** (%)[a]
3a	**4a**	**5a**	H	H	H	OMe	H	49	36
3b	**4a**	**5b**	H	Cl	H	OMe	H	51	35
3c	**4a**	**5c**	H	NO_2	H	OMe	H	22	30
3d	**4b**	**5d**	OMe	OMe	OMe	O*i*-Bu	H	54	30
3e	**4c**	**5e**	H	OMe	H	OMe	Me	32	48
3a	**4d**	**5f**	H	H	H	OEt	Et	49	43
3a	**4e**	**5g**	H	H	H	OMe	*n*-Pr	49	56
3e	**4e**	**5h**	H	OMe	H	OMe	*n*-Pr	32	86
3f	**4f**	**5i**	OMe	H	H	OMe	*n*-Hex	30	30
3a	**4g**	**5j**	H	H	H	OMe	*n*-Oct	49	70
3d	**4h**	**5k**	OMe	OMe	OMe	OMe	$(CH_2)_3Ph$	54	37
3a	**4h**	**5l**	H	H	H	OMe	$(CH_2)_3Ph$	49	32
3b	**4h**	**5m**	H	Cl	H	OMe	$(CH_2)_3Ph$	51	33
3b	**4i**	**5n**	H	Cl	H	OMe	OMe	51	30
3d	**4j**	**5o**	OMe	OMe	OMe	Et	Me	54	12

[a] Yields of isolated products.



Scheme 2 Regioselectivity of the cyclization of **3a** with **4a**



Scheme 3 Transformation of **5a** into **6**

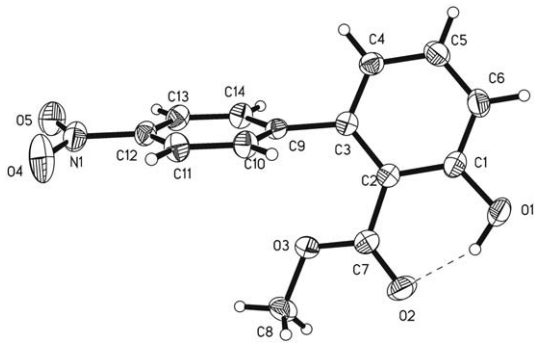
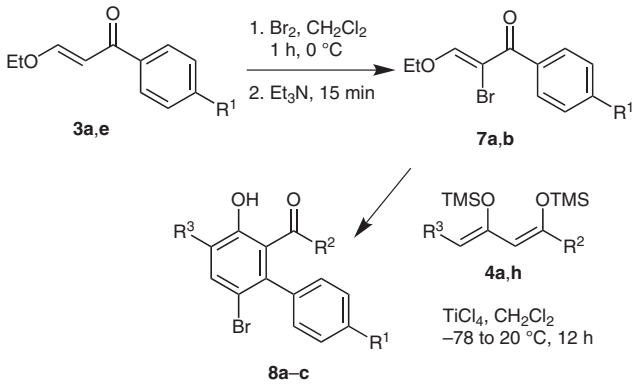


Figure 1 Molecular structure of **5c**

butadienes **4a**,**h** afforded the 6-aryl-5-bromosalicylates **8a**–**c**. Noteworthy, these reactions represent what are, to the best of our knowledge, the first [3+3] cyclizations of bromine-containing substrates. The transformations are of synthetic utility, since the bromide group can be further functionalized by palladium(0)-catalyzed cross-coupling reactions and other transformations. Noteworthy, highly substituted brominated arenes are not readily available by electrophilic substitutions, due to the formation of regioisomers. The structure of **8a** was independently confirmed by X-ray crystal structure analysis (Figure 2).[16]

In conclusion, we reported a convenient and regioselective synthesis of 6-arylsalicylates by formal [3+3] cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 1-aryl-3-ethoxyprop-2-en-1-ones which were prepared by Heck reaction of benzoyl chlorides with ethylvinyl ether. In this



Scheme 4 Synthesis of 5-bromo-6-arylsalicylates **8a–c**

Table 2 Synthesis of 5-Bromo-6-arylsalicylates **8a–c**

3	7	4	8	R^1	R^2	R^3	Yield of **7** (%)[a]	Yield of **8** (%)[a]
3a	**7a**	**4a**	**8a**	H	OMe	H	61	50
3a	**7a**	**4h**	**8b**	H	OMe	Me		52
3e	**7b**	**4h**	**8c**	OMe	OMe	Me	36	48

[a] Yields of isolated products.

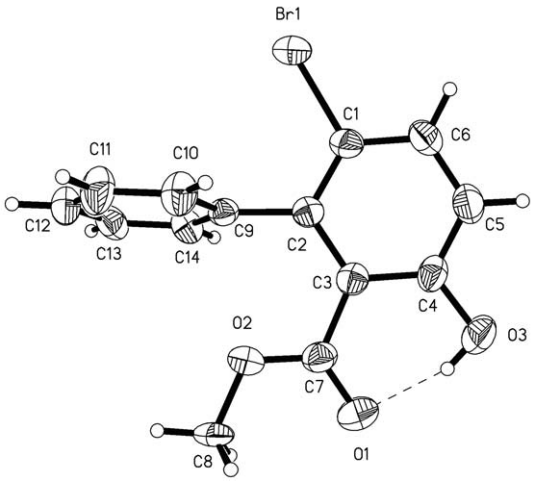


Figure 2 Molecular structure of **8a** (only one of the two symmetry-independent molecules is shown)

context, the first [3+3] cyclizations of brominated substrates are reported.

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(14) **Typical Procedure for the Heck Reaction of Ethylvinyl Ether with Acid Chlorides**
To a mixture of ethylvinyl ether (2.90 g, 40.0 mmol) and of Et_3N (1.20 g, 12.0 mmol) in a pressure tube was added $Pd(OAc)_2$ (20 mg, 0.1 mmol) under Ar atmosphere. The mixture was stirred until a clear yellow solution was formed. To the mixture were added benzoylchloride (1.20 g, 10.0 mmol), and the mixture was stirred at 80 °C for 24 h. The mixture was poured into Et_2O (50 mL) and the solid (triethylammonium hydochloride) was filtered off. The filtrate was concentrated under reduced pressure and the residue was purified by chromatography (SiO_2, heptanes–EtOAc = 10:1 → 5:1) to give **3a** as a slightly yellow oil (3.80 g, 55%).

(15) **General Procedure for the Synthesis of Salicylates 5**
To a CH_2Cl_2 solution (1 mL) of **3a** (176 mg, 1.0 mmol) and **4a** (260 mg, 1.0 mmol) was added a CH_2Cl_2 solution (1 mL) of $TiCl_4$ (0.12 mL, 1.0 mmol) at –78 °C. The temperature of the solution was allowed to warm to 20 °C within 14 h. To the mixture was added CH_2Cl_2 (10 mL) and HCl (10 mL, 10%). The organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (heptane–EtOAc, 10:1) to give **5a** as a slightly yellow oil (0.081 g, 36%).
Methyl 6-phenylsalicylate (**5a**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.47 (s, 3 H, OCH_3), 6.80 (d, ^3J = 7.4 Hz, 1 H, CH), 6.99 (d, ^3J = 7.4 Hz, 1 H, CH), 7.20–7.43 (m, 6 H, CH), 10.60 (s, 1 H, OH). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 52.1 (OCH_3), 112.5 ($CH_{Ph/Ar}$), 117.0, 123.0, 127.3, 128.0, 128.5, 134.1, 143.1, 145.3, 161.7, 171.8 (CO). IR (neat) = 3060 (m), 2952 (m), 1667 (s), 1601 (s), 1572 (m), 1501 (w), 1439 (s), 1343 (m), 1271 (s), 1220 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 228 (36) [M^+], 196 (100), 168 (53), 139 (34). ESI–HRMS: *m/z* calcd for $C_{14}H_{12}O_3$ [M + 1]$^+$: 228.07864; found: 228.07866.

(16) CCDC-679813 and CCDC-679814 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.