

A novel approach to functionalized (*E*)-1,4-diaryl-1-butenes by Heck reaction and their applications for the construction of dibenzylbutyrolactone lignan skeletons by radical cyclization

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Abstract—A highly regio- and stereoselective $[\text{Pd}(\text{allyl})\text{Cl}]_2$ catalyzed Heck reaction of aryl iodides and electronically neutral terminal olefins generated in situ by fluoride induced protodesilylation of alkenylsilanol derivatives under mild conditions has been developed. The products, viz. terminally substituted styrenes and (*E*)-1,4-diaryl-1-butenes were obtained in very good yields. The dibenzylbutyrolactone lignan skeletons have been prepared employing two regio- and stereoselective Bu_3SnH -mediated radical cyclization routes.

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Lignans¹ constitute a class of natural products with a great diversity of structures and significant pharmacological activities. The classification of lignans is based on their carbon skeleton as shown in Figure 1. The most common feature in these molecules is two aryl groups separated by a C-4 unit (Fig. 1). Due to their unique structures and biological activities, they are the targets of extensive synthetic research.²

We envisage a functionalized 1,4-diaryl-1-butene **1** as a potent precursor for the synthesis of all the different types of lignans (Fig. 1). Herein, we report a general and convenient synthetic protocol for functionalized 1,4-diaryl-1-butenes and the application of one such functionalized 1,4-diaryl-1-butene for the construction of dibenzylbutyrolactone lignan skeletons.

We have recently developed³ a general method for the preparation of 1-substituted alkenylsilanols **2**/disiloxanes **3** from the corresponding alkenyl(phenyl)silanes **4**⁴ (Scheme 1) and used them in Hiyama–Denmark^{5–7} type cross-coupling reactions with aryl iodides. Our exploratory studies³ on this cross-coupling reaction of

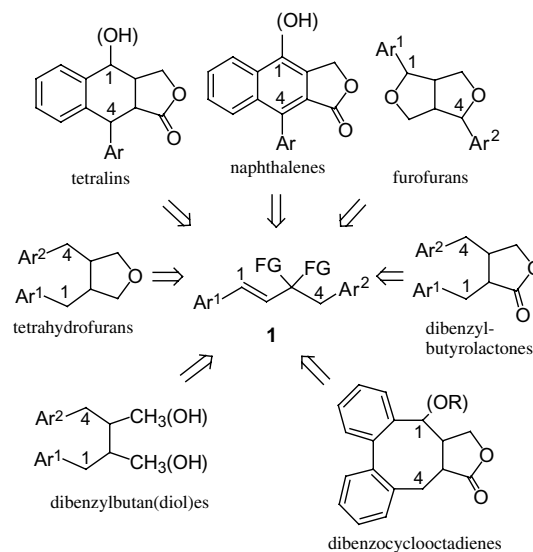
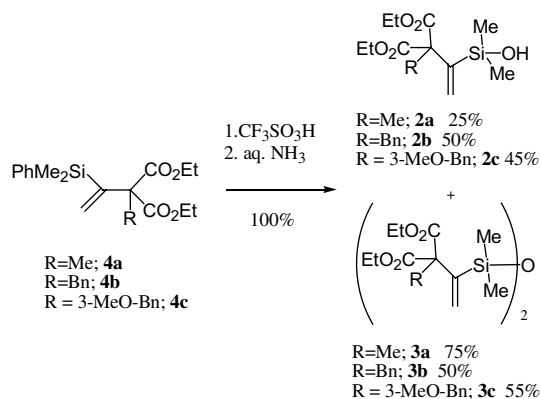


Figure 1.

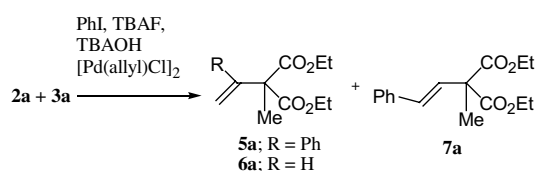
a mixture of **2a** and **3a** with iodobenzene using $[\text{Pd}(\text{allyl})\text{Cl}]_2$ as the catalyst and tetrabutylammonium fluoride (TBAF) or a combination of TBAF and tetrabutylammonium hydroxide (TBAOH)⁸ as the promoter in various solvents gave a mixture of 1-substituted styrene **5a**, protodesilylated olefin **6a** and the *cis*-coupled styrene derivative **7a** (Scheme 2).

Keywords: Heck reaction; Stereoselective synthesis; Styrene derivatives; Radical cyclization; Dibenzylbutyrolactones.

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Scheme 1.



Scheme 2.

The ratio of the products varied depending on the reaction conditions. We probed³ the formation of the *cine*-coupled product and confirmed that it did not form by the direct cross-coupling⁹ of the silanol **2a** or disiloxane **3a**. Under the coupling conditions, the silanes first undergo a rapid fluoride induced protodesilylation to terminal olefin **6a**, which then undergoes a Heck reaction with iodobenzene in the presence of [Pd(allyl)Cl]₂ to give **7a**.

In general, traditional Heck reaction of aryl iodides proceeds smoothly with terminal alkenes substituted with electron-withdrawing groups.¹⁰ However, electronically neutral or electron-rich alkenes were less common as substrates.¹¹ Therefore, it was a challenge to establish

suitable conditions for regio- and stereoselective Heck reactions of iodoarenes with electronically neutral functionalized terminal olefins such as **6a** generated in situ from the reaction of the corresponding silanol/disiloxane **2a/3a** with TBAF.

In our initial cross-coupling studies, reaction of silanes **2a/3a**, iodobenzene (1.5 equiv), a combination of TBAF (1.5 equiv) and TBAOH (1 equiv) and [Pd(allyl)Cl]₂ at room temperature for 40 h gave the desired terminally substituted styryl product **7a** in 42% isolated yield.¹² At this stage we introduced tetrabutylammonium chloride (TBACl)¹³ and replaced TBAOH with Et₃N. After a large number of variations of the proportions of reagents, optimized coupling conditions were found. The reaction could be carried out efficiently in the presence of TBACl (1 equiv), Et₃N (0.75 equiv), TBAF (1.5 equiv) and [Pd(allyl)Cl]₂¹⁴ (0.05 equiv) with heating of the mixture at 80 °C for 40 h. The desired product **7a** was obtained in 75% isolated yield exclusively as the (*E*)-isomer without a trace of the regioisomer **5a**. The scope of this coupling reaction was first generalized with silanol **2a**/disiloxane **3a** with a few functionalized iodo-arenes (Table 1, entries 1–5). The styryl derivatives, **7a–e** were formed in very good yields and with excellent regio- and stereoselectivities. When benzyl substituted silanols **2b,c**/disiloxanes **3b,c** were examined under the optimized conditions using various aryl iodides, (*E*)-1,4-diaryl-1-butenes **1a–h** were obtained in very good yields again, with complete regio- and stereocontrol. The results are summarized in Table 1.

We successfully prepared the dibenzylbutyrolactone lignan skeletons from 1,4-diaryl-1-butene **1a** following two routes as depicted in Scheme 3.¹⁷ The diester **1a** was first hydrolyzed to the racemic acid **8** (mp 117 °C). In the first route, the acid was converted to its phenylselenomethyl ester **9**¹⁸ and then a tin hydride-mediated radical cyclization provided the *trans*-dibenzylbutyrolactone **10**¹⁹ as the major product (*trans/cis* = 78/22). The *trans*-disubstituted lactone was expected to be the dominant

Table 1. Coupling of silanols/siloxanes with various aryl iodides^{15,16}

Entry	Ar	R	Product	% Yield
1	Ph-	Me	7a	75
2	4-MeO-C ₆ H ₄ -	Me	7b	75
3	2-MeO-4-Me-C ₆ H ₃ -	Me	7c	80
4	1-Naphth-	Me	7d	68
5	4-AcNH-C ₆ H ₄ -	Me	7e	72
6	4-MeO-C ₆ H ₄ -	Bn	1a	75
7	4-AcNH-C ₆ H ₄ -	Bn	1b	75
8	1-Naphth-	Bn	1c	65
9	4-Me-C ₆ H ₄ -	Bn	1d	76
10	2-MeO-4-Me-C ₆ H ₃ -	Bn	1e	73
11	Ph-	3-MeO-C ₆ H ₄ -CH ₂ -	1f	71
12	4-MeO-C ₆ H ₄ -	3-MeO-C ₆ H ₄ -CH ₂ -	1g	80
13	4-AcNH-C ₆ H ₄ -	3-MeO-C ₆ H ₄ -CH ₂ -	1h	75

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