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Fast Chelation-Controlled β,β -selective Heck Diarylation of Vinyl Ethers

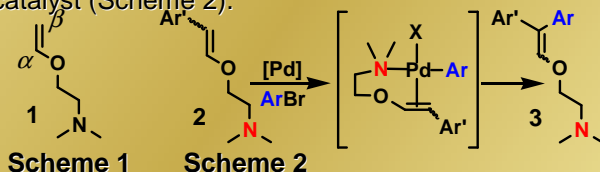
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Introduction

In modern medicinal and combinatorial chemistry, reaction optimization rear up as a bottleneck that can severely restrict the productivity. Rapid and reproducible synthetic techniques are therefore required. We have previously reported that highly β -selective (terminal) arylations of vinyl ethers can be accomplished by the use of the metal chelating amine auxiliary **1** (Scheme 1).^{1,2} We now wanted to develop a fast one-pot technique to yield a diarylated electron rich olefin using a low concentration of a thermostable catalyst (Scheme 2).



Results and Discussion

Suitable conditions for fast β,β -diarylation of chelating **1** and **2** under non-inert conditions were developed (Table 1).³ Herrmann's palladacycle was chosen as catalyst due to its high thermal stability and no more than 0.5 mol-% of this palladium source was required for this two-step transformation.⁴ Within 10-55 minutes of directed microwave heating at 160-200 °C acceptable yields were isolated of symmetrical **3** using a variety of aryl bromides.

Starting from a β -monophenylated scaffold a series of non-symmetrical β,β -diarylated compounds were produced similarly (Table 2).

The produced compounds show similarity with different therapeutic drugs (Scheme 3) and are thus interesting for medicinal applications.

Conclusion

✓ A high-speed protocol for regioselective tandem β,β -diarylation of electron-rich vinyl ethers using a thermostable catalyst in low concentration has been developed.

Table 1. Symmetric β,β -bisarylated compounds

1 $\xrightarrow[0.005 \text{ equiv. palladacycle}]{10\% \text{ aq. DMF, NaOAc, LiCl, K}_2\text{CO}_3}$ 3

Compound	Temp (°C)	time (min)	$\alpha,\beta/\beta,\beta$	Yield (%)	Compound	Temp (°C)	time (min)	$\alpha,\beta/\beta,\beta$	Yield (%)
	160	10	8/92	38		160	55	12/88	59
	180	10	6/94	52		180	30	12/88	55
	200	10	7/93	45		200	10	14/86	46
	160	55	5/95	80		160	360	23/77	9
	180	55	5/95	69		180	55	29/71	36
	160	20	10/90	65 ¹					
	180	10	10/90	67 ¹					

¹ 2 equiv. phenyl bromide was used

Table 2. Non-symmetric β,β -diarylated compounds

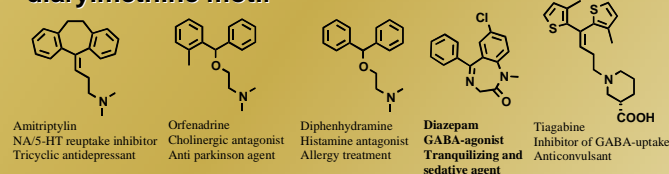
2 $\xrightarrow[0.005 \text{ equiv. palladacycle}]{10\% \text{ aq. DMF, NaOAc, LiCl, K}_2\text{CO}_3}$ 3

Compound	Temp (°C)	time (min)	$\alpha,\beta/\beta,\beta$	Yield (%)	Compound	Temp (°C)	time (min)	$\alpha,\beta/\beta,\beta$	Yield (%)
	160	120	5/95	32		180	20	3/97	62 ²
	180	55	5/95	41		200	10	3/97	62 ²
	200	30	7/93	39					
	200	120	14/86	25 ¹		160	360	2/98	41
		180	120	3/97		47			
	160	20	4/96	75		200	55	2/98	42
	180	10	6/94	65					
	200	10	6/94	64					

¹ 10% aq. dimethylacetamide was used as solvent

² 2 equiv. of 2-naphthyl bromide was used

Scheme 3. Some pharmaceuticals containing the diarylmethine motif



ACKNOWLEDGMENT. We thank the Swedish Foundation for Strategic Research, the Swedish Research Council and Biotage AB.

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