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Ruthenium-Catalyzed Synthesis of Functionalized 1,3-Dienes

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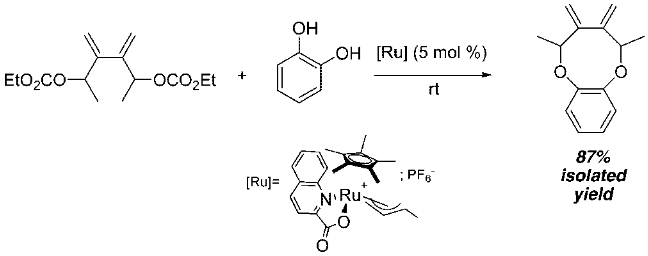
ABSTRACT



Functionalized 1,3-diene derivatives have been prepared by regioselective allylation of various nucleophiles with 1,3-dienic carbonates in the presence of a (*N,O*-carboxylate) allylruthenium precatalyst.

Allylation reactions catalyzed by transition-metal complexes have attracted much interest as a powerful tool in organic synthesis for C−C and C−heteroatom bond formation.[1] Recently, ruthenium catalysts have been largely used in reactions involving unsymmetrical allylic substrates to promote regioselective formation of branched compounds containing a chiral center.[2,3] Regioselective allylation with simple allylic substrates such as hexenyl, crotyl, or cinnamyl derivatives has been studied, but only a few catalytic systems have been explored to gain access to more highly functionalized compounds.[4] Notably, transition metal-catalyzed allylation reactions involving 1,2-disubstituted allylic substrates featuring a conjugated diene substructure have received little attention.[5]

Herein we report a Cp*Ru-based catalytic system that allows a regioselective allylation of a variety of nucleophiles using mono- and dicarbonates to produce functionalized 1,3-dienes with synthetic potential.[5c,6] The 1,3-dienic allylic substrates involved in this study are represented in Figure 1 along with the tested ruthenium precatalysts [Cp*Ru(MeCN)$_3$]-[PF$_6$] **I**,[2c,7] [Cp*Ru(*t*-Bu$_2$-bipy)(MeCN)][PF$_6$] **II**,[3a] and [Cp*Ru

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10.1021/ol8023488 CCC: $40.75

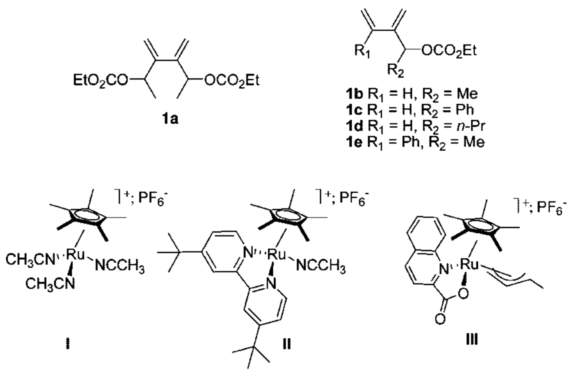


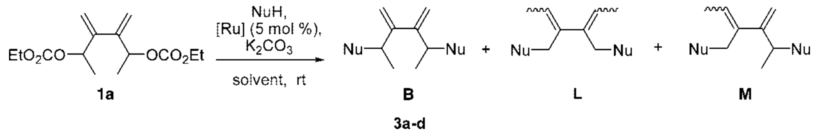
Figure 1. Allylic substrates and ruthenium precatalysts.

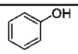
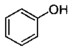
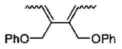
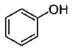
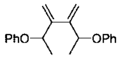
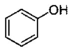
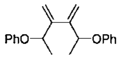
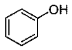
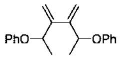
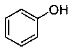
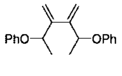
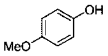
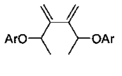
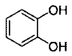
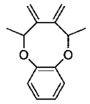
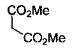
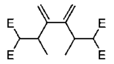
(2-quinolinecarboxylato)(crotyl)][PF_6] **III**.[3c] The new 1,3-dienecarbonates **1a**−**e** were prepared as a *rac*/*meso* mixture (Figure 1) via the well-described enyne cross-metathesis reaction from the corresponding alkynyl carbonates under an ethylene atmosphere using the Grubbs' second-generation carbene complex [$RuCl_2(H_2IMes)({=}CHPh)(PCy_3)$] **IV** as catalyst.[5c,8,9]

Allylation of phenol **2a** was attempted using a combination of 1 equiv of the 1,3-dienedicarbonate **1a** and 2 equiv of phenol in the presence of K_2CO_3 (Table 1). Precatalyst **I** bearing three labile acetonitrile ligands (Figure 1) was inactive and led to the recovery of **1a** (entry 1), likely due to a simple displacement of two acetonitrile ligands in **I** by **1a** acting as a diene,[10] generating an unreactive species. The presence of less labile ligands might be expected to hinder the coordination of **1a** as a diene, and we anticipated that precatalysts bearing a bipyridine,[3a] *P*,*O*-carboxylate,[11] or *N*,*O*-carboxylate ligand,[12] which have proven efficiency for allylation-type reactions, would be more suitable in the case of diene substrates. Accordingly, the involvement of the bipyridine complex **II** as precatalyst showed consumption of **1a** leading, however, to a mixture of B/L/M compounds (Table 1, entry 2) along with the presence of unidentified side products.[13]

More profitable was the use of precatalyst **III**, which resulted in a complete consumption of **1a** affording **3a** in an 86% isolated yield and noteworthy >98:1:1 B/L/M selectivity in favor of the disubstituted branched product (entry 3). The additional presence of a base such as potassium carbonate was essential to generate the phenoxide anion as

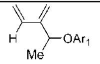
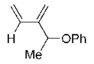
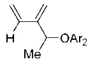
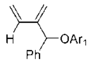
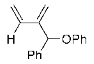
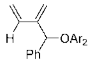
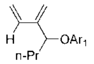
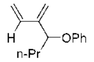
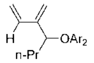
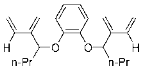
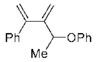
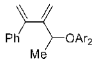
Table 1. Allylation of NuH Using 1,3-Dienedicarbonate **1a**[a]



entry	nucleophile		catalyst	solvent	B/L/M[b]	major product		yield[c] (%)
1		**2a**	**I**	CH_3CN	-	-	-	0
2		**2a**	**II**	CH_3CN	2:7:1		-	46
3		**2a**	**III**	CH_3CN	>98:1:1		**3a**	86
4		**2a**	**III**	Acetone	>98:1:1		**3a**	84
5		**2a**	**III**	CH_2Cl_2	>98:1:1		**3a**	80
6		**2a**	**III**	DMC	>98:1:1		**3a**	90
7		**2b**	**III**	CH_3CN	>98:1:1		**3b**	93
8[d]		**2c**	**III**	CH_3CN	>98:1:1		**3c**	87
9		**2d**	**III**	CH_3CN	>98:1:1		**3d**	87

[a] All reactions were carried out at 0.05 M concentration in the specified solvent at rt for 14 h under an inert atmosphere with **1a**/NuH/[Ru]/K_2CO_3 in a 1/2.2/0.05/2.2 molar ratio. [b] B (branched)/L (linear)/M (mixed) ratio determined by ^1H NMR on the crude mixture. [c] Isolated yields. [d] Reaction performed with **1a**/NuH/[Ru]/K_2CO_3 in a 1/1/0.05/2.2 molar ratio.

Table 2. Ruthenium-Catalyzed Allylation of ArOH with 1,3-Diene Monocarbonates **1b**−**e**[a]

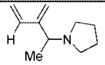
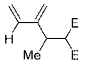
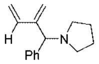
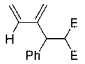
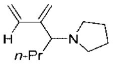
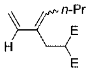
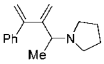
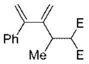
entry	reagent	NuH	B/L[b]	major product		yield[c] (%)
1	**1b**	**2b**	99:1		**4b**	71
2	**1b**	**2a**	98:2		**4a**	75
3	**1b**	**2c**	97:3		**4c**	87
4	**1c**	**2b**	95:5		**5b**	82
5	**1c**	**2a**	95:5		**5a**	86
6	**1c**	**2c**	88:12		**5c**	78
7	**1d**	**2b**	>99:1		**6b**	71
8	**1d**	**2a**	97:3		**6a**	50
9	**1d**	**2c**	97:3		**6c**	51
10[d]	**1d**	**2c**	94:6		**6f**	69
11	**1e**	**2a**	>99:1		**7a**	53
12	**1e**	**2c**	>99:1		**7c**	58

[a] All reactions were carried out at 0.05 M concentration in CH_3CN at rt for 14 h under an inert atmosphere with **1**/**2**/cat.**III**/K_2CO_3 in a 1/1.2/0.05/1.2 molar ratio, Ar_1= *p*-methoxyphenyl, Ar_2= *o*-hydroxyphenyl. [b] B (branched)/L (linear) ratio determined on the crude mixture by ^1H NMR. [c] Isolated yields. [d] **1**/**2c** in a 2.4/1 molar ratio was used.

nucleophile. Similarly, very high B/L/M selectivities in favor of the disubstituted branched product were obtained using acetone, dichloromethane, or dimethylcarbonate (DMC) (Table 1, entries 4−6). Attempts to react the diacetate analog of **1a** were unsuccessful. Remarkably, such excellent >98:1:1 B/L/M selectivities in favor of the disubstituted branched product were also obtained when *p*-methoxyphenol **2b**, catechol **2c**, or dimethyl malonate **2d** were used as nucleophile, leading to **3b**, the eight-membered ring diether **3c**, and the (bis)alkylated product **3d**, respectively (Table 1, entries 7−9). Compounds **3a**−**d** having two stereogenic centers were obtained as *rac*/*meso* mixtures analyzed by ^1H NMR.

These promising results also suggested that a new route was opened for the synthesis of functionalized 1,3-dienes starting from 1,3-dienic monocarbonate substrates **1b**−**e**. The scope of this reaction for allylation of various phenols through the involvement of allylic substrates **1b**−**e** is summarized in Table 2. Reaction of dienic substrates **1b**−**e** using precatalyst **III** led to good regioselectivities in favor of the corresponding branched ethers **4**−**7** in good to excellent isolated yields. High regioselectivities were obtained for the allylation reaction of ArOH with dienic substrates **1b** and **1d** featuring an aliphatic side chain (Table 2, entries 1−3 and 7−10). The presence of a phenyl group at the R_2 position resulted in lower regioselectivities (88:12 to 95:5) (Table 2, entries 4−6), whereas excellent results were obtained with dienic compound **1e** featuring a phenyl group at R_1 (Table 2, entries 11 and 12).

Table 3. Formation of Functionalized 1,3-Dienes Starting from Dimethyl Malonate **2d** and Pyrrolidine **2e**[a]

entry	reagent	NuH	B/L[b]	major product		yield [c] (%)
1	**1b**	**2e**	99:1		**4e**	81
2	**1b**	**2d**	8:2		**4d**	66
3	**1c**	**2e**	99:1		**5e**	72
4	**1c**	**2d**	6:4		**5d**	76
5	**1d**	**2e**	99:1		**6e**	67
6	**1d**	**2d**	2:8		**6d**	76
7	**1e**	**2e**	99:1		**7e**	68
8	**1e**	**2d**	99:1		**7d**	67

[a] All reactions were carried out at 0.05 M concentration in CH_3CN or CH_2Cl_2 at rt for 14 h under an inert atmosphere with **1**/**2**/cat. **III**/K_2CO_3 in a 1/1.2/0.05/1.2(0) molar ratio. [b] B (branched)/L (linear). [c] Isolated yields.

The allylation of carbonucleophile and amine for the formation of carbon−carbon and carbon−nitrogen bonds was then investigated with precatalyst **III**. Reactions were conducted at room temperature in acetonitrile for malonate and dichloromethane without additional base for amines (Table 3). Under our optimized conditions, in all cases reactions of dienic substrates **1** with pyrrolidine **2e** led to the exclusive formation of the branched products in satisfactory yields (Table 3, entries 1, 3, 5, and 7). It should be mentioned that slow degradation was observed after purification of these compounds, highlighting their instability.

Under similar conditions but in the presence of K_2CO_3 to generate the dimethyl malonate anion, the reaction of dienic susbtrates **1b** and **1c** with dimethyl malonate led to the formation of the allylated compounds with much lower regioselectivity (Table 3, entries 2 and 4). Moreover, linear selectivity was observed for the dienic substrate **1d** featuring the *n*-Pr side chain (Table 3, entry 6). In contrast with these results, exclusive branched selectivity was demonstrated

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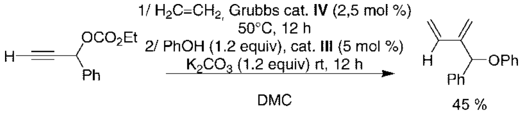
using the dienic substrate **1e**, indicating that the regioselectivity strongly depended on the nature of the starting allylic carbonate (Table 3, entry 8).

Having in hand this method to gain access to functionalized dienes, we undertook the preparation of these compounds directly from the corresponding alkynyl carbonates through one-pot metathesis−allylation catalysis.[14] Thus, the two-step metathesis−allylation sequence was performed in dimethyl carbonate, allowing the formation of the expected compound **5a** in 45% yield (Scheme 1).

Scheme 1. One-Pot Metathesis−Allylation Sequence



5a

In conclusion, we have shown that the [RuCp*(*N*,*O*-carboxylato)(η^3-butenyl)][PF$_6$] complex **III** is an efficient catalyst for the functionalization of dienic carbonates via regioselective allylation reactions. This reactivity reveals for the first time the ability of a ruthenium catalyst to perform the activation of 1,2-disubstituted allylic carbonates and their highly regioselective nucleophilic substitution in favor of branched isomers, and thus provides a new route to functional dienes that have potential in both synthesis and polymer science. The association of ene-yne cross metathesis and allylation constitutes a straightforward route to new conjugated dienes from ethylene, propargylic carbonates, and nucleophiles.

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Supporting Information Available: Experimental procedures and characterization data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) See Supporting Information for general protocol.

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(13) In principle, the formation of the B, L, and M regioisomers might result in the observation of up to seven species due to stereoisomerism.

(14) For allylic alkylation−RCM sequence see: Kammerer, C.; Prestat, G.; Gaillard, T.; Madec, D.; Poli, G. *Org. Lett.* **2008**, *10*, 405.