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A New One-Pot Synthetic Approach to the Highly Functionalized (*Z*)-2-(Buta-1,3-dienyl)phenols and 2-Methyl-2*H*-chromenes: Use of Amine, Ruthenium and Base-Catalysis

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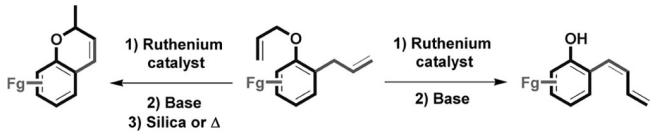
Keywords: Heterocycles / Phenols / Multi-catalysis reactions / Ring closing metathesis

A practical and simple one-pot multi-catalysis process for the synthesis of highly substituted benzo[*b*]oxepines **5**, (Z)-2-(buta-1,3-dienyl)phenols **6** and 2-methyl-2*H*-chromenes **7** from simple starting materials was achieved for the first time through ring-closing metathesis/base-induced ring opening/[1,7]-sigmatropic hydrogen shift reactions. The synthesis of privileged (Z)-2-(buta-1,3-dienyl)phenols **6** via base-induced ring opening of highly functionalized benzo[*b*]oxepines **5** is described

Introduction

Functionalized 2-(buta-1,3-dienyl)phenols and 2-methyl-2*H*-chromenes are of considerable importance in a variety of industries. They are, for instance, versatile building blocks for the synthesis of natural products.[1] As such, the development of new and more general catalytic methods for their preparation is of significant interest.[1] Recently Sherburn et al.[2a] discovered the phosphane-mediated reaction of 2-hydroxybenzaldehyde with allyltriphenylphosphonium bromide in the presence of strong base providing a 2-(buta-1,3-dienyl)phenol in moderate yield.

Herein we describe a novel one-pot and multi-catalysis technology for the synthesis of highly substituted (*Z*)-2-(buta-1,3-dienyl)phenols and 2-methyl-2*H*-chromenes starting from highly substituted dienes [Equation (1)]. A ruthenium/base/silica-catalyzed one-pot ring-closing metathesis (RCM) and ring-opening/[1,7]-sigmatropic hydrogen shift reactions are crucial steps in the reaction sequence. Functionalized 2-(buta-1,3-dienyl)phenols are useful materials as additives for rubbers and plastics, antioxidants, antibacterial agents, antibiotics and hair dyeing.[1] The base-induced ring opening of highly substituted 2,5-dihydrobenzo[*b*]-oxepines has not been reported before in the literature up to now.



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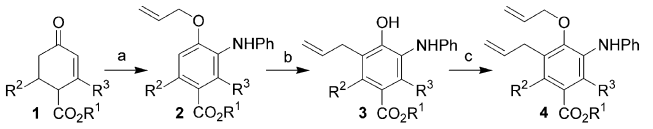
Results and Discussion

Based on our recent discovery of piperdine/K_2CO_3-catalyzed cascade enamine amination/iso-aromatization/alkylation (EA/IA/A) reaction of Hagemann's esters **1** with nitrosobenzene and allyl bromide leading to functionalized olefins **2**,[3] we reasoned that these olefins **2** might be a suitable starting material for the synthesis of highly functionalized dienes **4** as precursors for RCM reaction [Equation (2)]. Then we initiated our synthesis by the combination of cascade EA/IA reaction, *O*- and *C*-allylations and diene metathesis as key steps for the synthesis of highly substituted benzo[*b*]oxepines **5** starting from Hagemann's ester **1a** and nitrosobenzene as shown in Equation (2). The piperidine/K_2CO_3-catalyzed cascade EA/IA/A reaction of **1a**, nitrosobenzene and allyl bromide furnished the monoene amine **2a** in 95% yield. Claisen rearrangement of **2a** in DMF at 190 °C for 18 h yielded the expected phenol **3a** in 75% yield, which on *O*-allylation with allyl bromide and K_2CO_3 gave the diene amine **4a** in 80% yield. Six more functionalized dienes **4** were synthesized in very good yields using different Hagemann's esters **1b**–**g**. Interestingly, Claisen rearrangement of *tert*-butyl 4-allyloxy-2-methyl-3-(phenylamino)benzoate (**2c**) in DMF at 190 °C for 18 h furnished the decarboxylated phenol **3c**, which on *O*-allylation with allyl bromide and K_2CO_3 furnished the diene amine **4c** in 85% yield [see Equation (2) and also the Supporting Information for more details]. Interestingly, RCM reaction of free diene amine **4a** using Grubbs' first-generation cata-

lyst [Cl_2Ru=CHPh$(PCy_3)_2$] in CH_2Cl_2 at 25 °C for 2 h furnished the benzo[*b*]oxepine **5a** in 99% yield (Table 1). The technical advantage of this RCM reaction is the ruthenium catalysis applied to the free diene amine **4a** without the need of in situ salt formation.[4] Maybe the secondary amine group ($HNAr_2$) in **4a** does not interact with the ruthenium catalyst, because the nucleophilicity of the amine is decreased as a result of its direct interaction with two electron-deficient phenyl groups.

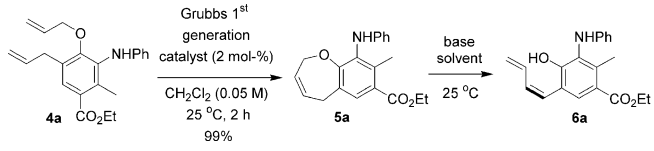


1a: R^1 = Et, R^2 = H, R^3 = Me; **1b**: R^1 = Me, R^2 = H, R^3 = Me; **1c**: R^1 = *t*Bu, R^2 = H, R^3 = Me
1d: R^1 = Et, R^2 = Me, R^3 = Me; **1e**: R^1 = Et, R^2 = Ph, R^3 = Me; **1f**: R^1 = Et, R^2 = Ph, R^3 = H
1g: R^1 = Me, R^2 = H, R^3 = H

(2)

(a) Ph–N=O, piperidine (5 mol-%), DMF (0.6 M), 25 °C, 1 h; K_2CO_3 (5 equiv.), H_2C=$CHCH_2Br$ (3 equiv.), 25 °C, 24 h, 50–98%; (b) DMF (1.0 M), 190 °C, 18 h, 73–80%; (c) K_2CO_3 (1.5 equiv.), H_2C=$CHCH_2Br$ (1.2 equiv.), EtOH (0.1 M) or DMF (0.5 M), 25 °C, 24 h, 80–95%.

Table 1. Reaction optimization.



Entry	Solvent [0.05 M]	Base [equiv.]	Time [h]	Yield **6a** [%][a]
1	NMP	NaH (2.0)	1	96
2	NMP	NaOMe (2.0)	1	96
3	NMP	*t*BuOK (2.0)	0.5	96
4	NMP	*t*BuOK (1.0)	2	90
5	NMP	Bu_3P (0.25)	48	–
6	*t*BuOH	*t*BuOK (2.0)	0.5	76
7	DMF	NaH (2.0)	2	96
8	**DMSO**	**NaH (2.0)**	**1**	**97**
9[b]	**DMSO**	***t*BuOK (2.0)**	**0.5**	**97**
10	THF	NaH (2.0)	17	55

[a] Yield refers to the column purified product. [b] Reaction performed in both two steps and one-pot conditions.

Once the benzo[*b*]oxepine **5a** was formed the base-induced ring opening (BIRO) was initiated as shown in Table 1. Interestingly—as we expected—treatment of 2 equiv. of NaH with **5a** in *N*-methylpyrrolidin-2-one (NMP) at 25 °C for 1 h furnished the ring-opened product *cis*-**6a** as major single isomeric product with 96% yield and >99% *Z*-selectivity (Table 1, entry 1). The ring-opening reaction of benzo[*b*]oxepine **5a** was further studied by using other bases like NaOMe, *t*BuOK and Bu_3P; among these *t*BuOK gave the best results as shown in Table 1, entries 2–5. The BIRO reaction in protic polar/aprotic polar solvents like *t*BuOH, DMF and DMSO also furnished the product *cis*-**6a** with good yields (entries 6–8). Reaction in THF gave the ring-opened product *cis*-**6a** with poor yield (entry 10). The ruthenium-catalyzed RCM reaction of diene **4a** and *t*BuOK-induced ring opening of the resulting benzo[*b*]oxepine **5a** was conducted according to the one-pot technique and furnished the expected product *cis*-**6a** in 97% yield with >99% *Z*-selectivity (Table 1, entry 9). We envisioned the optimized condition to be addition of 2 equiv. of *t*BuOK to the mixture of in situ generated **5a** in DMSO at 25 °C to furnish the substituted (*Z*)-2-(buta-1,3-dienyl)phenol **6a** in 97% yield with >99% *Z*-selectivity (Table 1, entry 9).

With the optimized reaction conditions in hand, the scope of the ruthenium- and base-induced RCM/BIRO one-pot reactions was investigated with variety of functionalized dienes **4** as shown in Table 2. A series of 6-substituted Hagemann's esters **1b**–**g** were converted into diene amines **4b**–**g** in good yields as shown in Equation (2). RCM reaction of free diene amines **4b**–**g** using Grubbs' first-generation catalyst (2 mol-%) in CH_2Cl_2 at 25 °C for 2 h furnished the benzo[*b*]oxepines **5b**–**g** in 95–97% yield, which on treatment with 2 equiv. of *t*BuOK at 25 °C for 0.5 h furnished the expected highly functionalized selective (*Z*)-2-(buta-1,3-dienyl)phenols **6b**–**g** with good yields under both two-step and one-pot conditions (Table 2, entries 1–5). Interestingly, enyne metathesis followed by base-induced ring opening of enyne **4h** furnished the expected product *cis*-**6h** in 55% yield (Table 2, entry 6). To demonstrate the scope of the ruthenium- and base-induced RCM/BIRO one-pot reactions, we synthesized simple dienes **4i**–**n** from corresponding phenols **1i**–**n** through *O*-allylation/Claisen rearrangement/*O*-allylation sequence (see Supporting Information for details) and transformed them into the expected single isomeric products *cis*-**6i**–**n** in very good yields via RCM/BIRO reactions (Table 2, entries 7–11). Structure and regio-chemistry of (*Z*)-2-(buta-1,3-dienyl)phenols **6** was confirmed by X-ray structure analysis on *cis*-**6a** as shown in Figure 1.[5]

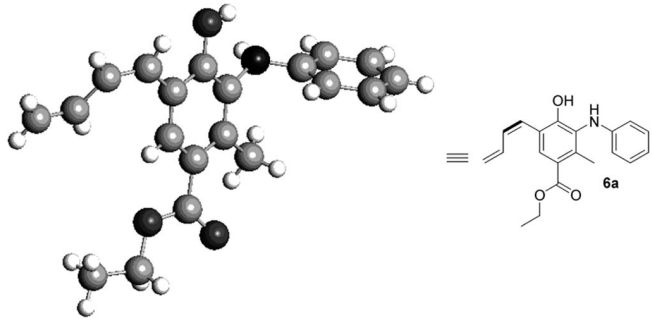
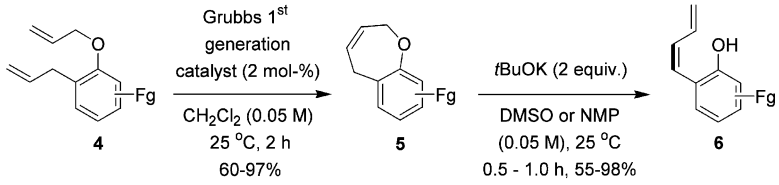
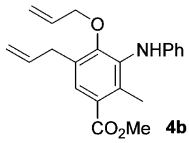
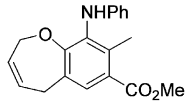
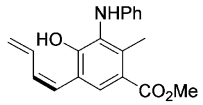
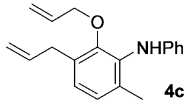
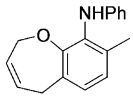
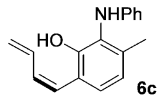
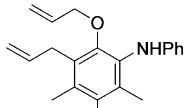
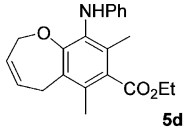
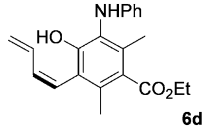
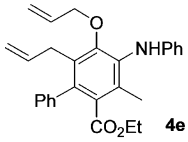
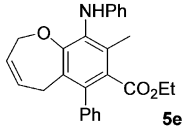
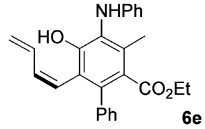
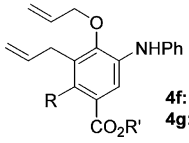
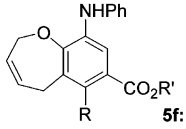
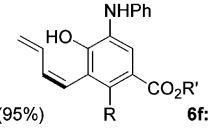
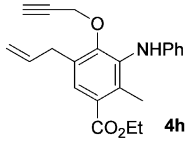
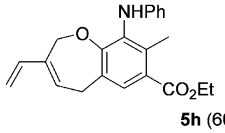
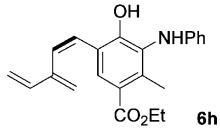
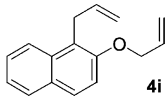
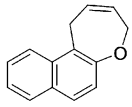
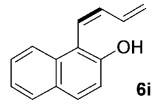
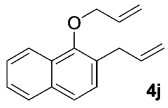
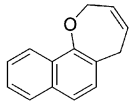
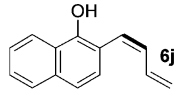
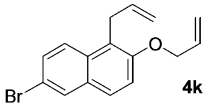
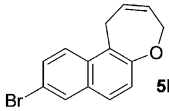
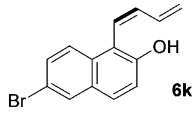
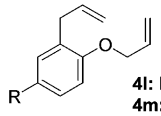
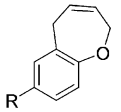
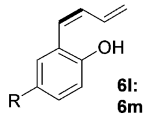
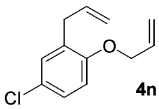
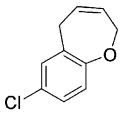
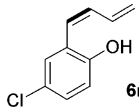


Figure 1. Crystal structure of ethyl (*Z*)-5-(buta-1,3-dienyl)-4-hydroxy-2-methyl-3-(phenylamino)benzoate (**6a**).

Some of the (*Z*)-2-(buta-1,3-dienyl)phenols **6** are unstable at 25 °C and slowly rearrange to the 2-methyl-2*H*-chromenes **7** by [1,7]-sigmatropic hydrogen shift ([1,7]-SHS) followed by rapid cyclization.[6] Compounds *cis*-**6f** and *cis*-**6h**–**k** are unstable at 25 °C and are rapidly converted into the functionalized 2-methyl-2*H*-chromenes **7f** and **7h**–**k** af-

Table 2. Synthesis of the substituted (*Z*)-2-(buta-1,3-dienyl)phenols **6**.[a]

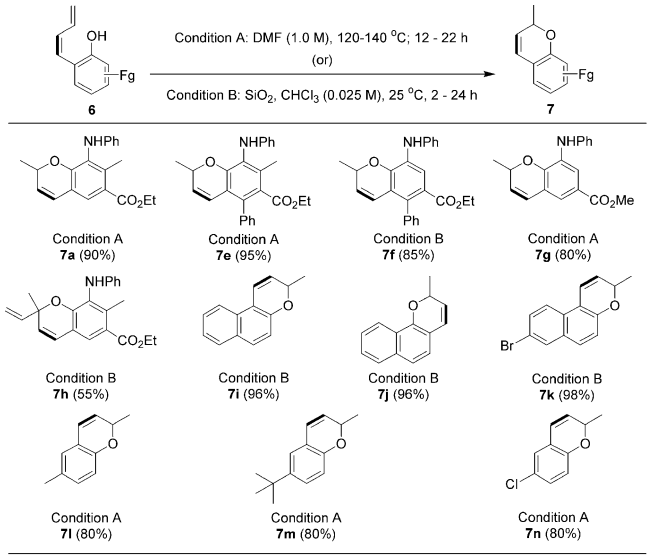


Entry	Diene **4**	Benzo[b]oxepine **5**	2-Buta-1,3-dienyl-phenols **6**
1	 **4b**	 **5b** (97%)	 **6b** (95%)
2	 **4c**	 **5c** (97%)	 **6c** (75%)
3	 **4d**	 **5d** (97%)	 **6d** (95%)
4	 **4e**	 **5e** (96%)	 **6e** (95%)
5	 **4f:** R = Ph **4g:** R = H	 **5f:** R = Ph (95%) **5g:** R = H (97%)	 **6f:** R = Ph (95%) **6g:** R = H (95%)
6	 **4h**	 **5h** (60%)	 **6h** (55%)
7	 **4i**	 **5i** (95%)	 **6i** (98%)
8	 **4j**	 **5j** (95%)	 **6j** (98%)
9	 **4k**	 **5k** (90%)	 **6k** (98%)
10	 **4l:** R = Me **4m:** R = *t*Bu	 **5l:** R = Me (90%) **5m:** R = *t*Bu (95%)	 **6l:** R = Me (90%) **6m:** R = *t*Bu (90%)
11	 **4n**	 **5n** (95%)	 **6n** (90%)

[a] Yield refers to the column-purified product.

ter aqueous workup. This reaction can be accelerated by heat or addition of silica and $CHCl_3$ to the crude phenols **6** (see Table 3). With synthetic and pharmaceutical applications in mind,[1] we extended the transformation of other phenols **6** into functionalized 2-methyl-2*H*-chromenes **7** by a novel thermal or silica-induced [1,7]-SHS reaction followed by rapid cyclization. Reaction of *cis*-**6a** in DMF at 120–140 °C for 20 h furnished the expected 2-methyl-2*H*-chromene **7a** in 90% yield, but the same reaction (catalyzed by $SiO_2/CHCl_3$ at 25 °C for 7 days) furnished **7a** with only 50% conversion (Table 3, entry 1). Functionalized 2-methyl-2*H*-chromenes **7** were generated in good yields with high selectivity as shown in Table 3. This method will show much impact on synthesis of highly substituted 2-methyl-2*H*-chromenes **7** for medicinal applications.[1] As shown in Table 3, Condition A (thermal activation) is the best method for the conversion of different (*Z*)-2-(buta-1,3-dienyl)phenols **6** into 2-methyl-2*H*-chromenes **7**.

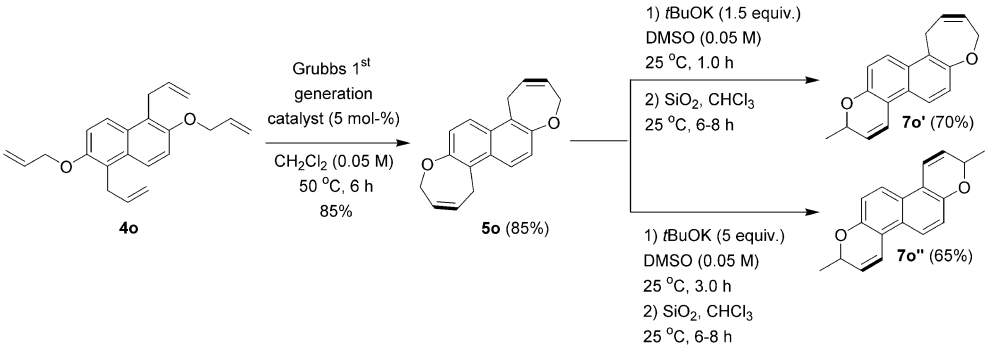
Table 3. Chemically diverse libraries of 2-methyl-2*H*-chromenes **7**.[a]



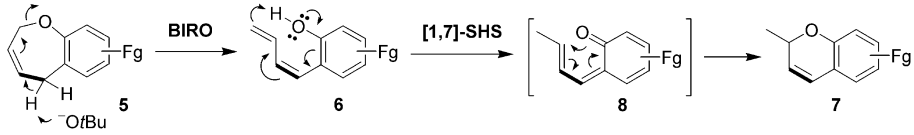
[a] Yield refers to the column purified product.

In order to check the general applicability of the RCM/BIRO/[1,7]-SHS reaction sequence, we tried to synthesize the C_2-symmetric 2,8-dimethyl-2,8-dihydro-1,7-dioxachrysene **7o′′** [Equation (3)]. RCM reaction of 1,5-diallyl-2,6-bis(allyloxy)naphthalene (**4o**) at 50 °C for 6 h in CH_2Cl_2 furnished the C_2-symmetric benzo[*b*]oxepine **5o** in 85% yield, which on treatment with 1.5 equiv. of *t*BuOK followed by treatment with $SiO_2/CHCl_3$ at 25 °C for 6–8 h furnished the non-symmetric 2-methyl-2*H*-chromene **7o′** in 70% yield [Equation (3)]. The same RCM reaction when applied to **4o** at 50 °C for 6 h in CH_2Cl_2 followed by reaction with 5 equiv. of *t*BuOK at 25 °C for 3 h and then treatment with $SiO_2/CHCl_3$ at 25 °C for 6–8 h furnished the C_2-symmetric chrysene **7o′′** in 65% yield [Equation (3)].

A possible reaction mechanism for the BIRO/[1,7]-SHS reaction sequence is given in Scheme 1. The first step could be the base-catalyzed formation of a carbanion (the allylic/benzylic hydrogen of **5** is acidic) that will rearrange according to a concerted reaction pathway to give the ring-opened product *cis*-**6**. A [1,7]-sigmatropic shift of the phenolic hydrogen in *cis*-**6** would give rise to the *ortho*-quinone methide **8**, which rapidly cyclizes to yield **7** with recovery of the thermodynamic stability through oxa-6π electrocyclization or [3,3]-rearrangement. Interestingly, we did not find the formation of [1,2]-Wittig-rearrangement-type products via alternative deprotonation in α-position to oxygen in the benzo[*b*]oxepines **5**.[7]



(3)



Scheme 1. Proposed reaction mechanism.

Conclusions

In summary, we have found a selective, diversity-oriented synthesis of highly functionalized benzo[*b*]oxepines **5**, (*Z*)-2-(buta-1,3-dienyl)phenols **6**, and 2-methyl-2*H*-chromenes **7** from simple starting materials via EA/IA/A, RCM, BIRO and [1,7]-SHS reactions under amine, ruthenium and base catalysis. This chemistry (RCM/BIRO/[1,7]-SHS) performed in one-pot with good yields and selectivity. Further work is in progress to utilize novel combination of RCM, BIRO and [1,7]-SHS reactions in synthetic chemistry.

Experimental Section

Experimental procedures, characterization data for new products, and complete details about the syntheses are available in the Supporting Information (see also the footnote on the first page of this article).

Acknowledgments

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[5] CCDC-686540 contains the supplementary crystallographic data for **6a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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