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Direct Construction of 2,3-Dihydroxy-2,3-diaryltetrahydrofurans via *N*-Heterocyclic Carbene/Base-Mediated Domino Reactions of Aromatic Aldehydes and Vinyl Selenone

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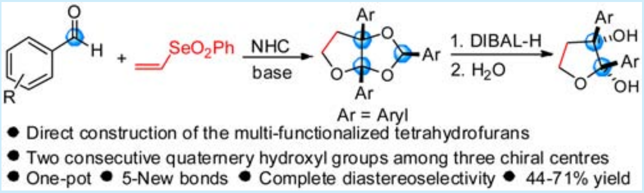
Ⓢ *Supporting Information*

ABSTRACT: A one-pot, stereoselective construction of 2,3-dihydroxy-2,3-diaryltetrahydrofurans has been achieved via *N*-heterocyclic carbene (NHC)/base-mediated domino reactions of aldehydes and vinyl selenone. The products containing two contiguous quaternary hydroxyl functionalities among the three stereocenters are obtained advantageously as either acetals or ketals through the formation of five new chemical bonds in a single operation. This report constitutes an altogether different reactivity of vinyl selenone in comparison with the corresponding sulfones and phosphonates under NHC/base-mediated reactions.



- Direct construction of the multi-functionalized tetrahydrofurans
- Two consecutive quaternery hydroxyl groups among three chiral centres
- One-pot • 5-New bonds • Complete diastereoselectivity • 44-71% yield

The catalytic stereoselective synthesis of functionalized scaffolds in a concise manner is a highly desirable and challenging endeavor in organic synthesis; e.g., multisubstituted tetrahydrofuran moieties present in numerous natural products and pharmaceutical ingredients.[1] In that direction, one-pot multicomponent reactions[2] and domino reactions[3] are vital tools. *N*-Heterocyclic carbenes (NHC) alone, or in combination with co-catalysts like Bronsted acids, Lewis acids, or transition-metal complexes, have enabled the discovery of a wide range of such reactions via new modes of activation.[4,5]

The synthesis of organoselenides/-selenones has recently attracted considerable attention because of their biological properties.[6] More significantly, the insertion of a selenide/selenone group is often accompanied by self-induced unexpected, yet interesting, transformations like vicinal group functionalization and the formation of rings/stereocenters via rearrangement because of a weaker C−Se σ-bond than even a closely resembling C−S bond.[7] Despite these aforesaid properties, metal-free catalytic asymmetric synthesis has remained relatively unexplored. Marini and Melchiorre's amine catalyzed α-selenenylation of aldehydes,[8i] Jacobsen's selenocyclization of alkenes in the presence of hydrogen-bond donor catalyst,[8e] and Zhu's Bronsted base-catalyzed addition of isocyanoacetates to vinyl selenones[7g] are some of the elegant methods for preparing chiral organoselenium compounds.[8] The group of Marini prepared spirolactones[7h] and cyclopropanes,[7k] whereas Zhu et al. reported oxazolidin-2-one[7c] and 1,3-oxazinan-2-one[7e] synthesis, taking advantage of the unprecedented self-rearrangement of the in situ generated organoselenones.

Our interest in expanding the horizons of NHC catalysis to unexplored or less explored domains,[9] on one hand, and the attractive properties of organoselenones, on the other hand, led us to explore the NHC-catalyzed addition of acyl anions, enolates, and homoenolates of aldehydes and enals to vinyl selenone and its other derivatives, which has so far proven elusive in the literature. It is worth noting here that Biju and co-workers reported Stetter reactions of aldehydes first with vinyl sulfones in 2012 and later with vinyl phosphonates in 2014 (eqs 1 and 2, Scheme 1).[10,11] We began our studies using 4-bromobenzaldehyde and vinyl selenone (Table 1). In analogy with sulfones and phosphonates, due to their comparable reactivity, the formation of the Stetter product via addition of an acyl anion equivalent to the vinyl selenone was anticipated. To our surprise, we obtained a highly functionalized

Scheme 1. NHC/Base-Mediated Reaction of Aldehydes and Vinyl Selenone

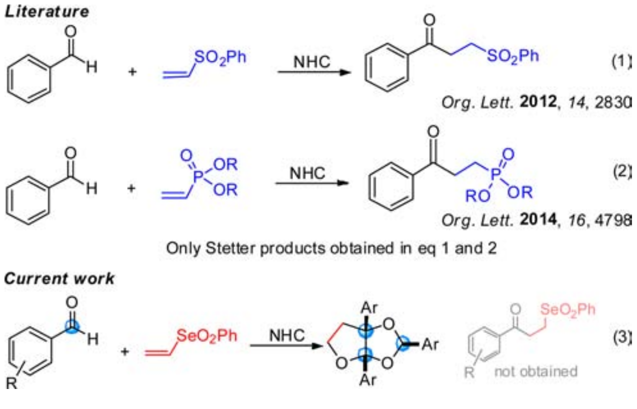


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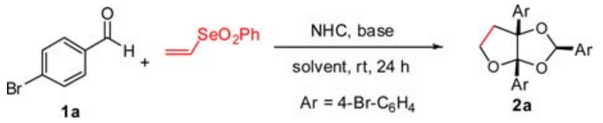
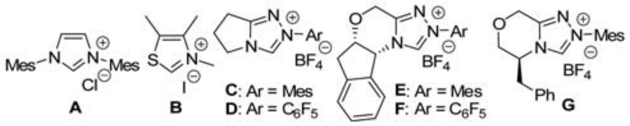
Table 1. Optimization of the Reaction Conditions[a]



entry	NHC	base	solvent	yield (%)[b]
1	--	DBU	CH_3CN	0
2	**A** or **B**	DBU	CH_3CN	trace
3	**C**	DBU	CH_3CN	38
4	**D**	DBU	CH_3CN	12
5	**E**	DBU	CH_3CN	21
6	**F**	DBU	CH_3CN	14
7	**G**	DBU	CH_3CN	17
8	**C**	DABCO	CH_3CN	28
9	**C**	K_2CO_3	CH_3CN	24
10	**C**	^{t}BuOK	CH_3CN	41
11	**C**	NMM	CH_3CN	22
12	**C**	Cs_2CO_3	CH_3CN	62
13	**C**	Cs_2CO_3	THF	33
14	**C**	Cs_2CO_3	$CHCl_3$	24
15	**C**	Cs_2CO_3	DMF	31
16	**C**	Cs_2CO_3	DMSO	53
17	**C**	Cs_2CO_3	toluene	28
18	**C**	Cs_2CO_3	TFE	26
19[c]	**C**	Cs_2CO_3	CH_3CN	59
20[d]	**C**	Cs_2CO_3	CH_3CN	48
21[e]	**C**	Cs_2CO_3	CH_3CN	58
22[f]	**C**	Cs_2CO_3	CH_3CN	63



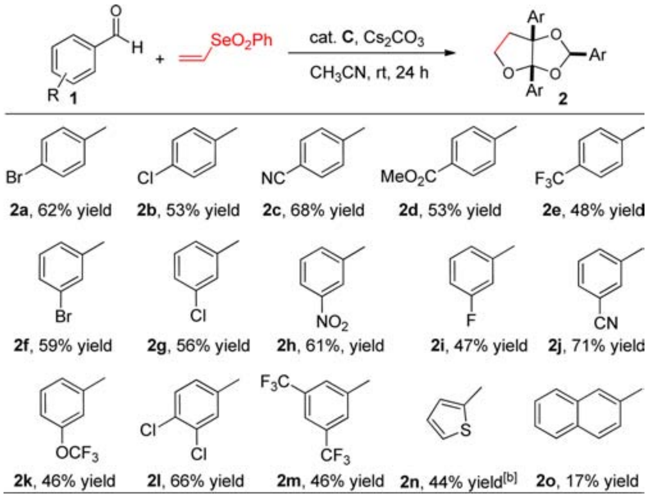
[a]Reaction condition unless otherwise specified: **1a** (0.4 mmol), vinyl selenone (0.1 mmol), NHC (20 mol %), base (0.15 mmol), solvent (1.0 mL) at rt. [b]Isolated yields of **2a** based on vinyl selenone. The product was obtained as single diastereomer based on ^1H NMR analysis of the crude reaction mixture. [c]1.0 mmol of **1a** was used. [d]Reaction performed at 70 °C. [e]0.3 mmol of Cs_2CO_3 was used. [f]30 mol % NHC was used. DBU = 1,8-diazabicycloundec-7-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane, TFE = trifluoroethanol, NMM = *N*-methylmorpholine, Mes =2,4,6-trimethylphenyl.

tetrahydrofuran with two consecutive quaternary hydroxyl functionalities among the three newly generated chiral centers (eq 3, Scheme 1).

The serendipitous discovery of the first one-pot construction of this challenging moiety, with potential to access a large number of analogues, encouraged us to further optimize the reaction conditions. Our investigation commenced by examining different NHC precatalysts in CH_3CN in the presence of DBU as the base (Table 1). Imidazolium precatalyst **A** was ineffective, while thiazolium catalyst **B** self-dimerized under the reaction conditions (entry 2, Table 1, and Table SI-1). Achiral triazolium salts **C** and **D** furnished the desired product **2a** in 38% and 12% yield, respectively, with high diastereoselectivity, since no other diastereomer could be traced by the ^1H NMR analysis of the crude reaction mixtures. The use of aminoindanol-derived triazolium salts **E** and **F** led to poor results (entries 5 and 6). Replacement with a phenylalanine-based NHC salt **G** again resulted in an erosion of yield (entry 7). The screening of various solvents and bases using precatalyst **C** (entries 8−18) eventually furnished **2a** in 62% overall yield using Cs_2CO_3 as the base in CH_3CN solvent (entry 12). It is worth mentioning here that even though the overall yield for **2a** was moderate over three steps, the average yield for each step was >85%. Further tuning of the other reaction parameters like molar ratios of the substrates, catalyst loading, and temperature variations did not lead to any noticeable improvement in the yield (entries 19−22).

With these optimal conditions in hand, we next investigated the generality of the reaction with respect to the aldehydes (Scheme 2). In general, electron-deficient aldehydes performed much better in this reaction than the corresponding electron-rich aldehydes, giving products in moderate to good overall yield (**2a**−**m**). Benzaldehyde and its electron-rich variants produced benzoin products (in poor yield) along with a trace amount of the desired products. A reasonable impact of the substitution pattern was observed; e.g., *para*- and *meta*-substituted aldehydes were tolerated well in the reaction, whereas *ortho*-substituted aldehydes remained unreactive or decomposed (**2a**−**m**). A heteroaromatic aldehyde was also compatible (**2n**). Aliphatic aldehydes either remained unreacted or decomposed under the reaction conditions. A single-crystal X-ray analysis of **2a** unambiguously furnished the structure of the product.[12] The structure and relative configuration of all other products were assigned by analogy.

Scheme 2. NHC/Base-Mediated Reactions of Aldehydes and Vinyl Selenone[a]

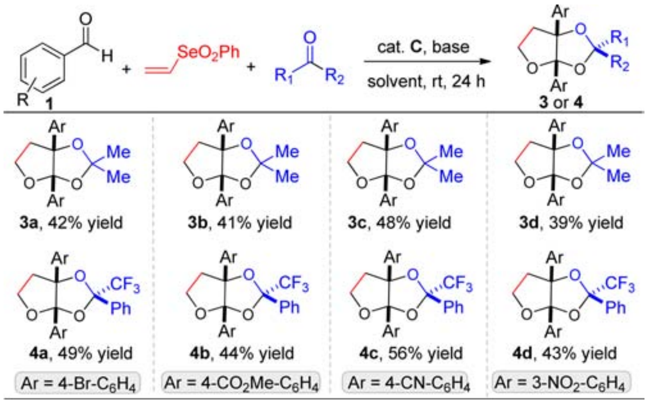


[a]Isolated yields under optimized condition (as in entry 12, Table 1). All of the products were obtained as single diastereomer based on ^1H NMR analysis of the crude reaction mixture. [b]The reaction was performed at 0 °C.

Taking our protocol a step further, we examined the tolerance of ketones as the third substrate in the reaction mixture (instead of third molecule of the aldehyde, refer to Scheme 5). After a brief reaction optimization (see Table SI-2), acetone was found to give the corresponding acetonide-protected *cis*-dihydroxydiaryltetrahydrofuran products in moderate to good yields using 1,1,3,3-tetramethylguanidine (TMG) as the base (**3a**−**d**, Scheme 3). 2,2,2-Trifluoroacetophenone also participated in the reaction smoothly under conditions similar to those of Table 1 (**4a**−**d**, Scheme 3).

To gain mechanistic insights into this one-pot reaction, a set of control experiments were performed. When a preformed

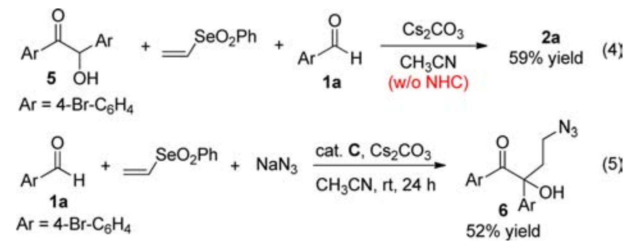
Scheme 3. NHC/Base-Mediated Reactions of Aldehydes, Vinyl Selenone, and Ketones[a]



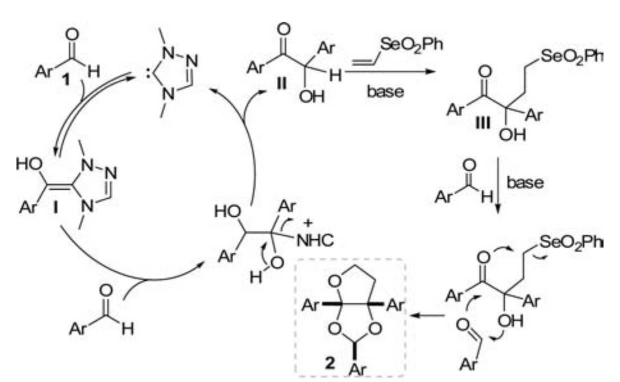
[a] Reaction conditions for the products **3**: **1** (0.255 mmol), vinyl selenone (0.116 mmol), cat. **C** (20 mol %), TMG (0.174 mmol), acetone (1.5 mL) at rt. Reaction conditions for the products **4**: **1** (0.255 mmol), vinyl selenone (0.116 mmol), cat. **C** (20 mol %), Cs_2CO_3 (0.174 mmol), CH_3CN (1.5 mL) at rt. Isolated yields of **3** or **4** based on vinyl selenone. The products were obtained as single diastereomers on the basis of ^1H NMR analysis of the crude reaction mixture. The structure of **4** was assigned on the basis of NMR comparison with **2**. TMG = 1,1,3,3-tetramethylguanidine.

benzoin product **5**[13] was subjected to our optimized conditions in the absence of NHC, the desired product **2a** was obtained (eq 4, Scheme 4). On the other hand, we isolated azide derivative **6** in 52% yield after running the reaction in the presence NaN_3 under optimal conditions (eq 5, Scheme 4). Based on these control experiments, our postulated mechanism is detailed in Scheme 5. The NHC-catalyzed reaction of the aldehyde produces benzoin product **II**, which undergoes further base-mediated Michael addition to the vinyl selenone giving intermediate **III**. The intermediate **III** next reacts with the third molecule of aldehyde (or ketone) in domino fashion to eventually give the dihydroxydiaryltetrahydrofuran products **2** (or **3** or **4**) either in acetal- or ketal-protected form.

Scheme 4. Mechanistic Studies

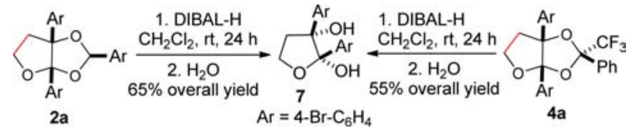


Scheme 5. Postulated Reaction Mechanism



The acetal- as well as the ketonide-protected tetrahydrofuran products (**2a** and **4a**) could be easily converted to free dihydroxy derivative **7** in good yields in the presence of DIBAL-H in CH_2Cl_2, followed by hydrolysis during aqueous workup (Scheme 6).[7f,14]

Scheme 6. Preparation of Dihydroxytetrahydrofuran 7



In conclusion, we have established the first direct, one-pot construction of challenging multifunctionalized tetrahydrofurans with two contiguous quaternary hydroxyl functionalities among the three stereocenters generated through the NHC/base-mediated reaction of aldehydes and vinyl selenones. Advantageously, the reaction can be designed to obtain the products either in acetal or ketal protected form. In addition, the benign nature of the reaction and the complexity achieved in a single operation are expected to encourage further studies on the relatively less explored organoselenone chemistry under metal-free organocatalysis in general and, more specifically, under NHC catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03501.

Experimental procedure, characterization data, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(12) CCDC 1510446 contains supplementary crystallographic data for compound **2a**. 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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