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Phosphine-Catalyzed Domino Reaction for the Synthesis of Conjugated 2,3-Dihydrofurans from Allenoates and Nazarov Reagents

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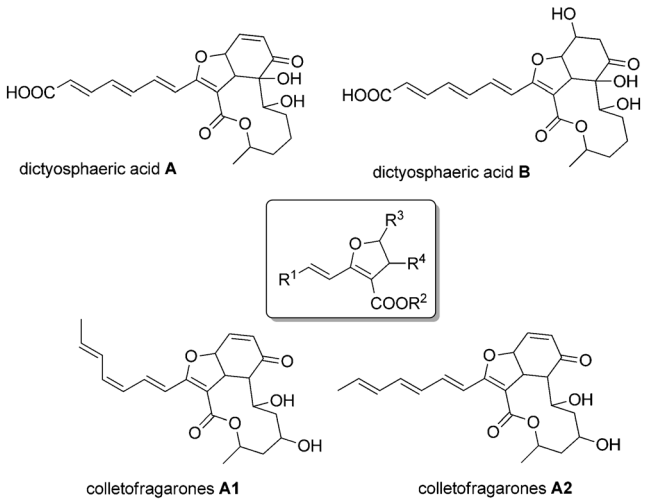
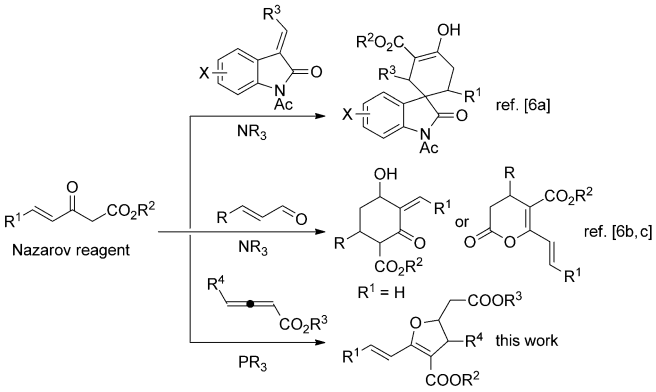
The remarkable significance of 2,3-dihydrofurans and their derivatives in chemical and biological research has motivated chemists to develop various approaches for their construction.[1] In addition, functionalization of 2,3-dihydrofurans often allows for further structural elaboration and adornment.[1d] Recently, efforts have been made towards the development of organocatalyzed domino processes,[2,3] such as the [4+1],[2a–c] [3+2] annulation,[2d–h] multi-component condensation.[2i,j] Nonetheless, a limited substrate scope, low atom efficiency, and low diastereoselectivity often challenge the above methods.[1,2a] Therefore, a facile new synthetic method with high atom efficiency is still needed. In particular, methods for the synthesis of conjugated 2,3-dihydrofurans, which constitute the core framework of an increasing number of biologically active molecules (Scheme 1), have rarely been reported.[4] These biologically active molecules pose a significant synthetic challenge due to their structural complexity and the need for a flexible and convergent route.[5] Thus, the potential clinical significance of this scaffold has led to a demand for efficient methods for their synthesis. The presence of a C=C bond conjugated to an enol in 2,3-dihydrofurans increases the possibilities for their structural modulation and enhances their synthetic utility. Therefore, a new synthetic method that allows an easy preparation of such structures with high atom efficiency is highly desirable.



Scheme 1. Natural products containing the conjugated 2,3-dihydrofuran scaffold.

The Nazarov reagent, which possesses nucleophilic carbon and oxygen and an electronically poor C=C bond, has gradually received attention from the organocatalytic community for designing new domino processes.[6] A number of pioneering cycloaddition reactions involving the Nazarov reagent have emerged (Scheme 2). Jørgensen and co-workers reported a tandem Michael/Morita–Baylis–Hillman reaction (MBH) leading to the formation of cyclohexenone derivatives.[6b] Gong et al. demonstrated that a C-5-substituted Nazarov reagent was capable of directing the reaction to a novel [3+3] cycloaddition.[6c] Recently, this group also reported that, in the presence of a bifunctional catalyst, Nazarov reagents can be used for the construction of spiro[4-cyclohexeanone-1,3′-oxindoline] derivatives.[6a] The groups of Deslongchamps and Takemoto independently incorporated the Nazarov reagent into domino processes for the synthesis of natural products.[6d–g] In recent years, phosphine-catalyzed domino reactions[7] have become powerful tools for the preparation of carbocycles and heterocycles.[8,9] However, so



Scheme 2. Comparison of organocatalyzed reactions with Nazarov reagents.

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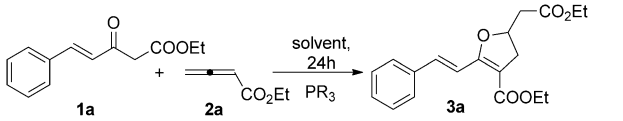
far phosphine-mediated reactions of Nazarov reagents have not been reported. Based on the specific reactivity patterns of the Nazarov reagent and our previous work on phosphine-catalyzed domino annulations,[10] we started to investigate the reaction between allenoates and Nazarov reagents. Herein, we report a phosphine-catalyzed domino reaction for the efficient construction of conjugated 2,3-dihydrofuran moieties.

We initiated our investigation by subjecting allenoate **2a** to Nazarov reagent **1a** in the presence of PPh_3 (100 mol%) in toluene at room temperature. Only a trace amount of product **3a** was obtained (Table 1, entry 1). Screening of solvents revealed that the protic solvent EtOH worked best, affording **3a** in 80% yield (entry 5). The structure and stereochemistry of **3** was determined by using NMR spectroscopy, high-resolution mass spectrometry (HRMS), and single-crystal X-ray analysis (**3c**).[11] When aprotic solvents such as CH_2Cl_2 and CH_3CN were used, no product or only traces of product were observed (entries 2–3). The yield, to some extent, was more sensitive to the temperature than the catalyst loading. Increasing the reaction temperature resulted in an improvement in yield (entries 8–9). Decreasing the amounts of catalyst from 100 mol% to 15 mol% had little effect on the yield (entries 10–14). Even with 5 mol% catalyst loading, the reaction proceeded smoothly to give the desired products (entry 15). The use of more nucleophilic phosphines led to lower yields (entries 16–18), possibly because of a lower stability of the catalyst and polymerization of the starting materials.

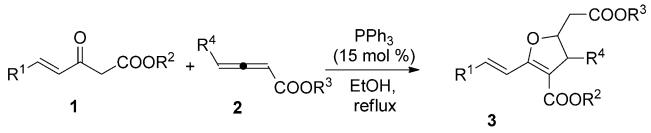
Table 1. Screening of catalysts and conditions for the domino reaction.[a]



Entry	cat. [mol%]	Solvent	T [°C]	Yield [%][b]
1	PPh_3 (100)	Toluene	rt	trace
2	PPh_3 (100)	CH_2Cl_2	rt	trace
3	PPh_3 (100)	CH_3CN	rt	trace
4[c]	PPh_3 (100)	EtOH	rt	56
5	PPh_3 (100)	EtOH	rt	80
6	PPh_3 (100)	Pr^iOH	rt	56
7	PPh_3 (100)	MeOH	rt	78
8	PPh_3 (50)	EtOH	rt	59
9	PPh_3 (50)	EtOH	reflux	78
10	PPh_3 (30)	EtOH	reflux	84
11	PPh_3 (20)	EtOH	reflux	87
12[d]	PPh_3 (20)	EtOH	reflux	90
13[e]	PPh_3 (20)	EtOH	reflux	80
14[d]	PPh_3 (15)	EtOH	reflux	86
15[d]	PPh_3 (5)	EtOH	reflux	78
16[d]	PPh_2Et (15)	EtOH	reflux	61
17[d]	$PPhEt_2$ (15)	EtOH	reflux	67
18[d]	PBu_3 (15)	EtOH	reflux	trace

[a] Reaction conditions: 1.0 equiv **1a** (0.5 mmol), 1.5 equiv **2a** in 2.0 mL solvent. The reaction time was 24 h. [b] Isolated yields. [c] The reaction time was 6 h. [d] Ratio of **1a**/**2a** is 0.5. [e] Ratio of **1a**/**2a** is 0.4.

Table 2. Scope of the domino reactions in the presence of phosphine.[a]



Entry	R^1	R^2	R^3	R^4	t [h]	Yield [%][b]
1	C_6H_5 (**1a**)	Et	Et	H	24	86 (**3a**)
2	C_6H_5 (**1a**)	Et	Me	H	24	85 (**3b**)
3	C_6H_5 (**1a**)	Et	Bn	H	25	59 (**3c**)
4[c]	2-$NO_2C_6H_4$ (**1b**)	Et	Et	H	19	49 (**3d**)
5[c]	2-$NO_2C_6H_4$ (**1b**)	Et	Me	H	15	60 (**3e**)
6	2,4-ClC_6H_3 (**1c**)	Et	Et	H	24	93 (**3f**)
7	2,4-ClC_6H_3 (**1c**)	Me	Me	H	10	88 (**3g**)
8	4-BrC_6H_4 (**1d**)	Me	Et	H	29	76 (**3h**)
9	4-BrC_6H_4 (**1d**)	Me	Me	H	20	65 (**3i**)
10[d]	3-FC_6H_4 (**1e**)	Me	Me	H	15	63 (**3j**)
11	4-MeC_6H_4 (**1f**)	Et	Me	H	24	78 (**3k**)
12	4-$OMeC_6H_4$ (**1g**)	Et	Et	H	32	62 (**3l**)
13	4-$OMeC_6H_4$ (**1g**)	Et	Bn	H	32	55 (**3m**)
14[e]	2,4-ClC_6H_3 (**1c**)	Et	Et	Me	30	36 (**3n**)
15[e]	4-BrC_6H_4 (**1d**)	Me	Et	Me	24	40 (**3o**)
16[f]	Me	Et	Et	H	24	56 (**3p**)

[a] See the experimental section for details. [b] Isolated yields. [c] Z configuration of the double bond in the Nazarov reagent. [d] Allenoate **2** was added dropwise to the solution over 1 h. [e] P(p-ClC_6H_4)$_3$ (20 mol%) was used as catalyst. *Trans/cis* > 95:5. [f] Hydroquinone (100 mol%) was used as an additive, and PPh_3 (20 mol%) was used as the catalyst.

Experiments that probed the generality of this domino reaction were then performed under the optimized conditions. As summarized in Table 2, this reaction displayed a broad scope with regard to Nazarov reagents. The reaction had a good tolerance of steric and electronic properties of substituents on the aromatic group. Even with the strong electron-withdrawing NO_2 substituent (entries 4–5), the reaction gave rise to the corresponding products in moderate yield. By contrast, the steric property on allenoates **2** showed a remarkable influence on the yield (entries 1–3). Notably, the configuration of Nazarov reagents did not change during this domino process (entries 4–5). In addition, the reaction resulted in high stereoselectivity with slightly reduced yield when γ-substituted allenoates were used (entries 14–15) which, due to their steric effect[8u–w] and versatile and lower reactivity,[8,10a] have received less attention. Furthermore, C5-methyl-substituted Nazarov reagents also delivered the alkyl-substituted product **3p** in moderate yield (entry 16). This is particularly relevant to apply this strategy to the synthesis of the aforementioned natural products.

To demonstrate the role of the solvent and gain insight into the mechanism, a series of experiments were performed. Our initial thought was that the transformation was induced by H_2O to catalyze the proton transfer.[8q,s,x] To explore this possibility, reactions in CD_3OD and MeOH/D_2O (5:1) were carried out. In CD_3OD, deuterated product **3a** was obtained in 67% yield with 60-90% incorporation of deuterium at the α, β, and γ-carbons (Scheme 3, top), while only 19% of **3a** was obtained (22% of **1a** was recovered), with 20-38% incorporation of deuterium at the α, β, and γ-

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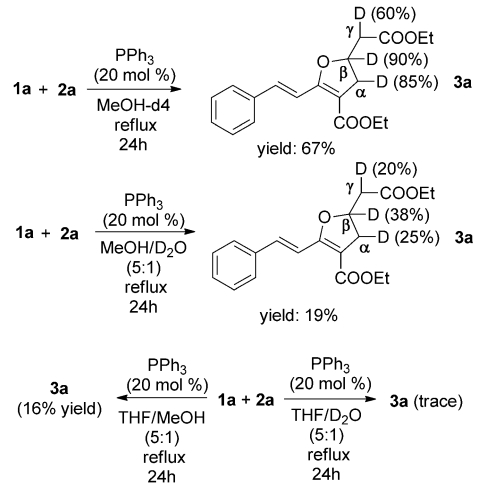
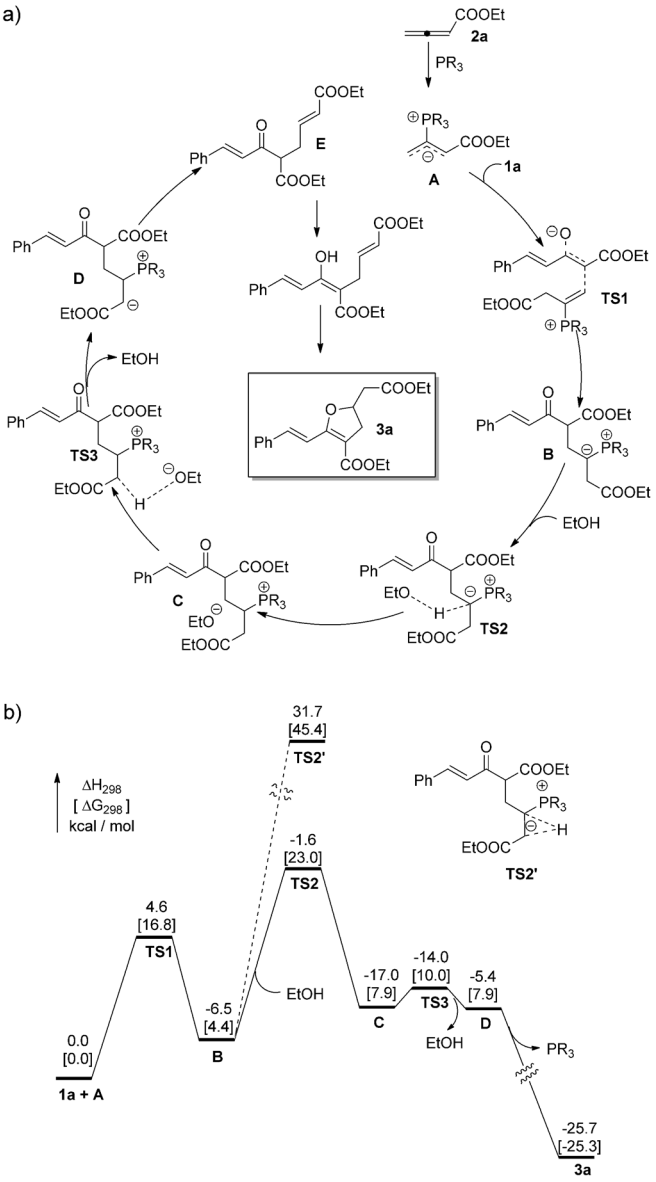


Scheme 3. Reactions performed to examine the role of the solvent.

carbons (Scheme 3, middle), when MeOH/D_2O was used. These results, to some extent, indicated that H_2O inhibited the reaction. In addition, as the pK_a values of methanol (pK_a = 15.5) and H_2O (pK_a = 14) are similar, H–D exchange between MeOH and H_2O occurs, which could explain why 20–38% incorporation of deuterium took place in MeOH/D_2O. Furthermore, the conclusion that D_2O disfavors the reaction was supported by further experiments in which THF/D_2O (5:1) delivered trace amounts of **3a**, while THF/CH_3OH (5:1) gave **3a** in 16% yield (Scheme 3, bottom). These results indicated that CD_3OD is a better proton donor than H_2O in this reaction.

According to the experimental results and previous studies by Lu and co-workers,[12] we proposed the mechanism outlined in Scheme 4a. To gain insight into the reaction mechanism, the reaction was studied by means of DFT calculations (Scheme 4b, see the Supporting Information for details). All DFT calculations were performed with the Gaussian 03 program package.[13a] The geometry optimization of all the minima and transition states (TS) involved were performed at the B3LYP levels of theory with the 6-31+G(d) basis set used.[13b,c] The vibrational frequencies were computed at the same level of theory to check whether each optimized structure is an energy minimum or a transition state and to evaluate its zero-point vibrational energy (ZPVE). In the proposed mechanism, the reaction is triggered by nucleophilic addition of PPh_3 to the allenoates, producing the zwitterionic intermediate **A**.[7] Intermediate **A** then deprotonates the Nazarov reagent **1a** and this is followed by umpolung addition[14] to generate zwitterionic intermediate **B**, which subsequently can be protonated to form a new intermediate **C**. The intramolecular concerted [1,2]-proton shift process (**TS2′**) is highly energy demanding with a free energy of activation of 41.0 kcal mol^{-1}. By contrast, protonation of ylide **B** (**TS2**) followed by ethanol-catalyzed [1,2]-proton shift is much easier (20.7 kcal mol^{-1}). Though lower than that of the concerted [1,2]-proton shift, the energy barrier is still so high that the reaction has to be



Scheme 4. a) Possible mechanism. b) DFT computed surface energies of the main processes for the formation of **3** by a domino reaction.

conducted at a relatively high temperature (such as in ethanol under reflux conditions) and for a long reaction time. After **TS3** the ethanol-catalyzed [1,2]-proton shift is completed. Elimination of the catalyst from intermediate **D** gives then umpolung adduct **E**.[14] Finally, a facile oxo-Michael addition affords the final product **3a**. However, due to the existence of an acidic proton (in the keto ester moiety) in intermediate **B**, other potential reaction mechanisms cannot be completely ruled out. For example, in alcohol as the solvent, the intermediate **B** might be in rapid and reversible equilibrium with the zwitterionic intermediate **B'**, which can undergo S_N2 substitution to give product **3a** (Scheme 5).

In summary, we have developed an efficient method for the construction of highly substituted conjugated 2,3-dihy-

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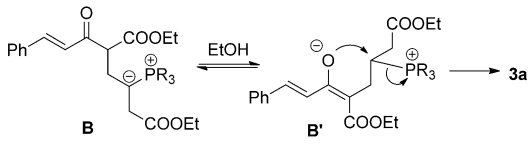

Scheme 5. Another potential mechanism.

drofuran frameworks with high atom economy. Nazarov reagents were used for the first time in a phosphine-catalyzed domino reaction and successfully used to construct five-membered ring compounds. The DFT mechanistic study indicates that the essential role of the alcohol is to catalyze the [1,2]-proton transfer. Further efforts on the application of this domino reaction in natural product synthesis and the development of an asymmetric version are in progress.

Experimental Section

General information for the preparation of compounds **3**: Nazarov reagent **1** (0.5 mmol, 1.00 equiv) and allenoate **2** (2.00 equiv) were dissolved in EtOH (2.0 mL). Subsequently, PPh_3 (0.15 equiv) was added and the reaction mixture was stirred at reflux. After complete conversion, as indicated by TLC, all volatiles were removed in vacuo, and the residue was purified by column chromatography (petroleum ether (60–90 °C)/ethyl acetate = 10:1).

Acknowledgements

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Keywords: allenoates · dihydrofurans · domino reactions · Nazarov reagent · phosphine

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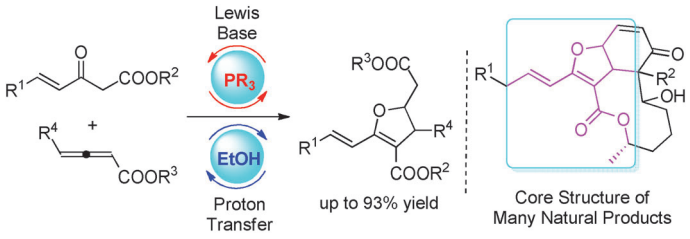
COMMUNICATION

Domino Reactions

Peizhong Xie, Wenqing Lai, Zhishuai Geng, You Huang, Ruyu Chen* _____ ■■■■–■■■■

Phosphine-Catalyzed Domino Reaction for the Synthesis of Conjugated 2,3-Dihydrofurans from Allenoates and Nazarov Reagents



A new domino reaction for Nazarov reagents: An efficient approach was developed for the construction of highly functionalized conjugated 2,3-dihydrofuran skeletons. Nazarov reagents were used for the first time in a phosphine-catalyzed domino reaction and successfully used to construct five-membered ring compounds using alcohol as the solvent. DFT calculations indicate that alcohol is essential for the catalysis of the [1,2]-proton transfer.

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