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Cyclization of Polarized Divinyl Ketones under Aqueous and Ambient Conditions

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Abstract. An 'on-water' protocol has been developed for the synthesis of combretastatin A-4 (CA-4) analogues by cyclization of polarized triaryldivinyl ketones using hydrochloric acid as a promoter in 45–95% yields. The reaction time was reduced by about 30 times due to ultrasonic irradiation at ambient temperature. The other advantages of this new method are operational simplicity, easy workup, no column purification, and applicability on a gram-scale. It was shown that the amphiphilicity of the substrate and a low energy barrier of the reaction are a prerequisite for electrophilic and concerted reactions under aqueous and ambient conditions.

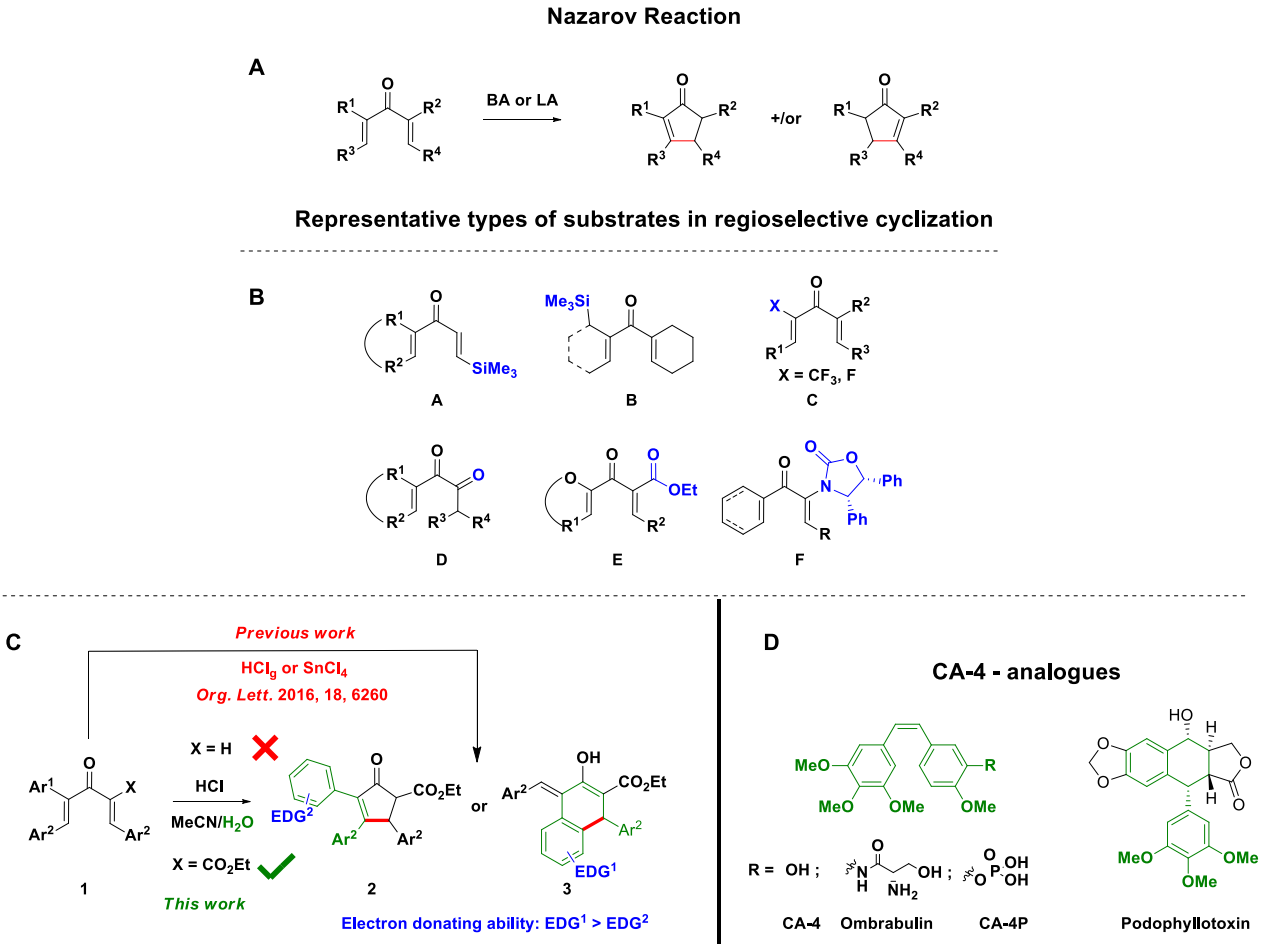
Keywords: Electrophilic substitution; Green chemistry; Lewis acids; Nazarov reaction; Polarized divinyl ketones; Synthetic methods.

Introduction

The Nazarov reaction is one of the most versatile methods for the synthesis of five-membered carbocycles.[1] This electrocyclic process converts a divinyl ketone to the cyclopentenone motifs under acidic conditions, and has a number of features that impart synthetic clout to its use. The reaction is tolerant to substituents on the dienone skeleton and is widely used for the synthesis of various biologically active compounds and natural products.[2,3] However, the Nazarov reaction, both in classical and interrupted versions, often does not proceed selectively and leads to a complex mixture of hardly separable products (Scheme 1A).[4] In addition, the cyclization is often facilitated by the use of a strong Lewis acid in a stoichiometric or super-stoichiometric amount.[1b-c,5,6] Therefore one of the most pressing issues of the modern development of the Nazarov reaction remains the control of the structure of substrates and catalysts, as well as optimization of the reaction conditions for the development of facile regio- and stereoselective protocols.[7] Such methods are especially valuable for the pharmaceutical industry, where the high yields of the desired products and requirements for the purity of the active pharmaceutical substance are in great demand. One such solution is to provide regioselective double bond formation in Nazarov cyclization by controlling dienone substituents (Scheme 1A).

Some of these issues were addressed by Denmark's silicon-directed Nazarov cyclization (structures **A** and **B** in the Scheme 1B).[8] The value of this approach lies in the ability to easily remove the silicone substituent, due to which the method was subsequently used as a key stage in many total synthesis of natural compounds.[9] Subsequently, other groups also have contributed in solving these issues. The most significant of them are the works of Ichikawa et al. (fluorine-directed regioselective reactions, structure **C**),[10,11] Tius et al. (the cyclization of α-keto enones, structure **D**),[12] Frontier et al. (the cyclization of the polarized divinyl ketones, structure **E**).[6c,13] A successful approach based on the use of oxazolidone as the α-substituent has been used in a number of studies by Flynn et al.[14] The oxazolidone substitute stabilizes the oxyallyl cation and thus allows one to control the stereo- and regioselectivity of the process.

All of these structure-controlled approaches are aimed either at stabilizing the oxyallyl cation in the transition state or at polarizing the dienone molecule with charge separation. Among these methods the polarization of a divinyl ketone system is a very promising approach and electron-donating and electron-withdrawing substituents are paired to create a polarized donor-acceptor relationship between the ends of the pentadienyl cation, enhancing reactivity. Another benefit of such systems is often the promotion of the reaction with a catalytic amount of catalyst due to a decrease in the energy barrier of the transition state.[6c,15] The great potential of polarized divinyl ketones containing an ester group has been demonstrated by Frontier et al.[13,16]



Scheme 1. Regioselective Nazarov cyclization.

The interest in polarized dienones containing an ester group was also dictated by their facile removal or functionalization, which, in turn, expands their application areas.

Recently, as part of our ongoing project to develop effective methods for the synthesis of CA-4 analogues, we also studied the cyclization of polarized triaryldivinyl ketones containing an ester group (Scheme 1C).[17] The reaction pathway despite the use of a polarized system depends on the electronic nature of the aryl substituent at the *α*-position of the carbonyl group. Electron-deficient arenes favor the classic Nazarov cyclization with the formation of triarylcyclopentenones **2**, while electron-rich substituents promote electrophilic substitution reaction (Friedel-Crafts alkylation) leading to dihydronaphthalenes **3**. However, despite the high regioselectivity of the process and no formation of a mixture of products, it remained unclear whether this selectivity depends on the reaction conditions or the nature of the catalyst, or whether it is determined only by structural features, in particular, the electronic nature of the *α*-substituent. On the other hand, despite the dissimilarity of these reactions schemes, both products obtained are analogues of CA-4 and may be of great interest for medicinal chemistry, since combretastatins A-4 occupy a special place among ligands capable of binding to colchicine-binding site of tubulin for inhibiting the proliferation of cancer cells.[18,19] In addition, some CA-4 derivatives, such as CA-4P, podophyllotoxin, and ombrabulin are completed multiple clinical trials (Scheme 1D)[20] and ombrabulin has been awarded as an orphan drug by the European Medicines Agency.[21] Taking into account the foregoing, in this work we studied the cyclization of polarized divinyl ketones under various conditions and proposed a green and product selective protocol for these valuable biologically active compounds under aqueous and ambient conditions. It should be noted, to the best of our knowledge, previously polarized dienones have not been studied in aqueous media.

Results and Discussion

We commenced our study with testing various Lewis and Brønsted acids in the cyclization of triaryldivinyl ketones under both homogeneous and heterogeneous conditions. Since it was previously found that the cyclization of triaryldivinyl ketones

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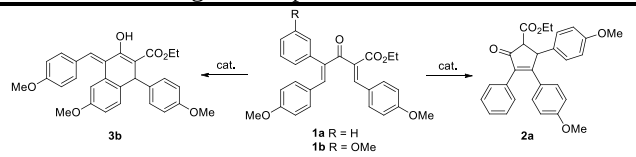
depends on the nature of the aryl residue at the *α*-position, two divinyl ketones differing in substituents were selected as the model substrates to find out the optimized reaction conditions. The results are summarized in Table 1. Initially the reaction was carried out employing stoichiometric amount of Lewis or Brønsted acid as the catalyst in anhydrous dichloromethane solvent. Various conditions for the cyclization of divinyl ketones were tested and it was found that both reactions under anhydrous conditions proceed with good yields, however, in the presence of $FeCl_3$, $SnCl_4$, $TiCl_4$ and $BF_3{\cdot}OEt_2$, the reaction proceeds at a relatively low temperature (0 to –5 °C). When the temperature was lowered to –30 °C, no significant increase in product yield was observed (entries 1 and 4). Raising the reaction temperature to 22 °C (room temperature) leads to a decrease in yields (entries 3, 6, 8, 10, 12, 14), it is especially noticeable for titanium and tin chlorides. Phosphorus pentachloride as a Lewis acid has proven to be a very mild catalyst even at room temperature. Despite the good chlorinating properties of the latter, the formation of chlorinated products was not observed.

Table 1. Screening of the optimized reaction conditions[a]



Entry	Catalyst[b]	Temp. (°C)	Yield[c] (%)	
			2a	**3b**
1	$SnCl_4/CH_2Cl_{2(abs)}$	–25 to –30	80	75
2	$SnCl_4/CH_2Cl_{2(abs)}$	0 to –5	78	71
3	$SnCl_4/CH_2Cl_{2(abs)}$	20–22	36	33
4	$TiCl_4/CH_2Cl_{2(abs)}$	–25 to –30	70	63
5	$TiCl_4/CH_2Cl_{2(abs)}$	0 to –5	64	56
6	$TiCl_4/CH_2Cl_{2(abs)}$	20–22	28	30
7	$BF_3{\cdot}Et_2O/CH_2Cl_{2(abs)}$	0 to –5	52	61
8	$BF_3{\cdot}Et_2O/CH_2Cl_{2(abs)}$	20–22	48	55
9	$FeCl_3/CH_2Cl_{2(abs)}$	0 to –5	80	72
10	$FeCl_3/CH_2Cl_{2(abs)}$	20–22	60	54
11	$PCl_5/CH_2Cl_{2(abs)}$	0 to –5	85	80
12	$PCl_5/CH_2Cl_{2(abs)}$	20–22	80	75
13	$HCl/CH_2Cl_{2(abs)}$	0 to –5	90	81
14	$HCl/CH_2Cl_{2(abs)}$	20–22	80	73
15	$CF_3COOH/CH_2Cl_{2(abs)}$	0 to –5	75	71
16	$CF_3COOH/CH_2Cl_{2(abs)}$	20–22	60	56
17	$TSA/MeCN/H_2O$	20–22	59	55
18	$TSA/EtOH/H_2O$	20–22	NR	60
19	$HCl/CH_3CN/H_2O$[d,e]	20–22	95	95
20	$HCl/EtOH/H_2O$[d,e]	20–22	90	85

[a] Concentration of **1** = 0.1M.
[b] 1 equiv of catalyst.
[c] Yields were determined by ^1H NMR using acetonitrile as an internal standard.
[d] Concentration of **1** = 0.03M.
[e] Concentration of HCl = 0.3 M.

Under homogeneous conditions in the presence of Lewis acids even at 0 °C, the reaction proceeds very fast (within 5–20 minutes), although the formation of some side processes is also observed. Brønsted catalysts (HCl_g or CF_3COOH) were also tested and the best results were obtained for hydrogen chloride where the desired products **2a** and **3b** were obtained in 90 and 81% yields, respectively. Raising the reaction temperature to room temperature also leads to a decrease in yields (entries 14 and 16**)**.

The major limitation of the reactions under homogeneous conditions is the use of stoichiometric amounts of catalysts, leading to costly purifications and the generation of significant amounts of waste, which contains toxic metal-containing substances. In addition, the Nazarov cyclization and other electrophilic reactions catalyzed by Lewis acid, as a rule, require additional purification and drying of solvents and reagents. In this regard, we decided to test also the aqueous conditions for triaryldivinyl ketones cyclization using water-soluble *p*-toluenesulfonic and hydrochloric acids as catalysts. Two other factors that inspired this study are the polarization and amphiphilicity of the explored divinyl ketones. The first of them lowers the energy barrier, and as a result facilitates and accelerates the reaction. Amphiphilic substrates under "on-water" conditions are prone to aggregate and form supramolecular aggregates, which can greatly facilitate the process.[22,23] Furthermore, water is a polar solvent with ET(30) = 61.3, and the reactions with more polar transition states than initial ones, will be favorable in water.[24,25] Even when the rate acceleration is negligible, the use of water as a medium has other advantages including ease of product isolation and the environmental safety. The only limiting factor of these cyclizations under aqueous conditions is that the presence of an external nucleophile (the nucleophile in this case is water) can contribute to the occurrence of both interrupted Nazarov cyclization and the Michael reaction. To the best of our knowledge, the classical Nazarov reaction under aqueous conditions was not previously described, although several examples of the interrupted Nazarov reaction in the presence of water were reported.[26]

To explore the cyclization of triaryldivinyl ketones under heterogeneous conditions, various conditions were tested: $TSA/MeCN/H_2O$, $TSA/EtOH/H_2O$, $HCl/EtOH/H_2O$ and $HCl/CH_3CN/H_2O$. Since triaryldivinyl ketones are practically insoluble in water, the substrates and catalyst were dissolved in a minimum amount of acetonitrile or ethanol before being mixed with water to create an "on water" effect. In both cases, a substrate emulsion in water is formed. In the water/acetonitrile mixture in the presence of *p*-toluenesulfonic acid as a catalyst the desired products were obtained in medium yields (entry 17). However, replacement of acetonitrile with ethanol promotes only electrophilic substitution; the Nazarov reaction does not proceed under these conditions, and the original substrate was returned completely (entry 18).

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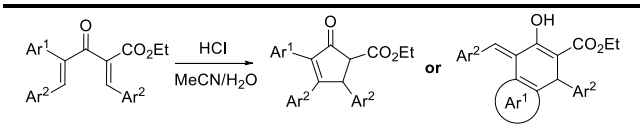
Very impressive results were obtained under aqueous conditions in a mixture of acetonitrile/water catalyzed by hydrochloric acid. It turned out that both Nazarov cyclization and intramolecular electrophilic substitution under these conditions proceed with high yields (entry 19). Moreover, the formation of the interrupted Nazarov product, as well as the reaction of divinyl ketones with an external nucleophile (water) was not observed. An important feature of this protocol is that the resulting products do not require additional purification.

To explore the general applicability of the present protocol, we carried out the reaction using various readily available polarized divinyl ketones under the optimized conditions and the results are summarized in Table 2.

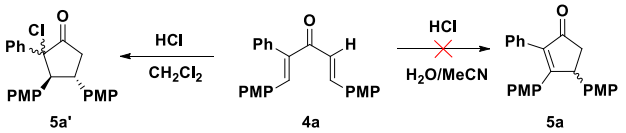
Table 2. Substrate scope of triaryldivinyl ketone cyclization[a]



Entry	Substrate	Ar^1[b]	Ar^2	Time (h)[c]	Product	Yield (%)
1	**1a**	Ph	PMP	3/72	**2a**	95
2	**1b**	MMP	PMP	1.5/46	**3b**	82
3	**1c**	MMP	Ph	4.5/120	**3c**	80
4	**1d**	Ph	Ph	–/360	**2d**	NR[d]
5	**1e**	MMP	IV	2/68	**3e**	45
6	**1f**	MMP	TMP	1/24	**3f**	72
7	**1g**	PMP	PMP	2.5/72	**2g**	90
8	**1h**	PMP	Ph	6/168	**2h**	73
9	**1i**	PMP	TMP	2.5/68	**2i**	80
10	**1j**	PMP	IV	–/360	**2j**	NR
11	**1k**	TMP	PMP	1.5/44	**3k**	78
12	**1l**	TMP	DMP	1/24	**3l**	95
13	**1m**	TMP	IV	2/64	**3m**	52
14	**1n**	TMP	TMP	1.5/48	**3n**	85

[a] Reaction conditions: **1** (0.03 M) in MeCN/H_2O/HCl_{conc} (1:1:1); 22 °C.
[b] PMP = 4-methoxyphenyl, MMP = 3- methoxyphenyl, IV = 3-hydroxy-4-methoxyphenyl, TMP = 3,4,5-trimethoxyphenyl, DMP = 2,4-dimethoxyphenyl.
[c] Reaction time: with/without ultrasonication.
[d] NR = no reaction.

In nearly all cases, the yields of the desired products were quite high, ranging from 62 to 95%. Only in two cases the reaction did not proceed and the initial triaryldivinyl ketones were returned with insignificant losses (entries 4 and 10 in the Table 2). The chemical inertness of triphenyldivinyl ketone **1d** under these conditions (entry 4) is more likely due to the weak π-donor effect of phenyl groups, which, as a result, leads to an increase in the energy barrier of the reaction. It should be noted that this substrate in methylene chloride in the presence of hydrogen chloride (homogeneous conditions) gives the desired cyclopentenone with good yields; although the reaction proceeds much more slowly compared to other triaryldivinyl ketones, which is an indirect confirmation of the relatively high energy barrier. The reactions of divinyl ketones with an isovanilin moiety (entries 5, 10, 13 in Table 2) were very indicative. The electrophilic alkylation showed yields below average, and the Nazarov cyclization did not proceed at all. The decrease or loss of the reactivity of isovanilin divinyl ketones is probably due to the absence of a hydrophobic fragment in these molecules (due to the presence of the hydrophilic hydroxyl group), which, in turn, reduces the "on-water" effect. Although the introduction of the isovanilin substituent leads to a loss in the amphiphilicity, but the polarization of these systems persists; therefore, the yields of the target products in homogeneous solutions (CH_2Cl_2/HCl or CH_2Cl_2/Lewis acid) turned out to be very good. To test our hypothesis on the effect of amphiphilicity and polarization of triaryldivinyl ketones on these processes, we synthesized dienone **4a**, which does not contain an ester group, and explored its cyclization under both homogeneous and heterogeneous conditions (Scheme 2).

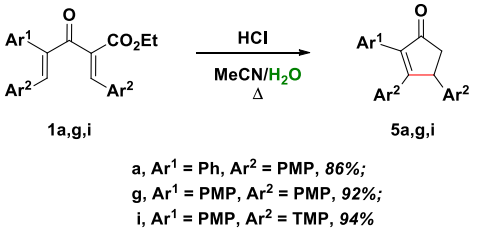


Scheme 2. The cyclization of unpolarized triaryldivinyl ketone **4a**.

Indeed, it was found that unpolarized divinyl ketone **4a** does not undergo cyclization under aqueous conditions, product **5a** was not isolated even in trace amounts, whereas under homogeneous conditions (CH_2Cl_2/HCl_g), a complex mixture of products was observed, the main of which was chloro-substituted triarylcyclopentanone **5a'**- product of interrupted Nazarov cyclization (the ^1H NMR-monitoring of **4a** cyclization in $CDCl_3$ and the ^1H NMR-spectrum of **5a'** are given in the ESI, see Fig. S1 and S2). Thus, the study of the cyclization of polarized divinyl ketones showed that amphiphilicity of the substrate and a low-energy barrier of the reaction are a prerequisite for electrophilic and concerted reactions under aqueous conditions.

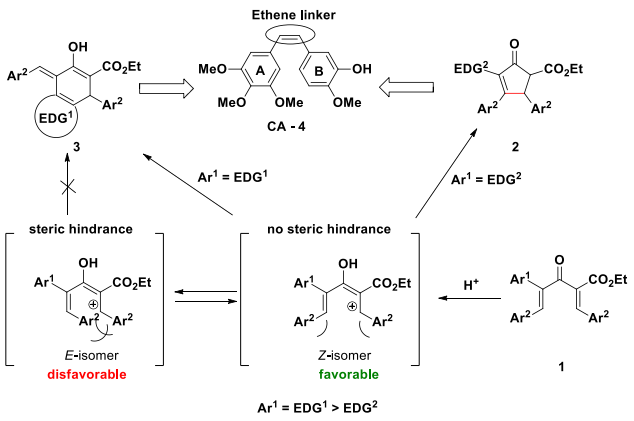
However, in spite of the good yields and the absence of the need for additional purification of the desired products, the reaction time under aqueous conditions was significantly longer compared to the homogeneous process. To optimize the reaction conditions under aqueous conditions, we tested two protocols. The first is to increase the reaction temperature, and the second approach is to accelerate the reaction rate using ultrasonic dispersion.[27] Raising the reaction temperature led to interesting results; it was found that the refluxing promotes one-pot Nazarov cyclization/decarboxylation giving

desired products **5** with excellent yields (Scheme 3), while the electrophilic substitution is accompanied by strong resinification resulting in the formation of an inseparable mixture, the main of which is dihydronaphthalene **3** (for the intramolecular electrophilic substitution of triaryldivinyl ketones under refluxing conditions see Fig. S3 in the ESI).



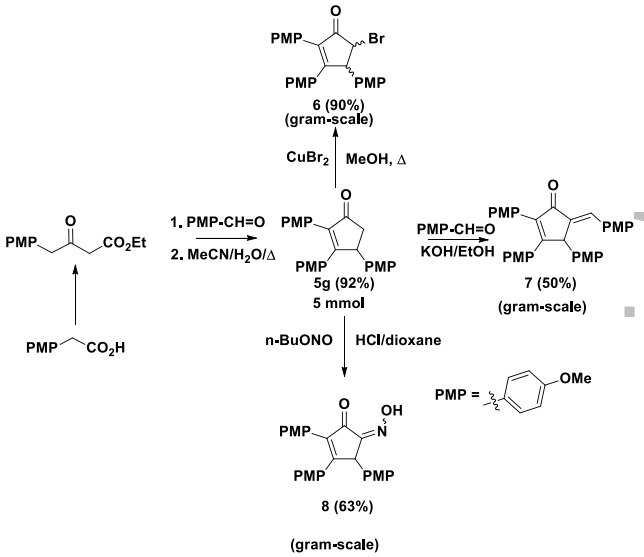
Scheme 3. One-pot Nazarov cyclization/decarboxylation.

The use of ultrasonic dispersion proved to be very effective, the rate of both Nazarov cyclization and intramolecular electrophilic substitution was accelerating by 30 times without reducing the yields of the desired products; the reaction time was reduced from 1–7 days to 1–6 hours. As noted above, the obtained products of both electrophilic substitution and Nazarov cyclization are *cis*-analogues of CA-4. Moreover, if the *cis*-form of triarylcyclopentenone is already dictated by the resulting structure, the formation of the *cis*-isomer of the dihydronaphthalene derivative is provided by the electrophilic substitution mechanism. Divinyl ketone **1** has two free double bonds that can undergo *cis/trans* isomerization to form both isomers.[28] However, in all cases, only the *cis*-isomer of dihydronaphthalene **3** was obtained (Scheme 4). The formation of a single isomer can be ascribed to the steric effect caused by aryl ring. Protonation of divinyl ketone **1** leads to the formation of a carbocation, which can exist in both *cis*- and *trans*-forms. However, only the *cis*-isomer can undergo cyclization, since in the *trans*-form, the attack of the carbocation by the aromatic ring is sterically hindered.



Scheme 4. Plausible mechanism of stereo-selective formation of dihydronaphthalenes **3**.

To demonstrate the synthetic application and to evaluate the scope of this protocol several transformations of triarylcyclopentenone **5g** were performed as shown in Scheme 5. Valuable functional groups such as bromine, ketoxime and arylidene groups could be easily included in high yields *via* facile transformations.[29]



Scheme 5. Gram-scale reaction and further derivatizations of **5g**.

In particular, bromo ketone **6** obtained with high yields is a good scaffold for traditional nucleophilic reaction affording biologically active compounds. The readily available ketoxime **8** and arylidene **7** are of interest as convenient intermediates for heterocyclization and as a promising light-sensitive switch. Thus, these examples demonstrate the practical applicability of this methodology for the preparation of densely substituted cyclopentenones.

Conclusion

In summary, we studied the cyclization of the polarized triaryldivinyl ketones both under homogeneous and heterogeneous conditions using various Lewis and Brønsted acids as catalyst. The best results were obtained when the reaction was carried out in a mixture of water–acetonitrile-hydrochloric acid (1: 1: 1 ratio), both Nazarov cyclization and intramolecular electrophilic substitution occur in high yields, and the resulting products do not require additional purification. The reaction proceeds at ambient conditions; an increase in the reaction temperature only favors the one-pot Nazarov/decarboxylation reaction, while ultrasonic dispersion promotes both cyclizations, significantly reducing the reaction time.

Experimental Section

General procedure. Divinyl ketone **1** (0.4 mmol) was dissolved in acetonitrile (4ml) and added to a mixture of water (4ml) with HCl (~36.5%, 4ml). After the mixture was stirred for 24–168 h (or was sonicated in running water bath for 1–6 h) at ambient temperature (20–22 °C). After completion of the reaction (TLC control), the product was filtered and washed with cold ethanol. The residue was purified by recrystallization from an appropriate solvent (cyclopentenones **2** from EtOH and dihydronaphthalenes **3** from a mixture of ethyl acetate and hexane – 1:6).

Acknowledgements

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