A mild, catalytic and efficient Nazarov cyclization mediated by phosphomolybdic acid[†]

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A mild, selective and efficient Nazarov cyclization of divinyl ketones catalyzed by phosphomolybdic acid (PMA) is described. The process demonstrates a broad substrate scope with functional group tolerance under short reaction times. PMA supported on silica gel is more efficient than the bulk catalyst and is recycled up to three times without significant activity loss.

The Nazarov cyclization¹ of divinyl ketones is a frequently encountered protocol for constructing five-membered carbocycles in pharmaceutically important target molecules and natural product synthesis.² The reaction proceeds either photochemically or in the presence of Lewis³ or Brønsted⁴ acids as catalysts. The synthetic versatility of this method was recently improved by interception of the cationic intermediate with a variety of nucleophiles affording functionalized cyclopentenones.⁵ A number of Brønsted acid catalysts have been adopted for Nazarov cyclization of different classes of divinyl ketone substrates; however, in a few cases, Brønsted acids are less preferred because of their low yield, long reaction time, high reaction temperature and high catalyst loading. Although Lewis acid catalysts, on the other hand, are equally efficient for transformation, some Lewis acids⁴ are limited only to polarized Nazarov substrates and require stringent anhydrous reaction conditions. Solid acids such as zeolites⁶ showed promising cyclization results, with high yields for less reactive Nazarov substrates. Interestingly, the synthetic utility of other solid acids has never been explored. Heteropoly acids (HPAs) are promising solid acids; they are redox and bifunctional catalysts in homogeneous as well as in heterogeneous conditions.⁷ These acids exhibit marked catalytic activities and unique selectivities, allowing cleaner processing compared with conventional liquid catalysts. Hence, HPAs are regarded as green catalysts, even though Nazarov cyclization under green (e.g., on silica gel) and solvent-free conditions using a microwave has been reported.⁸ Replacing conventional acids with HPAs for different transformations has significantly reduced reaction times and catalyst loading and generated milder reaction conditions. To the best of our knowledge, no examples of Nazarov cyclization catalyzed by HPAs exist.

This study describes the efficient and mild electrocyclization of different divinyl ketones in the presence of phosphomolybdic acid as a catalyst. This catalyst system features high yields,

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Table 1 Optimization of HPA catalyst for Nazarov cyclization

		5	HPA (x mol%) solvent, T (°C) 5a			
Entry	HPA	<i>x</i> (mol%)	Solvent	$T/^{\circ}\mathrm{C}$	Time/h	Yield (%) ^a
1	PMA	0.5	CH ₃ CN	RT	12.0	96
2	PMA	1.0	CH ₃ CN	RT	3.0	92
3	PMA	1.5	CH ₃ CN	RT	0.5	94
4	PMA	0.5	CH ₃ CN	40	2.0	95
5	PMA	0.5	Toluene	40	20.0	50
6	PMA	0.5	DMF	40	20.0	NR
7	PMA	0.5	CH ₂ Cl ₂	40	20.0	80
8	PMA	0.5	CHCl ₃	40	6.0	85
9	PMA	0.5	EtOH	40	20.0	Traces
10	PMA	0.5	THF	40	20.0	60
11	PMA	0.5	Water	40	20.0	32^{b}
12	PWA^{c}	0.5	CH ₃ CN	40	25.0	52
13	SWA^d	0.5	CH ₃ CN	40	25.0	30
14	SMA ^e	0.5	CH ₃ CN	40	25.0	32
^a Isolat acid. ^d	ted yields SWA—si	. ^b Water-tra	pped produced acid. ^e SM.	uct. ^{<i>c</i>} PV A—silic	WA—pho omolybdia	sphotungstic c acid.

short reaction times, functional group tolerance and efficient recyclability in the bulk as well as in the supported form.

Initial attempts at Nazarov cyclization of compound 5 were performed in acetonitrile with 0.5 mol% PMA as the catalyst at ambient temperature and produced cyclopentenone 5a in excellent yield after a long reaction time (Table 1, entry 1). Optimization of the catalyst loading (Table 1, entries 1–3) improved reaction efficiency and markedly reduced reaction time. An elevated temperature (Table 1, entries 1, 4) considerably enhanced reaction. Solvents other than acetonitrile (Table 1, entries 5-10) did not improve yield or shorten reaction time. Interestingly, the reaction in an aqueous medium⁹ afforded the expected Nazarov product, though in a low yield (Table 1. entry 11). The water-trapped Nazarov product was the major product obtained. Attempts to improve the yield of the normal Nazarov product via high catalyst loading, high temperature, a phase-transfer catalyst, and aqueous acetonitrile as a solvent were unsuccessful. Adding diisopropylamine to the aqueous reaction, as in the literature,9 neutralized acidic sites on PMA and no reaction was observed. When other heteropoly acids were used in the place of PMA the reactions were sluggish under identical conditions (Table 1, entries 12–14).

The optimized reaction conditions (0.5% PMA at 40 °C in CH₃CN) were exploited for structurally diverse divinyl ketones. Polarized substrates with a carboethoxy group at the α -position of the dienone were synthesized by adding the sodium enolate of ethyl acetate to α,β -unsaturated esters.

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Scheme 1 Synthetic route to Nazarov substrates.

Knoevenagel condensation¹⁰ of the resulting β -keto ester **2** with various aldehydes afforded the corresponding dienones **3** in good overall yields compared to the generally adopted acid chloride method^{3c} (Scheme 1). The synthetic routes to other substrates employed in this study are described in the ESI.[†]

All divinyl ketones 4-14 underwent smooth cyclization under the conditions employed, forming the corresponding cyclopentenones 4a-14a in excellent yields (Table 2). Reaction times and the amount of catalyst required were strongly dependent on the substituent pattern of the divinyl ketones. 2-Alkoxy dienones with an unsubstituted vinyl group required a longer reaction time than when using similar substrates carrying substituents either at the α -, or β -position (Table 2, entries 1-5). The 2-ethoxypentadienone 9 reacted at a considerably slower rate than its dihydropyranyl counterpart (Table 2, entry 6) with subsequent loss of the ethoxy group in the 9a product. Introducing the electron withdrawing carboxyethyl group at the α -position of **4** had no significant effect on reactivity, and dienone 10 required a longer reaction time than that of 4 (Table 2, entry 7). Similarly, for compound 12, with a methylene group in place of the alkoxy group of the dihydropyranyl ring, the double bond in the product is localized less selectively and reaction generated regioisomers 12a and 12b in a 3.5:1 ratio. A ten-fold increase in catalyst loading was desirable for complete conversion for cases of poorly polarized divinyl ketones (Table 2, entries 10 and 11). The yield, reaction time and broad substrate scope with this catalyst system are superior to those of any catalyst system used for similar transformations. The homo-Nazarov¹¹ variant using vinylcyclopropyl ketone 15 had a reactivity similar to that of its dihydropyranyl counterpart, and produced bicyclic cyclohexenone 15a in a higher yield and shorter reaction time (Table 2, entry 12) compared with those of the reported protocol.¹¹ Reactions performed with 10% PMA by weight supported on silica-gel at 0.5 mol% catalyst loading were more efficient than those with the bulk catalyst, resulting in a sharp reduction in reaction time (Table 2, entries 1, 3 and 12).

Divinyl ketones 16–19 with acid-labile functionalities were subjected to Nazarov cyclization to investigate the chemoselectivity of the present catalyst system (Table 3). A high yield of Nazarov product with no detectable deprotection or rearrangement was encountered in the case of substrates with a TBS ether (16) or an azide group (18). In other cases, a slight modification of the reaction conditions, such as lowering catalyst loading (in the case of MOM ether dienone 17) or using an alternative solvent (CH₂Cl₂ in the case of THP ether 19) that decelerates the electrocyclization reaction, afforded high yields of cyclopentenone with intact functionalities.

 Table 2
 Nazarov cyclization of different divinyl ketones in the presence of phosphomolybdic acid

Entry	Substrate		Time/h ^a	Product		Yield (%) ^{a,b}
1		4	0.5 (0.08)		4a	99 (99)
2		5	2.0		5a	95
3		6	48.0 ^c (2.0)	\sim	6a	62 (90)
4		7	0.25		7a	90
5		8	0.33	Ů,	8a	90
6	EIO	9	24	HOLO	9a	50 ^e
7		10	2.0		10a	99
8	OF COL	11	0.16		11a	98
9	OEt	12	0.16		12a	
					12b	90 (3.5:1)
10		13	0.75		13a	90 ^d
11	OEt OEt OMe	14	0.50		14a	88 ^d
12	O Come	15	1.5 (0.5)		15a	80 (82)

^{*a*} The values in parentheses refer to reactions performed with 0.5 mol% PMA/SiO₂. ^{*b*} Isolated yields. ^{*c*} Reaction was not complete after 48 h. ^{*d*} Performed with 5 mol% catalyst. ^{*e*} Ethyl group was hydrolyzed.

The most reactive supported catalyst was further exploited for catalyst reuse. The supported catalyst was effectively recycled up to three times without appreciable change in catalytic activity, as evidenced by the consistently high TOF (turnover frequency) for all the cycles (Table 3, entry 5). In each case, the catalyst used was washed repeatedly

Table 3 Functional group tolerance and recyclability studies



^{*a*} 0.1 mol% PMA was employed at room temperature. ^{*b*} Reaction performed in CH₂Cl₂. ^{*c*} THP deprotected compound was formed in 20% yield. ^{*d*} TOF (h^{-1}).

with CH₂Cl₂ and dried under high vacuum pressure prior to the next cycle.

In conclusion, PMA (in bulk and supported form) efficiently catalyzes electrocyclization of divinyl ketones under short reaction times in high yields. The supported catalyst system was more effective than the bulk catalyst system and permits recyclability of the used catalyst for up to three cycles with similar catalytic activity levels. This catalyst system is chemoselective and acid-labile functionalities remain intact during the cyclization process. The present method is therefore a promising and useful addition to existing catalyst systems for the construction of five-membered carbocycles in natural product synthesis.

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Notes and references

- 1 I. N. Nazarov and I. I. Zaretskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1941, 211.
- 2 Recent reviews on the Nazarov reaction: (a) K. L. Habermas and S. E. Denmark, *Organic Reactions*, John Wiley & Sons, New York, 1994, ch. 1, vol. 45; (b) C. Santelli-Rouvier and M. Santelli,

Synthesis, 1983, 429; (c) H. Pellissier, Tetrahedron, 2005, 61, 6479; (d) M. Tius, Eur. J. Org. Chem., 2005, 2193; (e) A. J. Frontier and C. Collison, Tetrahedron, 2005, 61, 7577. For selected examples of application see: (f) S. Elz and W. L. Heil, Bioorg. Med. Chem. Lett., 1995, 5, 667; (g) X. Li and R. Vince, Bioorg. Med. Chem., 2006, 14, 2942; (h) G. Romeo, L. Materia, V. Pittala, M. Modica, L. Salerno, M. Siracusa, F. Russo and K. P. Minneman, Bioorg. Med. Chem., 2006, 14, 5211; (i) H. Nagano and T. Takahashi, Bull. Chem. Soc. Jpn., 1978, 51, 3335; (i) P. A. Jacobi, D. G. Walker and I. M. A. Odeh, J. Org. Chem., 1981, 46, 2065; (k) R.-R. Juo and W. Herz, J. Org. Chem., 1985, 50, 700; (1) M. Miyashita, T. Kumazawa and A. Yoshikoshi, J. Org. Chem., 1984, 49, 3728; (m) A. Gopalan and P. Magnus, J. Org. Chem., 1984, 49, 2317; (n) A. Gopalan and P. Magnus, J. Am. Chem. Soc., 1980, 102, 1756; (o) M. Amat, M. Pérez, N. Llor, M. Martinelli, E. Molins and J. Bosch, Chem. Commun., 2004, 1602; (p) M. H. Schmitt and S. Blechert, Angew. Chem., Int. Ed. Engl., 1997, 36, 1474.

- 3 For selected examples see: (a) W. He, J. Huang, X. F. Sun and A. J. Frontier, J. Am. Chem. Soc., 2007, **129**, 498; (b) I. Walz, A. Bertogg and A. Togni, Eur. J. Org. Chem., 2007, 2650; (c) V. K. Aggarwal and A. J. Belfield, Org. Lett., 2003, **5**, 5075; (d) G. Y. Lin, C. Y. Yang and R. S. Liu, J. Org. Chem., 2007, **72**, 6753; (e) J. Nie, H. W. Zhu, H. F. Cui, M. Q. Hua and J. A. Ma, Org. Lett., 2007, **9**, 3053; (f) M. Fujiwara, M. Kawatsura, S. Hayase, M. Nanjo and T. Itoh, Adv. Synth. Catal., 2009, **351**, 123; (g) M. Kawatsura, Y. Higuchi, S. Hayase, M. Nanjo and T. Itoh, Synlett, 2008, 1009; (h) P. Chiu and S. Li, Org. Lett., 2004, **6**, 613; (i) J. A. Malona, J. M. Colbourne and A. J. Frontier, Org. Lett., 2006, **8**, 5661; (j) W. He, X. Sun and A. J. Frontier, J. Am. Chem. Soc., 2003, **125**, 14278; (k) G. Liang, S. N. Gradl and D. Trauner, Org. Lett., 2003, **5**, 4931.
- 4 For selected examples see: (a) P. Kraft and R. Cadalbert, Synthesis, 2002, 2243; (b) M. Ishikura, K. Imaizumi and N. Katagiri, Heterocycles, 2000, 53, 2201; (c) A. Fernández-Mateos, L. Mateos Burón, E. M. Martín de la Nava and R. Rubio González, J. Org. Chem., 2003, 68, 3585; (d) A. Fernández-Mateos, E. M. Martín de la Nava and R. Rubio González, Tetrahedron, 2001, 57, 1049; (e) C. Song, D. W. Knight and M. A. Whatton, Org. Lett., 2006, 8, 163; (f) D. L. J. Clive, M. Sannigrahi and S. Hisaindee, J. Org. Chem., 2001, 66, 954; (g) M. Amere, J. Blanchet, M.-C. Lasne and J. Rouden, Tetrahedron Lett., 2008, 49, 2541; (h) M. Rueping, W. Ieawsuwan, A. P. Antonchick and B. J. Nachtsheim, Angew. Chem., Int. Ed., 2007, 46, 2097.
- 5 (a) C. J. Rieder, R. J. Fradette and F. G. West, *Chem. Commun.*, 2008, 1572; (b) D. Song, A. Rostami and F. G. West, *J. Am. Chem. Soc.*, 2007, **129**, 12019; (c) F. Dhoro, T. E. Kristensen, V. Stockmann, G. P. A. Yap and M. A. Tius, *J. Am. Chem. Soc.*, 2007, **129**, 7256; (d) A. Rostami, Y. Wang, A. M. Arif, R. McDonald and F. G. West, *Org. Lett.*, 2007, **9**, 703; (e) T. N. Grant and F. G. West, *Org. Lett.*, 2007, **9**, 3789.
- 6 A. S. S. Sido, S. Chassaing, M. Kumarraja, P. Pale and J. Sommer, *Tetrahedron Lett.*, 2007, 48, 5911.
- 7 (a) I. V. Kozhevnikov, Chem. Rev., 1998, **98**, 171; (b) N. Mizuno and M. Misono, Chem. Rev., 1998, **98**, 199.
- 8 (a) M. Misono, I. Ono, G. Koyano and A. Aoshima, *Pure Appl. Chem.*, 2000, **72**, 1305; (b) K. Wilson and J. H. Clark, *Pure Appl. Chem.*, 2000, **72**, 1313; (c) F. Dhoro and M. A. Tius, *J. Am. Chem. Soc.*, 2005, **127**, 12472; (d) F. Douelle, L. Tal and M. F. Greaney, *Chem. Commun.*, 2005, 660.
- 9 M. Kokubo and S. Kobayashi, Chem.-Asian J., 2009, 4, 526.
- 10 W. He, I. R. Herrick, T. A. Atesin, P. A. Caruana, C. A. Kellenberger and A. J. Frontier, *J. Am. Chem. Soc.*, 2008, 130, 1003.
- 11 F. De Simone, J. Andrès, R. Torosantucci and J. Waser, Org. Lett., 2009, 11, 1023.