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Asymmetric synthesis of multiple quaternary stereocentre-containing cyclopentyls by oxazolidinone-promoted Nazarov cyclizations†

Rohan Volpe,^a Romain J. Lepage,^b Jonathan M. White,^c Elizabeth H. Krenske^b and Bernard L. Flynn^{*a}

Carbometalation of oxazolidinone (Ox)-substituted ynamides is used to generate highly substituted Ox-divinyl (and aryl vinyl) ketones for use in Nazarov cyclizations. The Ox-group serves as a remarkably effective chiral activating group, enabling the torquoselective Nazarov cyclization of these sterically congested substrates to be performed under mild conditions. It also serves as a charge-stabilizing group in the intermediate oxyallyl cation, suppressing undesired [1,2]-sigmatropic shifts of neighboring substituents and facilitating the regio- and stereoselective incorporation of nucleophiles to yield cyclopentanoids containing up to three contiguous all-carbon quaternary (4°) stereocentres.

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Introduction

The enantioselective synthesis of quaternary (4°) stereocentres is a major challenge in organic synthesis, hindering access to sp³-rich scaffolds in drug discovery and natural products synthesis.^{1,2} Particularly problematic is the enantioselective formation of multiple 4°-stereocentres, which requires control over both relative and absolute stereochemistry.

The Nazarov cyclization offers inherent control over relative stereochemistry through conservation of orbital symmetry and constitutes an attractive route to multistereocentre-containing cyclopentanoids.³ However, the potential of the Nazarov cyclization for 4°-stereocentre formation has not yet been fully realized due to two significant challenges: (i) stereoselective access to highly substituted divinyl (and aryl vinyl) ketone substrates⁴ and (ii) torquoselective⁵ ring closure. In a landmark study, Tius and co-workers⁶ reported chiral Brønsted acid-catalyzed Nazarov cyclizations of divinyl ketones **1** (Scheme 1a) leading to cyclopentenols **3** containing two new vicinal 4°-stereocentres (R¹⁻³ ≠ H) with high enantioselectivities (often er > 97 : 3). Careful design of the divinyl ketone **1** with dual-activating electron donor (OCHPh₂) and acceptor

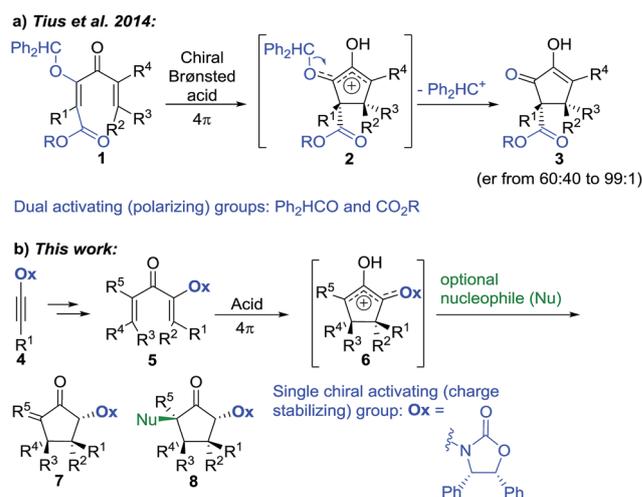
(CO₂R) elements was key to attaining efficient cyclization.⁶ Electrofugal release of Ph₂HC⁺ from the intermediate oxyallyl cation **2** further promoted the cyclization and suppressed competing Wagner–Meerwein rearrangements ([1,2]-sigmatropic shifts of R¹⁻³ within **2**). Herein, we report that highly substituted aryl vinyl and divinyl ketones **5** can be readily accessed through carbometalations of oxazolidinone (Ox)-substituted ynamides **4** (Scheme 1b).⁷ The Ox-group proves to be remarkably effective as a single chiral activating group for the Nazarov cyclizations of these highly substituted and sterically congested substrates **5**, giving *exo*-methylene cyclopentanones **7** under remarkably mild conditions, with excellent and predictable enantiocontrol. Furthermore, since no electrofugal release is required for

^aMonash Institute of Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville, Victoria 3052, Australia. E-mail: bernard.flynn@monash.edu

^bSchool of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, QLD 4072, Australia

^cBio21 Institute, School of Chemistry, University of Melbourne, Parkville, VIC 3010, Australia

† Electronic supplementary information (ESI) available: Experimental details and NMR spectra of all newly synthesized compounds. X-ray crystal data for (3*S*)-**23** and **E-24**. Details and further discussion of computational studies. CCDC 1814626 and 1814627. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8sc00031j



Scheme 1 Nazarov substrate activation modes for the enantioselective synthesis of 4°-stereocentres.



substrate activation or suppression of Wagner–Meerwein rearrangements, the oxyallyl cation **6** can be exploited in nucleophilic trapping^{7,8} to afford multistereocentre-centre-containing products **8** with up to three all-carbon 4°-stereocentres. The rapid assembly of such levels of complexity from a prochiral starting material highlights the powerful activating and stereocontrolling influence of the **Ox** group. Using theoretical calculations, we show that the exceptional activating properties of **Ox** originate from a combination of covalent and non-covalent transition-state stabilizing effects.

Results and discussion

Two different carbometalation strategies were developed to give access to **Ox**-containing divinyl and aryl vinyl ketones **5** (R^2 = alkyl/aryl, Table 1). Firstly, Cu-catalyzed

carbomagnesiation of **Ox**-ynamides **4** with Grignard reagents gave **9** ($M = \text{MgBr}$);⁹ alternatively, Rh-catalyzed carbocationation of **4** with ZnEt_2 gave **9** ($M = \text{ZnEt}$).¹⁰ Addition of iodine to organometallics **9** ($M = \text{MgBr}$ or ZnEt) gave the key building block alkenyliodides **10a** (68%) and **10b** (79%). Carbonylative Stille coupling (Method A) of **10a** and **10b** with tributyl(cyclohexen-1-yl)stannane afforded divinyl ketones **5a/a'** and **5b/b'**, respectively, each as a 5 : 1 mixture of *E/Z*-isomers about the **Ox**-substituted double bond (entries 1–4).¹¹ Despite this partial isomerization, the major isomers, **5a** and **5b**, were isolated in 55% and 52% yield, respectively. All other divinyl and aryl vinyl ketones **5** shown in Table 1 were accessed by reaction of **9** ($M = \text{MgBr}$) with the corresponding aldehyde followed by Dess–Martin periodinane oxidation of the crude alcohols (Method B) giving **5c–j** in yields of 31–91% (entries 5–12).

Table 1 Synthesis of Nazarov substrates **5** and their cyclization to 4°-stereocentre-containing cyclopentanoids **7**

Method A (carbonylative Stille): 10a/b vinylstannane, Pd(dtbpf)Cl ₂ (5 mol%), CuI (30 mol%), CO(g)					
Method B (1,2-addition, oxidation): 9 ($M = \text{MgBr}$), vinyl/aryl aldehyde, then Dess–Martin periodinane					
I_2					
9 $M = \text{MgBr}$ or ZnEt 10a $M = \text{I}$, $R^1 = \text{Ph}$, $R^2 = \text{Me}$, 68% 10b $M = \text{I}$, $R^1 = \text{Ph}$, $R^2 = \text{Et}$, 79%					
4/10 → 5 ^a	5 → 7 ^c (dr) ^d	4/10 → 5 ^a	5 → 7 ^c (dr) ^d	4/10 → 5 ^a	5 → 7 ^c (dr) ^d
1 5a 55% (A)	 7a 67% (>20:1)	5 5c 72% (B)	 7c 75% (>20:1)	9 5g 91% (B)	 7g 93% (>20:1)
2 5a' 10% (A) ^b	 7a' 73% (>20:1)	6 5d 39% (B)	 7d 42% ^e (2:1)	10 5h 60% (B)	 7h 50% (>20:1)
3 5b 52% (A)	 7b 86% (>20:1)	7 5e 31% (B)	 7e 45% (>20:1)	11 5i 85% (B)	 7i 76% (>20:1)
4 5b' 10% (A) ^b	 7b' 69% (>20:1)	8 5f 84% (B)	decomposition	12 5j 85% (B) PMP = <i>p</i> -methoxyphenyl	

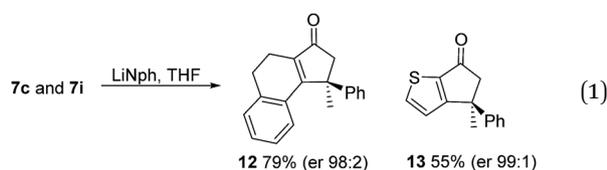
^a Nazarov substrates **5** formed from **4** using Method A (**A**) or Method B (**B**), as indicated. ^b Isolated as a minor isomer using Method A. ^c Cyclized with $\text{BF}_3 \cdot \text{THF}$ or TfOH in CH_2Cl_2 at various temperatures (ranging from -78 °C to 40 °C) depending on acid and substrate; see text and ESI for details. ^d Diastereomeric ratio (dr) refers to stereochemistry at C1 relative to **Ox** (determined by ^1H NMR). Some products **7** were isolated as a mixture of C2-epimers, indicated by a wavy bond (see ESI for ratio); these give a single enantiomer upon **Ox** removal (eqn (1), ref. 7). ^e Isolated yield of C1-(S) isomer, an additional 24% was isolated as a 3 : 1 (*R*) : (*S*)-C1 mix.



Nazarov cyclizations of divinyl and aryl vinyl ketones **5a–j** were performed using either $\text{BF}_3 \cdot \text{THF}$ or TfOH as catalyst in CH_2Cl_2 , giving cyclopentanoids **7a–i** (**5f** and **5j** did not cyclize) containing one new 4°-stereocentre (Table 1). Broadly speaking, these Nazarov cyclizations performed very well, particularly where the “inner” substituent (R^2) in **5** was Me, Et or Ph ($\text{BF}_3 \cdot \text{THF}$ or TfOH). Use of TfOH as catalyst allowed the Nazarov cyclization to be conducted at temperatures as low as -78°C , but generally the reactions were performed at 0°C to rt or in refluxing CH_2Cl_2 (40°C) using either TfOH or $\text{BF}_3 \cdot \text{THF}$.[‡] The torquoselectivities were very high ($\text{dr} > 20 : 1$ for C1 relative to **Ox**), with the sole exception of **7d** ($\text{dr} = 2 : 1$ (*S*) : (*R*)-C1, entry 6). X-ray crystal structure and density functional theory (DFT) studies have shown that **Ox** auxiliaries of this configuration consistently favor anticlockwise conrotation leading to R^1 - β stereochemistry (see below);^{7b} we have therefore assigned this stereochemistry to each product in Table 1. Most likely, the cyclization of **5d**, which required heating to 40°C due to the sterically encumbering isopropyl group ($\text{R}^2 = i\text{Pr}$), gave lower selectivity due to partial *Z/E*-isomerization of the oxazolidinyl-alkene prior to cyclization, rather than because of poor stereoinduction by the auxiliary (see also below).

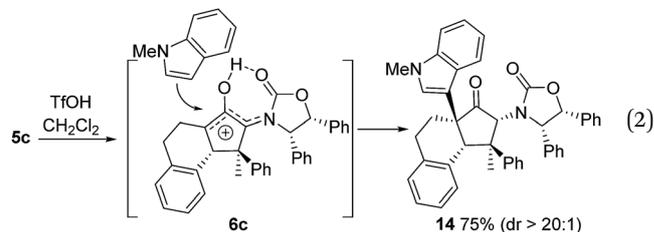
The presence of two aliphatic substituents on the tetrasubstituted alkene terminus, as in **5e**, led to slower cyclization, but the stereoinduction remained high (entry 7). Diaryl-substituted alkene **5f** underwent undesired side reactions to give multiple minor products along with return of starting material (entry 8). In a number of cases, the presence of epimers at C2 (the carbon bearing **Ox**) was apparent, but both epimers lead to the same product once the auxiliary is removed by reductive cleavage (see below). Cyclizations of electron-rich aryl vinyl ketones were successful (entries 9–11), even for the very hindered substrate **5h** where $\text{R}^2 = i\text{Pr}$. For the less activated aryl vinyl ketone **5j**, alkene isomerization to form β,γ -unsaturated ketone **11** became the dominant pathway and no Nazarov cyclization was observed.

As has been demonstrated in our previous study utilizing a diverse array of less substituted Nazarov products **7** ($\text{R}^2 = \text{R}^3 = \text{H}$), the oxazolidinone can be removed by reductive-cleavage using lithium naphthalenide (LiNph).^{7c} Two examples are given as part of this work (eqn (1)): reductive cleavage of the **Ox** group in **7c** and **7i** gave **12** (79%) and **13** (55%), respectively, both in high enantiomeric purity ($\text{er} > 98 : 2$).

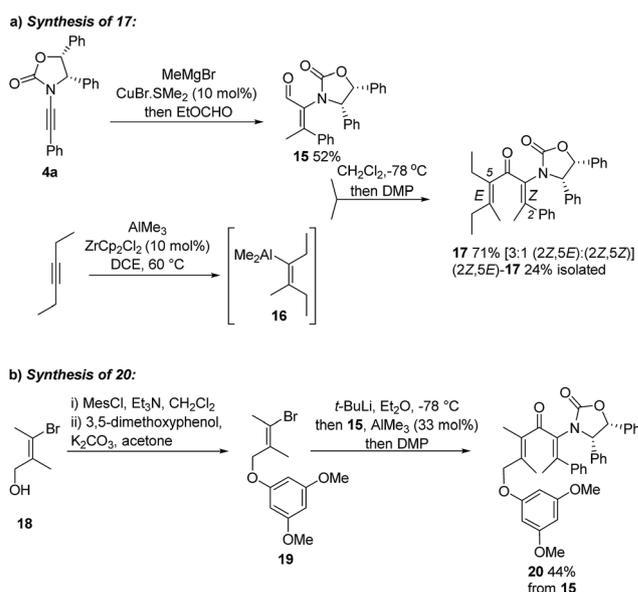


Also, as per our previous work, additional stereochemical complexity can be built up by nucleophilic trapping of the intermediate oxyallyl cations **6**.^{7c} Accordingly, the highly substituted divinyl ketone **5c** was converted into the indole-trapped product **14** (75%) (eqn (2)). Notably, this tandem

sequence generates four new contiguous stereocentres, including two 4°-centres, with excellent control over both relative and absolute stereochemistry: only a single isomer was observed.

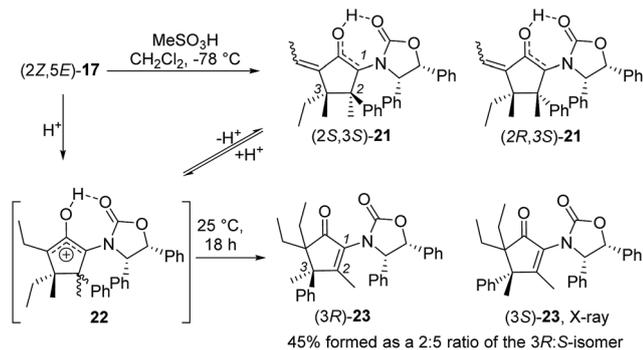


Having achieved stereoselective Nazarov cyclizations leading to products with adjacent 3° and 4°-stereocentres, we next addressed the formation of vicinal 4°-stereocentres. To prepare the fully substituted Nazarov substrate **17** we developed a convergent carbometalation approach starting from two alkynes: ynamide **4a** and 3-hexyne (Scheme 2a). Cu-catalyzed addition of MeMgBr to **4a**, followed by *in situ* formylation with ethylformate, afforded **15** (52%) stereoselectively. Carboalumination of 3-hexyne to give **16**,¹¹ followed by 1,2-addition of **16** to **15** and oxidation with DMP, gave divinyl ketone **17** (71%). The C2–C3 double bond retained its *Z* stereochemistry while the C5–C6 double bond was formed as a 3 : 1 *E* : *Z* mixture.^{12§} Separation of these isomers proved challenging; however, a pure sample of (*2Z,5E*)-**17** was isolated in 24% yield (from **15**). We also prepared the fully substituted ketone **20** (Scheme 2b) bearing a tethered nucleophile (electron-rich aryl group). Access to **20** commenced with formation of vinyl bromide **19** from bromoalcohol **18**.¹³ Lithiation of **19**, followed by addition to a solution of **15** and AlMe_3 (Lewis acid) and DMP oxidation of



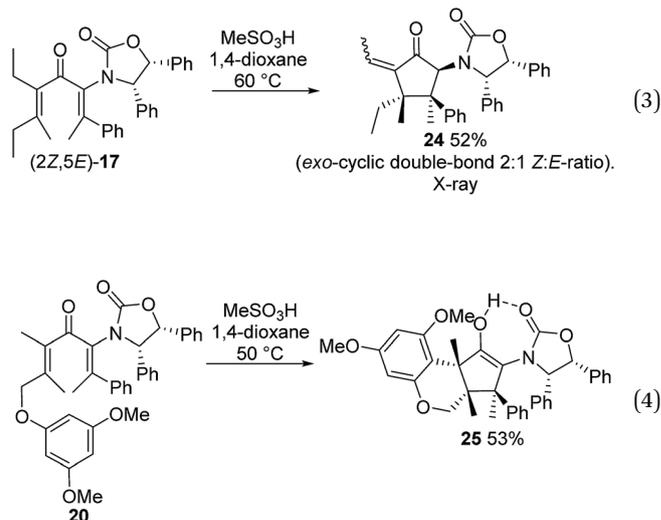
Scheme 2 Syntheses of fully substituted **Ox**-divinyl ketones **17** and **20**.



Scheme 3 Nazarov cyclization of 17 in CH₂Cl₂.

the crude carbinol (not shown) afforded **20** (44%) as a single alkene-stereoisomer.¶

Nazarov cyclization of (2*Z*,5*E*)-17 with MeSO₃H (CH₂Cl₂, −78 °C) gave **21** as a complex mixture of C2,3-diastereomers, keto/enol-tautomers and *E/Z*-isomers (Scheme 3). Warming the mixture to ambient temperature resulted in a double Wagner–Meerwein shift of the C3-ethyl and C2-phenyl substituents in the reversibly formed oxallyl cation **22** to give (3*R*)-**23** and (3*S*)-**23** in a 2 : 5 ratio (Scheme 3).¹⁴ The stereochemistry of these products was confirmed by X-ray crystallography of (3*S*)-**23**.‡ We believe that the origin of this epimeric mixture is partial double-bond isomerization of (2*Z*,5*E*)-17 to (2*E*,5*E*)-17 under the acidic conditions prior to Nazarov cyclization. While this isomerization was undesired, the rapid (<2 h) cyclisation of both isomers of **17** at −78 °C demonstrates the remarkable ability of the Ox group to activate the Nazarov reaction. Upon further experimentation with reaction conditions (acids and solvents) to avoid double-bond isomerization of (2*Z*,5*E*)-17 to (2*E*,5*E*)-17, we found that treatment of (2*Z*,5*E*)-17 with MeSO₃H in 1,4-dioxane with mild heating gave cyclopentanone **24** stereoselectively in 52% isolated yield (eqn (3)). The stereochemistry of (*E*)- and (*Z*)-**24** were confirmed by X-ray crystallography and 2D NMR, respectively.‡ Replacing CH₂Cl₂ with 1,4-dioxane as solvent appears to exert different effects on the rates of the various competing reactions involved in the formation of **21**, **23** and **24** (Scheme 3 and eqn (3)). Solvation of MeSO₃H by 1,4-dioxane likely reduces the rates of all of these reactions, however, its strongest effects appear to be the suppression of C2–C3 double-bond isomerization in **17** and Wagner–Meerwein rearrangement in **22**, leading to the observed stereo- and chemoselective formation of **24**.¹⁵ Cyclization of **20** (eqn (4)) under these conditions was also successful, yielding the intramolecularly trapped product **25** as the only product discernable by ¹H-NMR (53% isolated yield). Conversion of **20** to **25** forms two new rings and three contiguous 4°-stereocentres, underscoring the effectiveness of the Ox-controlled Nazarov reaction for synthesis of structurally complex, 4°-stereocentre-containing scaffolds. The asymmetric formation of three contiguous 4°-stereocentres entirely from prochiral carbons is a rare transformation; a Diels–Alder reaction reported by Nicolaou *et al.* is the only other example known to us.¹⁶



These Ox-promoted Nazarov cyclizations are remarkably facile, allowing efficient generation of sterically congested products at temperatures as low as −78 °C. This points to a powerful activating influence of the Ox auxiliary. In order to determine the origins of this activation, we performed DFT calculations (Fig. 1).‡ Calculations with M06-2X show that in the absence of an oxazolidinone, the activation energies (ΔG^\ddagger) for Nazarov cyclizations of **26**–**28** leading to zero, one, or

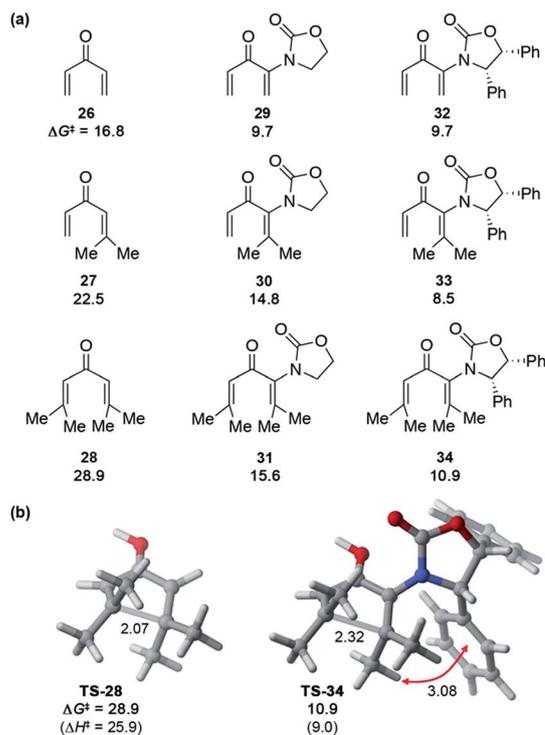


Fig. 1 (a) Activation barriers for H⁺-catalyzed Nazarov cyclizations of model divinyl ketones **26**–**34** and (b) transition states for cyclizations of **28** and **34**, calculated with M06-2X/6-311+G(d,p)//M06-2X/6-31G(d) in implicit (SMD) dichloromethane. Distances in Å, ΔH^\ddagger and ΔG^\ddagger in kcal mol⁻¹.



two 4°-centres are 16.8, 22.5, and 28.9 kcal mol⁻¹, respectively. Each new 4°-stereocentre raises the barrier by 6 kcal mol⁻¹.[‡] An achiral oxazolidinone devoid of Ph substituents (**OxH₂**, see 29–31) lowers the cyclization barrier by 7–13 kcal mol⁻¹ ($\Delta G^\ddagger = 9.7\text{--}15.6$ kcal mol⁻¹) relative to the oxazolidinone-free substrates, while the diphenyl-oxazolidinone (**Ox**, see 32–34) provides further activation still, leading to cyclization barriers of only 8.5–10.9 kcal mol⁻¹. These very low barriers are consistent with the facile ring closures observed for 5, 17, and 20.

The transition states (TSs) for **OxH₂**- and **Ox**-promoted cyclizations benefit from several stabilizing effects. Firstly, the nitrogen lone pair affords resonance stabilization of the incipient oxyallyl cation. Secondly, the oxazolidinone-containing TSs feature a longer forming C–C bond than the corresponding oxazolidinone-free TSs, leading to reduced steric repulsion between the Me groups about the forming C–C bond (see Fig. 1b). A third activating influence of **Ox** is evident from a comparison of the cyclizations of 33 and 34 (containing **Ox**) with those of 30 and 31 (containing **OxH₂**). The two **Ox**-substituted TSs have ΔG^\ddagger values about 6 kcal mol⁻¹ lower than those of the corresponding **OxH₂** derivatives. The additional activation by **Ox** can be traced to a CH– π interaction in the TS between the “inner” substituent on C2 (R², rotating downwards) and the nearby Ph substituent on **Ox** (see red arrow in Fig. 1). Together, these three TS-stabilizing influences of **Ox** make it an exceptionally powerful activating group, capable of reducing the barrier for vicinal 4°-centre formation by almost 18 kcal mol⁻¹ (28 vs. 34). Indeed, computations predict that when the R¹ substituent is an aryl group, like in many of our substrates (5, 17, and 20) (with R² = alkyl) the barrier for cyclization is even lower still.[‡]

Conclusions

To conclude, carbometalation of **Ox**-ynamides affords direct access to highly substituted **Ox**-divinyl and -aryl vinyl ketones, which undergo exceptionally facile Nazarov cyclizations leading to 4°-stereocentre-containing cyclopentanoids. In addition to the powerful activating and stereodirecting influence of **Ox** in the Nazarov cyclization, the **Ox** auxiliary helps suppress undesired Wagner–Meerwein rearrangements in the intermediate oxyallyl cations, and facilitates nucleophilic trapping of these intermediates enabling rapid assembly of multiple stereocentres (including vicinal 4°-stereocentres) with excellent stereochemical control. Theoretical studies allowed us to discover the electronic origin of the strong activating effect of the **Ox**, which is traced to a combination of covalent (lone pair donation to the incipient oxyallyl cation and reduced steric crowding about the newly forming bond) and non-covalent (CH– π interaction) effects which are generally applicable across most of the divinyl (or aryl vinyl) ketones reported here.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

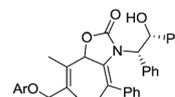
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Notes and references

[‡] See the ESI.[†]

[§] The basis of the isomerization of the C5-alkenyl unit has not yet been fully discerned. Treatment of 16 with I₂ gave only the expected *E*-iodoalkene, whereas 1,2-addition of 16 to 15 gives the corresponding carbinol (not shown) as ~3 : 1 mixture of the *E*- and *Z*-isomer.

[¶] In the absence of AlMe₃ the reaction affords mostly an acyl migration product involving ring opening of the oxazolidinone:



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