Chemical Science

EDGE ARTICLE

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Cite this: *Chem. Sci.*, 2018, **9**, 4644

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

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Received 4th January 2018
Accepted 19th April 2018

DOI: 10.1039/c8sc00031j

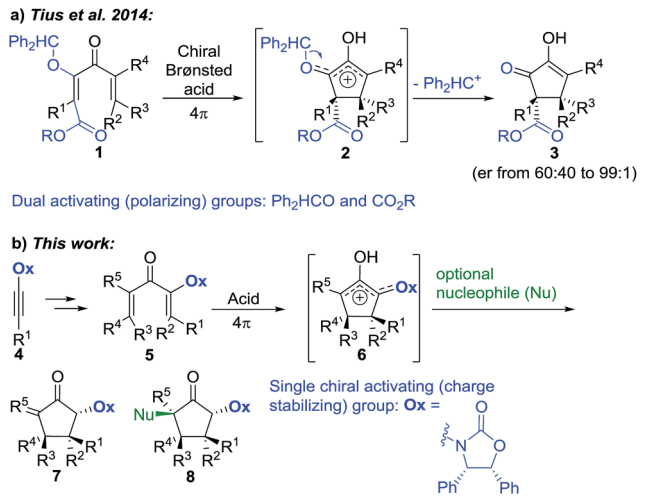
rsc.li/chemical-science

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.

Introduction

The enantioselective synthesis of quaternary (4°) stereocentres is a major challenge in organic synthesis, hindering access to sp^3-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 substrates[4] and (ii) torquoselective[5] ring closure. In a landmark study, Tius and co-workers[6] reported chiral Brønsted acid-catalyzed Nazarov cyclizations of divinyl ketones **1** (Scheme 1a) leading to cyclopentenols **3** containing two new vicinal 4°-stereocentres ($R^{1-3} \neq H$) with high enantioselectivities (often er > 97 : 3). Careful design of the divinyl ketone **1** with dual-activating electron donor ($OCHPh_2$) and acceptor (CO_2R) elements was key to attaining efficient cyclization.[6] Electrofugal release of Ph_2HC^+ from the intermediate oxyallyl cation **2** further promoted the cyclization and suppressed competing Wagner–Meerwein rearrangements ([1,2]-sigmatropic shifts of R^{1-3} 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



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

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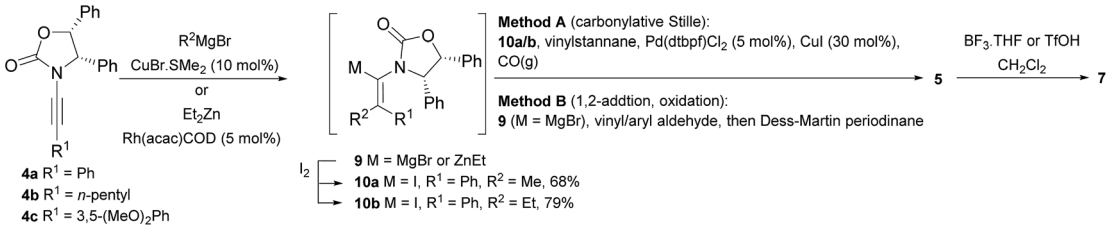
† Electronic supplementary information (ESI) available: Experimental details and NMR spectra of all newly synthesized compounds. X-ray crystal data for (3*S*)-**23** and *E*-**24**. Details and further discussion of computational studies. CCDC 1814626 and 1814627. For ESI and crystallographic data in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

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 = MgBr);[9] alternatively, Rh-catalyzed carbozincation of **4** with $ZnEt_2$ gave **9** (M = ZnEt).[10] Addition of iodine to organometallics **9** (M = 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 = 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**



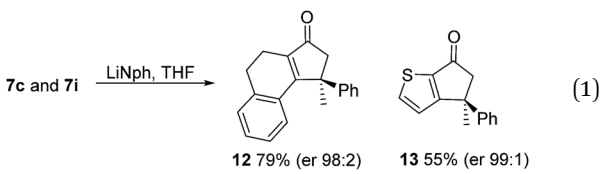
	4/10 → 5[a]	5 → 7[c] (dr)[d]	4/10 → 5[a]	5 → 7[c] (dr)[d]	4/10 → 5[a]	5 → 7[c] (dr)[d]
1	**5a** 55% (**A**)	**7a** 67% (>20:1)	5	**5c** 72% (**B**)	**7c** 75% (>20:1)	9	**5g** 91% (**B**)	**7g** 93% (>20:1)
2	**5a′** 10% (**A**)[b]	**7a′** 73% (>20:1)	6	**5d** 39% (**B**)	**7d** 42%[e] (2:1)	10	**5h** 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 = *p*-methoxyphenyl	**11**

[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 $BF_3 \cdot THF$ 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 $BF_3\cdot$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 ($BF_3\cdot$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 $BF_3\cdot$THF.‡ The torquoselectivities were very high (dr > 20 : 1 for C1 relative to **Ox**), with the sole exception of **7d** (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 (R^2 = *i*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).

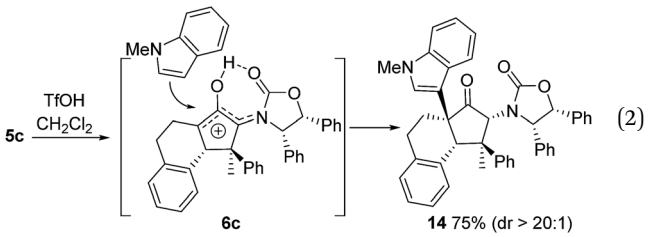
The presence of two aliphatic substituents on the tetrasubstituted alkene terminus, as in **5e**, led to slower cyclization, but the stereoinduction remained high (entry 7). Diaryl-substituted alkene **5f** underwent undesired side reactions to give multiple minor products along with return of starting 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 R^2 = *i*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** ($R^2 = R^3 =$ 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 (er > 98 : 2).



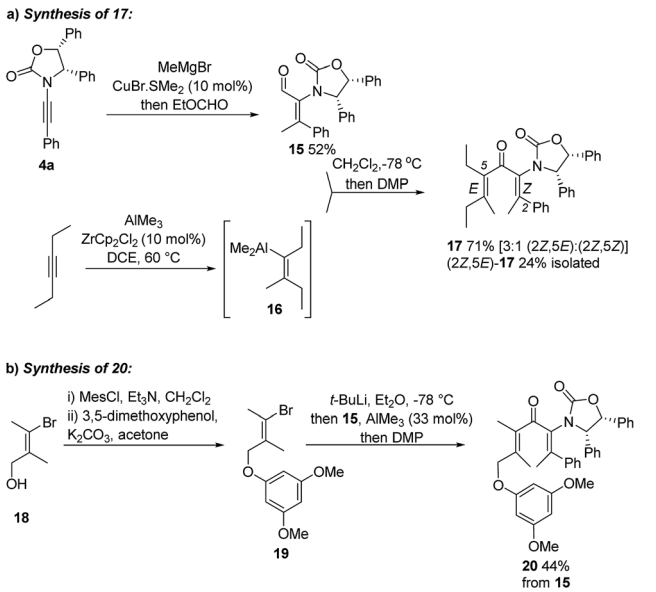
(1)

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.

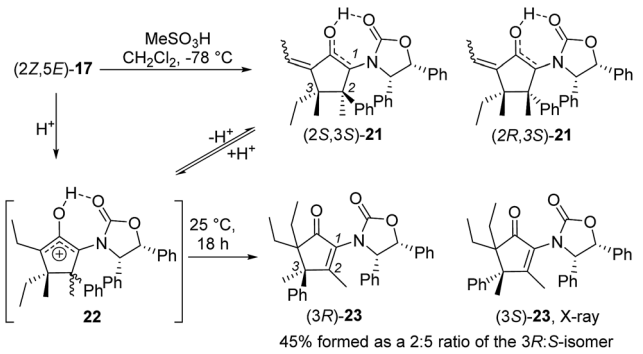


(2)

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 (2*Z*,5*E*)-**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



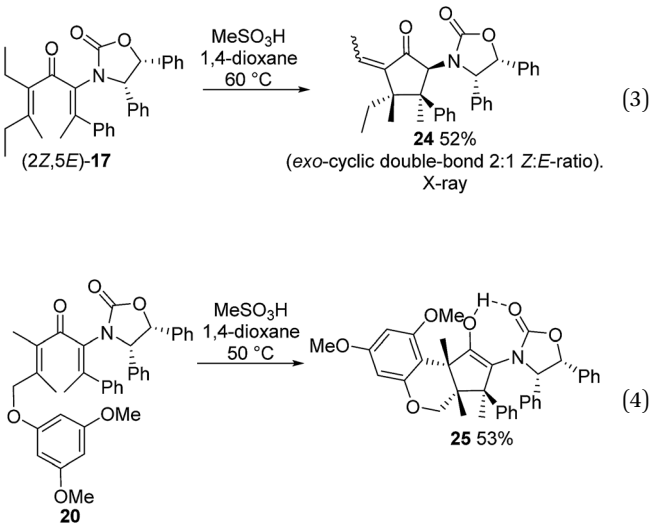
Scheme 2 Syntheses of fully substituted **Ox**-divinyl ketones **17** and **20**.



Scheme 3 Nazarov cyclization of **17** in CH_2Cl_2.

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

Nazarov cyclization of (2*Z*,5*E*)-**17** with $MeSO_3H$ (CH_2Cl_2, −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 oxyallyl 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 $MeSO_3H$ 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 CH_2Cl_2 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 $MeSO_3H$ 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 ^{1}H-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 ($\Delta G^{\ddagger}$) for Nazarov cyclizations of **26–28** leading to zero, one, or

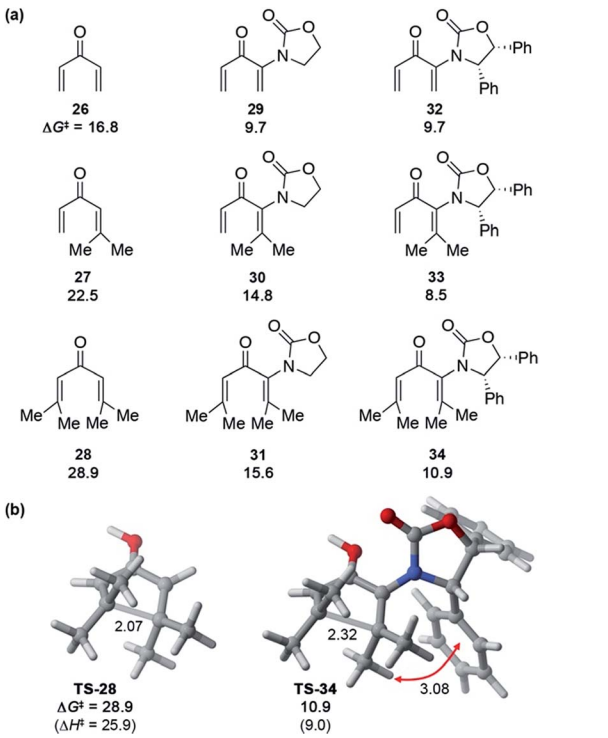


Fig. 1 (a) Activation barriers for H^+-catalyzed Nazarov cyclizations of model divinyl ketones **26–34** and (b) transition states for cyclizations of **28** and **34**, calculated with M06-2X/6-311+G(d,p)//M06-2X/6-31G(d) in implicit (SMD) dichloromethane. Distances in Å, $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ 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 (**OxH$_2$**, see **29–31**) lowers the cyclization barrier by 7–13 kcal mol^{-1} ($\Delta G^{\ddagger}$ = 9.7–15.6 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 **OxH$_2$**- 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 **OxH$_2$**). The two **Ox**-substituted TSs have $\Delta G^{\ddagger}$ values about 6 kcal mol^{-1} lower than those of the corresponding **OxH$_2$** derivatives. The additional activation by **Ox** can be traced to a CH–π interaction in the TS between the "inner" substituent on C2 (R^2, 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 R^1 substituent is an aryl group, like in many of our substrates (**5**, **17**, and **20**) (with R^2 = 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

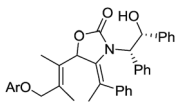
This research has been supported by the Australian Research Council (DP150103131 and FT120100632). Computer resources were provided by the Australian National Computational Infrastructure National Facility and by the University of Queensland Research Computing Centre.

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 I$_2$ 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 AlMe$_3$ the reaction affords mostly an acyl migration product involving ring opening of the oxazolidinone:



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