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

Rohan Volpe,<sup>a</sup> Romain J. Lepage,<sup>b</sup> Jonathan M. White,<sup>c</sup>  
Elizabeth H. Krenske<sup>b</sup> and Bernard L. Flynn<sup>\*a</sup>

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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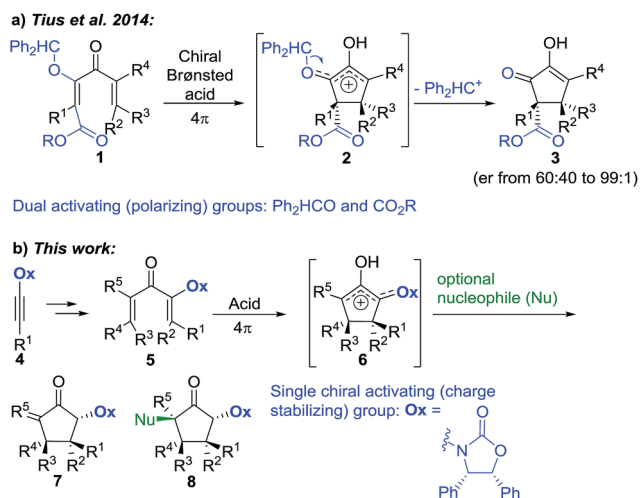
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## Introduction

The enantioselective synthesis of quaternary (4°) stereocentres is a major challenge in organic synthesis, hindering access to sp<sup>3</sup>-rich scaffolds in drug discovery and natural products synthesis.<sup>1,2</sup> 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.<sup>3</sup> 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<sup>4</sup> and (ii) torquoselective<sup>5</sup> ring closure. In a landmark study, Tius and co-workers<sup>6</sup> reported chiral Brønsted acid-catalyzed Nazarov cyclizations of divinyl ketones **1** (Scheme 1a) leading to cyclopentenols **3** containing two new vicinal 4°-stereocentres (R<sup>1-3</sup> ≠ H) with high enantioselectivities (often er > 97 : 3). Careful design of the divinyl ketone **1** with dual-activating electron donor (OCHPh<sub>2</sub>) and acceptor

(CO<sub>2</sub>R) elements was key to attaining efficient cyclization.<sup>6</sup> Electrofugal release of Ph<sub>2</sub>HC<sup>+</sup> from the intermediate oxyallyl cation **2** further promoted the cyclization and suppressed competing Wagner–Meerwein rearrangements ([1,2]-sigmatropic shifts of R<sup>1-3</sup> 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).<sup>7</sup> 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.

<sup>a</sup>Monash Institute of Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville, Victoria 3052, Australia. E-mail: bernard.flynn@monash.edu

<sup>b</sup>School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, QLD 4072, Australia

<sup>c</sup>Bio21 Institute, School of Chemistry, University of Melbourne, Parkville, VIC 3010, Australia

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substrate activation or suppression of Wagner–Meerwein rearrangements, the oxyallyl cation **6** can be exploited in nucleophilic trapping<sup>7,8</sup> 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** ( $M$  =  $MgBr$ );<sup>9</sup> alternatively, Rh-catalyzed carbозincation of **4** with  $ZnEt_2$  gave **9** ( $M$  =  $ZnEt$ ).<sup>10</sup> 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).<sup>11</sup> 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**

<b>4a</b> $R^1$ = Ph <b>4b</b> $R^1$ = <i>n</i> -pentyl <b>4c</b> $R^1$ = 3,5-(MeO) <sub>2</sub> Ph		<b>9</b> $M$ = $MgBr$ or $ZnEt$ <b>10a</b> $M$ = I, $R^1$ = Ph, $R^2$ = Me, 68% <b>10b</b> $M$ = I, $R^1$ = Ph, $R^2$ = Et, 79%			
4/10 → 5 <sup>a</sup>	5 → 7 <sup>c</sup> (dr) <sup>d</sup>	4/10 → 5 <sup>a</sup>	5 → 7 <sup>c</sup> (dr) <sup>d</sup>	4/10 → 5 <sup>a</sup>	5 → 7 <sup>c</sup> (dr) <sup>d</sup>
 <b>5a</b> 55% ( <b>A</b> )	 <b>7a</b> 67% (>20:1)	 <b>5c</b> 72% ( <b>B</b> )	 <b>7c</b> 75% (>20:1)	 <b>5g</b> 91% ( <b>B</b> )	 <b>7g</b> 93% (>20:1)
 <b>5a'</b> 10% ( <b>A</b> ) <sup>b</sup>	 <b>7a'</b> 73% (>20:1)	 <b>5d</b> 39% ( <b>B</b> )	 <b>7d</b> 42% <sup>e</sup> (2:1)	 <b>5h</b> 60% ( <b>B</b> )	 <b>7h</b> 50% (>20:1)
 <b>5b</b> 52% ( <b>A</b> )	 <b>7b</b> 86% (>20:1)	 <b>5e</b> 31% ( <b>B</b> )	 <b>7e</b> 45% (>20:1)	 <b>5i</b> 85% ( <b>B</b> )	 <b>7i</b> 76% (>20:1)
 <b>5b'</b> 10% ( <b>A</b> ) <sup>b</sup>	 <b>7b'</b> 69% (>20:1)	 <b>5f</b> 84% ( <b>B</b> )	decomposition	 <b>5j</b> 85% ( <b>B</b> ) PMP = <i>p</i> -methoxyphenyl	 <b>11</b>

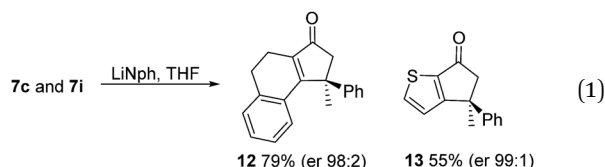
<sup>a</sup> Nazarov substrates **5** formed from **4** using Method A (**A**) or Method B (**B**), as indicated. <sup>b</sup> Isolated as a minor isomer using Method A. <sup>c</sup> Cyclized with  $BF_3 \cdot THF$  or  $TfOH$  in  $CH_2Cl_2$  at various temperatures (ranging from  $-78^\circ C$  to  $40^\circ C$ ) depending on acid and substrate; see text and ESI for details. <sup>d</sup> 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). <sup>e</sup> 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  $\text{TfOH}$  as catalyst in  $\text{CH}_2\text{Cl}_2$ , 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 ( $\text{R}^2$ ) in **5** was Me, Et or Ph ( $\text{BF}_3 \cdot \text{THF}$  or  $\text{TfOH}$ ). Use of  $\text{TfOH}$  as catalyst allowed the Nazarov cyclization to be conducted at temperatures as low as  $-78^\circ\text{C}$ , but generally the reactions were performed at  $0^\circ\text{C}$  to rt or in refluxing  $\text{CH}_2\text{Cl}_2$  ( $40^\circ\text{C}$ ) using either  $\text{TfOH}$  or  $\text{BF}_3 \cdot \text{THF}$ .<sup>‡</sup> 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  $\text{R}^1$ - $\beta$  stereochemistry (see below);<sup>7b</sup> we have therefore assigned this stereochemistry to each product in Table 1. Most likely, the cyclization of **5d**, which required heating to  $40^\circ\text{C}$  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).

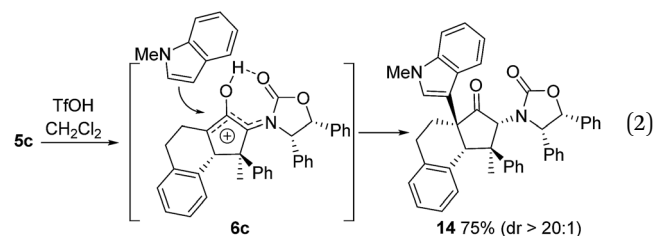
The presence of two aliphatic substituents on the tetrasubstituted alkene terminus, as in **5e**, led to slower cyclization, but the stereoinduction remained high (entry 7). Diaryl-substituted alkene **5f** underwent undesired side reactions to give multiple minor products along with return of starting 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  $\beta,\gamma$ -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 ( $\text{LiNph}$ ).<sup>7c</sup> 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 ( $\text{er} > 98 : 2$ ).

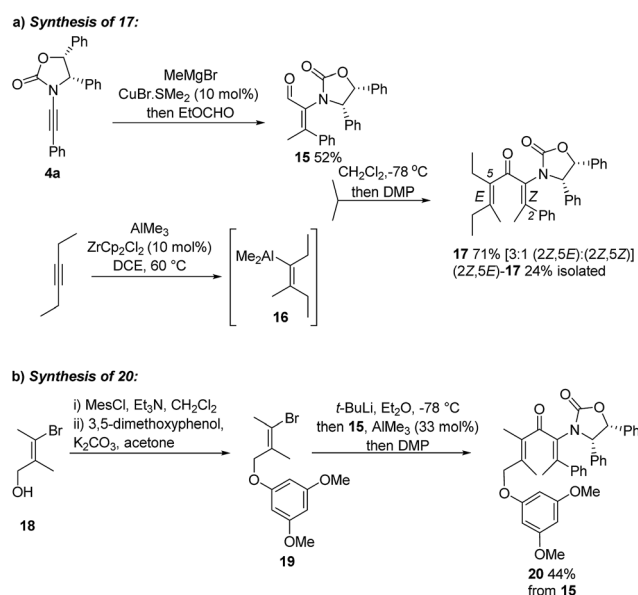


Also, as per our previous work, additional stereochemical complexity can be built up by nucleophilic trapping of the intermediate oxyallyl cations **6**.<sup>7c</sup> Accordingly, the highly substituted divinyl ketone **5c** was converted into the indole-trapped product **14** (75%) (eqn (2)). Notably,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

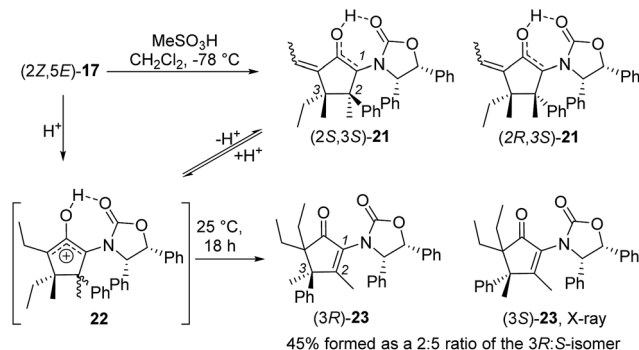


Having achieved stereoselective Nazarov cyclizations leading to products with adjacent 3° and 4°-stereocentres, we next addressed the formation of vicinal 4°-stereocentres. To prepare the fully substituted Nazarov substrate **17** we developed a convergent carbometalation approach starting from two alkynes: ynamide **4a** and 3-hexyne (Scheme 2a). Cu-catalyzed addition of  $\text{MeMgBr}$  to **4a**, followed by *in situ* formylation with ethylformate, afforded **15** (52%) stereoselectively. Carboalumination of 3-hexyne to give **16**,<sup>11</sup> 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.<sup>12§</sup> 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**.<sup>13</sup> Lithiation of **19**, followed by addition to a solution of **15** and  $\text{AlMe}_3$  (Lewis acid) and DMP oxidation of



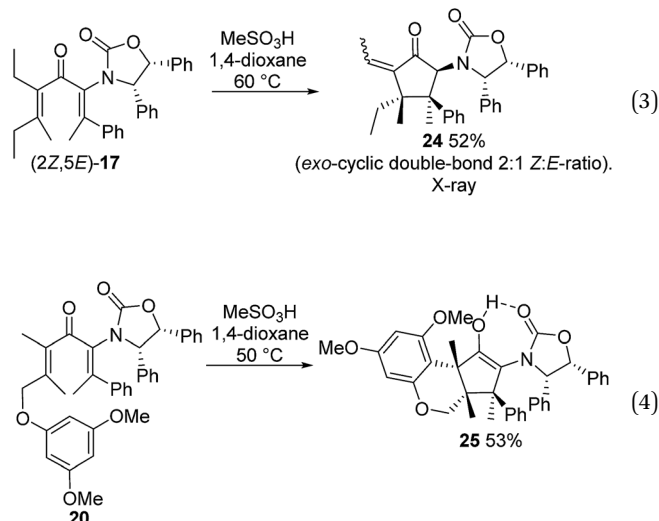
Scheme 2 Syntheses of fully substituted **Ox**-divinyl ketones **17** and **20**.



Scheme 3 Nazarov cyclization of 17 in CH<sub>2</sub>Cl<sub>2</sub>.

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

Nazarov cyclization of (2Z,5E)-17 with MeSO<sub>3</sub>H (CH<sub>2</sub>Cl<sub>2</sub>, −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).<sup>14</sup> 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 (2Z,5E)-17 to (2*E*,5E)-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 (2Z,5E)-17 to (2*E*,5E)-17, we found that treatment of (2Z,5E)-17 with MeSO<sub>3</sub>H 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<sub>2</sub>Cl<sub>2</sub> 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<sub>3</sub>H 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**.<sup>15</sup> Cyclization of **20** (eqn (4)) under these conditions was also successful, yielding the intramolecularly trapped product **25** as the only product discernable by <sup>1</sup>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.<sup>16</sup>



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

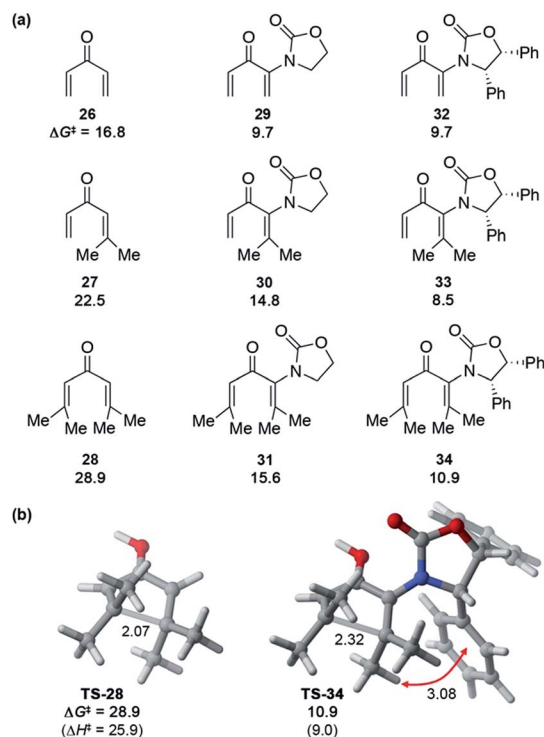


Fig. 1 (a) Activation barriers for H<sup>+</sup>-catalyzed Nazarov cyclizations of model divinyl ketones **26**–**34** and (b) transition states for cyclizations of **28** and **34**, calculated with M06-2X/6-311+G(d,p)//M06-2X/6-31G(d) in implicit (SMD) dichloromethane. Distances in Å,  $\Delta H^\ddagger$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





two 4°-centres are 16.8, 22.5, and 28.9 kcal mol<sup>-1</sup>, respectively. Each new 4°-stereocentre raises the barrier by 6 kcal mol<sup>-1</sup>.<sup>‡</sup> An achiral oxazolidinone devoid of Ph substituents (**OxH<sub>2</sub>**, see 29–31) lowers the cyclization barrier by 7–13 kcal mol<sup>-1</sup> ( $\Delta G^\ddagger = 9.7$ –15.6 kcal mol<sup>-1</sup>) 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<sup>-1</sup>. These very low barriers are consistent with the facile ring closures observed for 5, 17, and 20.

The transition states (TSs) for **OxH<sub>2</sub>**- 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<sub>2</sub>**). The two **Ox**-substituted TSs have  $\Delta G^\ddagger$  values about 6 kcal mol<sup>-1</sup> lower than those of the corresponding **OxH<sub>2</sub>** derivatives. The additional activation by **Ox** can be traced to a CH– $\pi$  interaction in the TS between the “inner” substituent on C2 (R<sup>2</sup>, 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<sup>-1</sup> (28 vs. 34). Indeed, computations predict that when the R<sup>1</sup> substituent is an aryl group, like in many of our substrates (5, 17, and 20) (with R<sup>2</sup> = alkyl) the barrier for cyclization is even lower still.<sup>‡</sup>

## Conclusions

To conclude, carbometallation 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– $\pi$  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

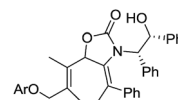
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## Notes and references

<sup>‡</sup> See the ESI.<sup>†</sup>

<sup>§</sup> The basis of the isomerization of the C5-alkenyl unit has not yet been fully discerned. Treatment of 16 with I<sub>2</sub> 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.

<sup>¶</sup> In the absence of AlMe<sub>3</sub> the reaction affords mostly an acyl migration product involving ring opening of the oxazolidinone:



- For a review on asymmetric quaternary stereocentre synthesis, see: K. W. Quasdorf and L. E. Overman, *Nature*, 2014, **516**, 181.
- For a review on sp<sup>3</sup>-rich scaffolds in drug discovery, see: A. Karawajczyk, F. Giordanetto, J. Benningshof, D. Hamza, T. Kalliokoski, K. Pouwer, R. Morgentin, A. Nelson, G. Müller, A. Piechot and D. Tzalis, *Drug Discovery Today*, 2015, **20**, 1310.
- For reviews on the Nazarov reaction, see: D. R. Wenz and J. Read de Alaniz, *Eur. J. Org. Chem.*, 2015, **2015**, 23; M. A. Tius, *Chem. Soc. Rev.*, 2014, **43**, 2979; F. G. West, O. Scadeng, Y.-K. Wu, R. J. Fradette and S. Joy in *Comprehensive Organic Synthesis II*, ed. P. Knochel, Elsevier, 2014, pp. 827–866; T. Vaidya, R. Eisenberg and A. J. Frontier, *ChemCatChem*, 2011, **3**, 1531; N. Shimada, C. Stewart and M. A. Tius, *Tetrahedron*, 2011, **67**, 5851; W. T. Spencer III, T. Vaidya and A. J. Frontier, *Eur. J. Org. Chem.*, 2013, **2013**, 3621.
- For a review on stereoselective synthesis of tetrasubstituted alkenes, see: P. Polak, H. Vanova, D. Dvorak and T. Tobrman, *Tetrahedron Lett.*, 2016, **57**, 3684.
- S. E. Denmark, M. A. Wallace and C. B. Walker, *J. Org. Chem.*, 1990, **55**, 5543.
- (a) A. Jolit, P. M. Walleiser, G. P. A. Yap and M. A. Tius, *Angew. Chem., Int. Ed.*, 2014, **53**, 6180; (b) A. Jolit, C. F. Dickinson, K. Kitamura, P. M. Walleiser, G. P. A. Yap and M. A. Tius, *Eur. J. Org. Chem.*, 2017, **2017**, 6067.
- For earlier studies employing less substituted **Ox**-divinyl ketones, see: (a) D. J. Kerr, M. Miletic, J. H. Chaplin, J. M. White and B. L. Flynn, *Org. Lett.*, 2012, **14**, 1732; (b) B. L. Flynn, N. Manchala and E. H. Krenske, *J. Am. Chem. Soc.*, 2013, **135**, 9156; (c) N. Manchala, H. Y. L. Law, D. J. Kerr, R. Volpe, R. J. Lepage, J. M. White, E. H. Krenske and B. L. Flynn, *J. Org. Chem.*, 2017, **82**, 6511.



- 8 (a) T. N. Grant, C. J. Rieder and F. G. West, *Chem. Commun.*, 2009, 5676; (b) Y. K. Wu and F. G. West, *Org. Lett.*, 2014, **16**, 2534; (c) Y. Kwon, R. McDonald and F. G. West, *Angew. Chem., Int. Ed.*, 2013, **52**, 8616; (d) Y.-K. Wu, C. R. Dunbar, R. McDonald, M. J. Ferguson and F. G. West, *J. Am. Chem. Soc.*, 2014, **136**, 14903.
- 9 Y. Minko, M. Pasco, H. Chechik and I. Marek, *Beilstein J. Org. Chem.*, 2013, **9**, 526.
- 10 B. Gourdet and H. W. Lam, *J. Am. Chem. Soc.*, 2009, **131**, 3802.
- 11 (a) A. M. Echavarren and J. K. Stille, *J. Am. Chem. Soc.*, 1988, **110**, 1557; (b) S. Ceccarelli, U. Piarulli and C. Gennari, *J. Org. Chem.*, 2000, **65**, 6254; (c) R. D. Mazzola, S. Giese, C. L. Benson and F. G. West, *J. Org. Chem.*, 2004, **69**, 220.
- 12 (a) E. Negishi, J. P. Maye and D. Choueiry, *Tetrahedron*, 1995, **51**, 4447; (b) E. Negishi, D. E. Van Horn and T. Yoshida, *J. Am. Chem. Soc.*, 1985, **107**, 6639.
- 13 D. P. Curran and S.-C. Kuo, *Tetrahedron*, 1987, **43**, 5653.
- 14 J. Huang, D. Leboeuf and A. J. Frontier, *J. Am. Chem. Soc.*, 2011, **133**, 6307.
- 15 Ethereal solvents are known to suppress Wagner-Meerwein rearrangement of the oxyallyl cation intermediate of Nazarov cyclization, see: ref. 14 and P. Chiu and S. Li, *Org. Lett.*, 2004, **6**, 613.
- 16 K. C. Nicolaou, J. Wang, Y. Tang and L. Botta, *J. Am. Chem. Soc.*, 2010, **132**, 11350.

