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

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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 oxallyl 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 sp3-rich scaffolds in drug discovery and natural products synthesis. 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. 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 and (ii) torquoselective ring closure. In a landmark study, Tius and co-workers reported chiral Brønsted acid-catalyzed Nazarov cyclizations of divinyl ketones 1 (Scheme 1a) leading to cyclopentenols 3 containing two new vicinal 4°-stereocentres (R1 = 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. Electrofugal release of Ph3HC+ from the intermediate ox allyl cation 2 further promoted the cyclization and suppressed competing Wagner–Meerwein rearrangements ([1,2]-sigmatropic shifts of R1 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). 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, giving exo-methylene cyclopentanones 7 under remarkably mild conditions, with excellent and predictable enantiocontrol. Furthermore, since no electrofugal release is required for

Scheme 1 Nazarlov substrate activation modes for the enantioselective synthesis of 4°-stereocentres.
substrate activation or suppression of Wagner–Meerwein rearrangements, the oxallyl cation 6 can be exploited in nucleophilic trapping\textsuperscript{a} to afford multistereocentre-centre-containing products 8 with up to three all-carbon 4\textsuperscript{th}-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\textsuperscript{2} = alkyl/aryl, Table 1). Firstly, Cu-catalyzed carbomagnesiation of Ox-ynamides 4 with Grignard reagents gave 9 (M = MgBr);\textsuperscript{a} alternatively, Rh-catalyzed carbozincation of 4 with ZnEt\textsubscript{2} gave 9 (M = ZnEt).\textsuperscript{a} Addition of iodine to organometallics 9 (M = MgBr or ZnEt) gave the key building block alkenyliodides 10a (68\%) and 10b (79\%). Carboxylative Stille coupling (Method A) of 10a and 10b with tributyl(cyclohexen-1-yl)stannane afforded divinyl ketones 5a/a\textsuperscript{0} and 5b/b\textsuperscript{0}, respectively, each as a 5 : 1 mixture of E/Z-isomers about the Ox-substituted double bond (entries 1–4).\textsuperscript{b} 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\textsuperscript{th}-stereocentre-containing cyclopentanoids 7

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method A (Carboxylative Stille):</th>
<th>Method B (1,2-addition, oxidation):</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/10</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>4</td>
<td>5\textsuperscript{a}</td>
<td>5\textsuperscript{a}</td>
</tr>
<tr>
<td>1</td>
<td>R\textsuperscript{2} = Ph</td>
<td>R\textsuperscript{2} = Ph</td>
</tr>
<tr>
<td>2</td>
<td>R\textsuperscript{2} = n-pentyl</td>
<td>R\textsuperscript{2} = n-pentyl</td>
</tr>
<tr>
<td>3</td>
<td>R\textsuperscript{2} = 3,5-(MeO\textsubscript{2})Ph</td>
<td>R\textsuperscript{2} = 3,5-(MeO\textsubscript{2})Ph</td>
</tr>
<tr>
<td>4</td>
<td>R\textsuperscript{2} = 3,5-(MeO\textsubscript{2})Ph</td>
<td>R\textsuperscript{2} = 3,5-(MeO\textsubscript{2})Ph</td>
</tr>
<tr>
<td>5</td>
<td>R\textsuperscript{2} = Ph</td>
<td>R\textsuperscript{2} = Ph</td>
</tr>
<tr>
<td>6</td>
<td>R\textsuperscript{2} = n-pentyl</td>
<td>R\textsuperscript{2} = n-pentyl</td>
</tr>
<tr>
<td>7</td>
<td>R\textsuperscript{2} = 3,5-(MeO\textsubscript{2})Ph</td>
<td>R\textsuperscript{2} = 3,5-(MeO\textsubscript{2})Ph</td>
</tr>
<tr>
<td>8</td>
<td>R\textsuperscript{2} = 3,5-(MeO\textsubscript{2})Ph</td>
<td>R\textsuperscript{2} = 3,5-(MeO\textsubscript{2})Ph</td>
</tr>
<tr>
<td>9</td>
<td>R\textsuperscript{2} = Ph</td>
<td>R\textsuperscript{2} = Ph</td>
</tr>
<tr>
<td>10</td>
<td>R\textsuperscript{2} = n-pentyl</td>
<td>R\textsuperscript{2} = n-pentyl</td>
</tr>
<tr>
<td>11</td>
<td>R\textsuperscript{2} = 3,5-(MeO\textsubscript{2})Ph</td>
<td>R\textsuperscript{2} = 3,5-(MeO\textsubscript{2})Ph</td>
</tr>
<tr>
<td>12</td>
<td>R\textsuperscript{2} = 3,5-(MeO\textsubscript{2})Ph</td>
<td>R\textsuperscript{2} = 3,5-(MeO\textsubscript{2})Ph</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Nazarov substrates 5 formed from 4 using Method A (A) or Method B (B), as indicated.\textsuperscript{b} Isolated as a minor isomer using Method A.\textsuperscript{c} Cyclized with BF\textsubscript{3}, THF or TIOH in CH\textsubscript{2}Cl\textsubscript{2} at various temperatures (ranging from −78°C to 40°C) depending on acid and substrate; see text and ESI for details.\textsuperscript{d} Diastereomeric ratio (dr) refers to stereochemistry at C1 relative to Ox (determined by \textsuperscript{1}H 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).\textsuperscript{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$_3$·THF or TfOH as catalyst in CH$_2$C$_2$, 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$_3$·THF or TfOH). Use of TfOH as catalyst allowed the Nazarov cyclization to be conducted at temperatures as low as $-78\,^\circ$C, but generally the reactions were performed at 0 °C to rt or in refluxing CH$_2$C$_2$ (40 °C) using either TfOH or BF$_3$·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$^2$-$\beta$ stereochemistry (see below);‡ 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$^2$ = iPr), 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$^2$ = iPr. 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 (R$^2$ = R$^3$ = H), the oxazolidinone can be removed by reductive-cleavage using lithium naphthalenide (LiNph).§ 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 $> 98 : 2$).

![Scheme 2](image_url)

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

Also, as per our previous work, additional stereochemical complexity can be built up by nucleophilic trapping of the intermediate oxallyl cations 6.¶ 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 $\textit{in situ}$ formulation with ethylformate, afforded 15 (52%) stereoselectively. Carboalumination of 3-hexyne to give 16,¶¶ 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.¶§ Separation of these isomers proved challenging; however, a pure sample of (Z,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.¶¶ Lithiation of 19, followed by addition to a solution of 15 and AlMe$_3$ (Lewis acid) and DMP oxidation of
Nazarov cyclization of (2Z,5E)-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 (3E)-23 and (3S)-23 in a 2:5 ratio (Scheme 3). The stereochemistry of these products was confirmed by X-ray crystallography of (3S)-23. We believe that the origin of this epimeric mixture is partial double-bond isomerization of (2Z,5E)-17 to (2E,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 (2E,5E)-17, we found that treatment of (2Z,5E)-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 24.³ Cyclication 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 Nicolau et al. is the only other example known to us.⁶

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‡) for Nazarov cyclizations of 26–28 leading to zero, one, or

![Scheme 3 Nazarov cyclization of 17 in CH₂Cl₂.](Image)

![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/6-31+G(d,p)//M06-2X/6-31G(d) in implicit (SMD) dichloromethane. Distances in Å, ΔH² and ΔG² in kcal mol⁻¹.](Image)
two 4'-centres are 16.8, 22.5, and 28.9 kcmol⁻¹, respectively. Each new 4'-stereocentre raises the barrier by 6 kcmol⁻¹.‡ An achiral oxazolidinone devoid of Ph substituents (OxH₂, see 29–31) lowers the cyclization barrier by 7–13 kcmol⁻¹ (ΔG‡ = 9.7–15.6 kcmol⁻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 kcmol⁻¹. These very low barriers are consistent with the facile ring closures observed for 5, 17, and 20.

The transition states (TSs) for Ox₂ and Ox-promoted cyclizations benefit from several stabilizing effects. Firstly, the nitrogen lone pair affords resonance stabilization of the incipient oxazolinyl 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‡ values about 6 kcmol⁻¹ lower than those of the corresponding Ox₂ 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 kcmol⁻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-nynamides 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 oxazolinyl 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 oxazolinyl 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 ESL‡
§ 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:


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.