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Oxazolidinone-Promoted, Torquoselective Nazarov Cyclizations

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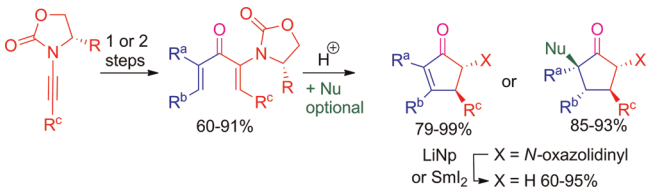
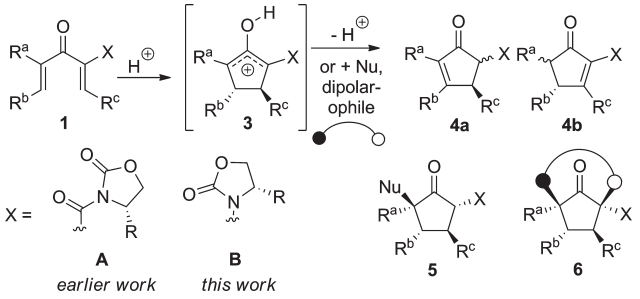
ABSTRACT



Oxazolidinones are powerful promoters of the Nazarov reaction, enabling the cyclization of conventionally resistant substrates to be achieved under mild conditions. They exert excellent regio- and torquoselective control in both the conventional Nazarov reaction giving cyclopentenones and in the "interrupted" Nazarov reaction, giving more highly substituted multistereocenter containing products.

Nazarov cyclization of divinyl and aryl vinyl ketones **1** offers access to a diverse array of cyclopentanoids **4**, including cyclopentenones, indenones, and other ring fused arrangements (Scheme 1).[1] This scope is further enhanced by the ability to trap the oxyallyl cation intermediate **3** with nucleophiles (Nu) and dipolarophiles, giving more elaborate cyclopentanoid products **5** and **6**.[2] The breadth of available cyclopentyl structures accessible by Nazarov cyclization and the capacity to use this reaction in multibond and multistereocenter forming reaction cascades provide significant impetus for the development of enantioselective (torquoselective) versions of this reaction.[3] While chiral acid catalysis is effective for activated substrates bearing strong electron donors, e.g., **1** (X = OR), most substrates require high acid concentrations and are not conducive to catalysis.[4] Accordingly, we have sought a chiral activating group X, which can promote the cyclization of even the most

Scheme 1. Nazarov Reaction



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(1) For reviews of the Nazarov reactions, see: (a) Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Chapter 5.6.3, pp 751. (b) Tius, M. *Eur. J. Org. Chem.* **2005**, 2193. (c) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (d) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. (e) Vaidya, T.; Eisenberg, R.; Frontier, A. J. *ChemCatChem* **2011**, *3*, 1531. (f) Shimada, N.; Stewart, C; Tius, M. A. *Tetrahedron* **2011**, *67*, 5851.

(2) For a recent review, see: (a) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676. For an alternative approach to trapping **3** based on Wagner–Meervein rearrangements, see: (b) Huang, J.; Lebuf, D.; Frontier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 6307. (c) Lebuf, D.; Huang, J.; Gandon, V.; Frontier, A. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 10981.

(3) For reviews on asymmetric Nazarov cyclizations, see refs 1e and 1f.

(4) (a) Liang, G.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, *5*, 4931. (b) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097. (c) Cao, P.; Deng, C.; Zhou, Y.-Y.; Sun, X.-L.; Zheng, J.-C.; Xie, Z.; Tang, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 4463.

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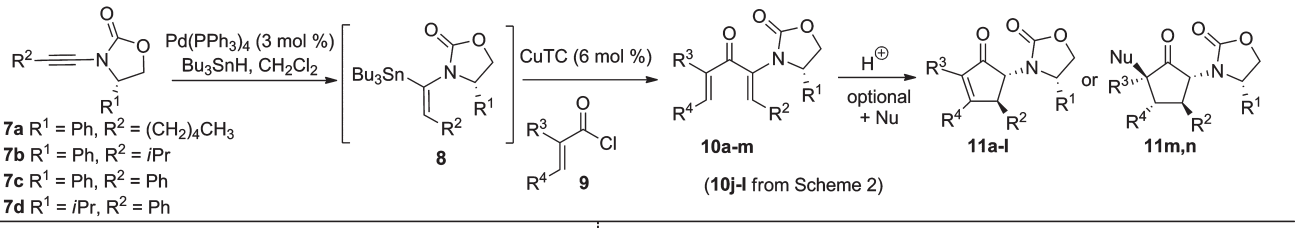
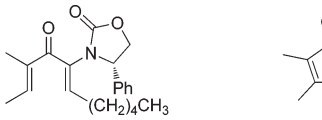
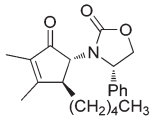
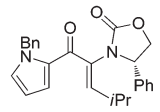
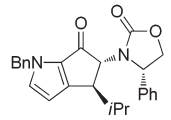
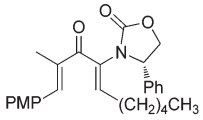
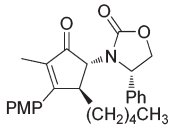
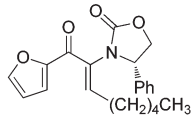
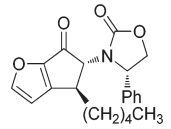
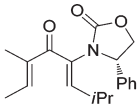
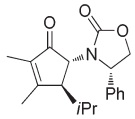
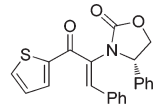
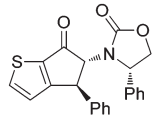
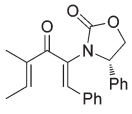
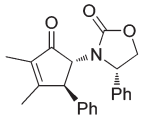
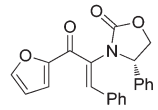
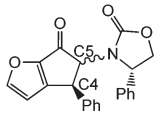
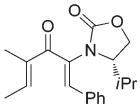
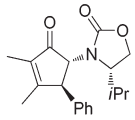
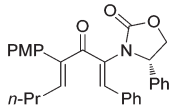
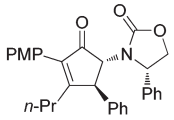
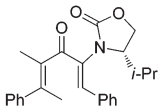
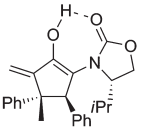
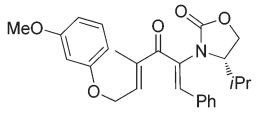
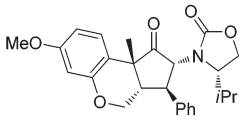
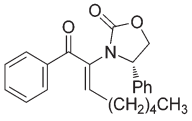
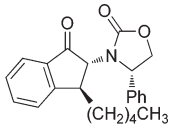
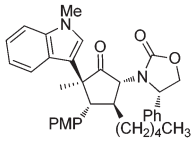
Table 1. Synthesis of Nazarov Precursors **10** and Their Cyclization to Cyclopentanoids **11**



entry	7 + 9 →10,[a] yield	11, yield (dr)[c,d]	entry	7 + 9 →10,[a] yield	11, yield (dr)[c,d]
1	 **10a**, 91%	 **11a**, 99% (> 20:1)	8	 **10h**, 79%	 **11h**, 94% (> 20:1)
2[b]	 **10b**, 60%	 **11b**, 99% (> 20:1)	9	 **10i**, 61%	 **11i**, 79% (> 20:1)[e]
3	 **10c**, 95%	 **11c**, 84% (> 20:1)	10	 **10j**, 95%	 **11j**, 97% (> 20:1)
4	 **10d**, 51%	 **11d**, 75% (>20:1)	11	 **10k**, 72%	 **11k**, 82% (>20:1)
5	 **10e**, 83%	 **11e**, 80% (> 20:1)	12[b]	 **10l**, 84%	 **11l**, 97% (> 20:1)
6	 **10f**, 43%	 **11f**, 99% (> 20:1)	13	 **10m** 79%	 **11m** 85% (> 20:1)
7	 **10g**, 82%	 **11g**, 76% (> 20:1)	14[b]	**10b** + *N*-methylindole	 **11n**, 93% (18:1)

[a] See the Supporting Information for details of these couplings. [b] PMP = 4-methoxyphenyl. [c] Yield is for major diastereomer (isolated), diastereomeric ratio (dr) determined using ^{1}H NMR of the crude reaction mixture; a dr > 20:1 indicates no other diastereomer was observable by ^{1}H NMR. [d] Reaction conditions: $MeSO_3H$ (2−10 equiv) in CH_2Cl_2, 1,2-dichloroethane, or toluene at rt or heating, depending on substrate; see the Supporting Information for details. [e] Cyclized using 2 equiv of TfOH in CH_2Cl_2 at 40 °C.

resistant substrates **1**, torquoselectively, and that can control the regiochemical placement of the double bond in **4a/b** and nucleophiles (Nu) in **5**.[5] In previous work, we explored the use of the Evans' oxazolidinones linked

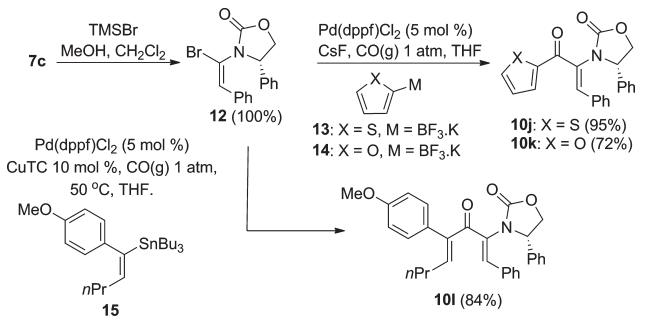
(5) For asymmetric Nazarov cyclization of allenyl vinyl ethers using chiral auxiliaries, see: (a) Berger, G. O.; Tius, M. A. *J. Org. Chem.* **2007**, *72*, 647. (b) See also ref 1f and references cited therein.

(6) (a) Kerr, D. J.; Metje, C.; Flynn, B. L. *Chem. Commun.* **2003**, 1380. (b) Kerr, D. J.; Flynn, B. L. *J. Org. Chem.* **2010**, *75*, 7073.

through a carbonyl group (X = **A**) in the torquoselective Nazarov cyclizations of **1** to **4a** (Scheme 1).[6] While this group had a significant influence of the regiochemical placement of the double bond, favoring **4a** over **4b**, only quite modest diastereomeric ratios (dr) could be achieved (dr = 3:1). In this work, we describe the preparation of Nazarov substrates **1** bearing a related auxiliary, wherein the carbonyl linker has been exluded (X = **B**). These auxiliaries promote the Nazarov cyclization of a broad range of substrates, giving excellent torquo- and regioselective access to **4a** and **5**.

Synthesis of Aryl Vinyl and Divinyl Ketones. The dearth of effective methods for the efficient stereoselective synthesis to divinyl and aryl vinyl ketones **1** is a limitation of the Nazarov reaction. In this work, we have developed ready access to a series of oxazolidinone substituted Nazarov substrates **10a**–**m** from ynamides **7** using several different palladium-mediated coupling techniques (Table 1 and Scheme 2).[7,8]

Scheme 2. Carbonylative Coupling Approaches to **10j**–**l**



A one-pot reductive coupling protocol was used in the preparation of the majority of Nazarov precursors **10** (Table 1).[6] This involves initial palladium-mediated *syn*-hydrostannylation of ynamides **7**→**8**, followed by addition of an acid chloride **9** and copper(I) thiophenecarboxylate (CuTC) cocatalyst to facilitate a Stille-type cross-coupling **8** + **9**→**10** (Table 1).[9] This protocol proved very effective in providing direct access to Nazarov substrates **10a**–**i**,**m** (43–95%), giving good yields in most cases (entries 1–9 and 13, Table 1). The modest yield obtained for **10d** (51%) was attributed to poor regioselectivity in the hydrostannylation of **7c**.[10] This arises as a result of the capacity of the group R^2 = Ph in **7c** to compete with the oxazolidinone in directing the tin to the α-carbon of the alkyne. This could be addressed by exchanging the phenyloxazolidinone for the isopropyloxazolidinone **7d**, which undergoes more regioselective *syn*-hydrostannylation **7d** → **8d**, giving a higher yield of **10e** (83%) in reductive coupling with **9a** (entry 5, Table 1).[10] Accordingly, the isopropyloxazolidinone was used in the preparation of all other Nazarov precursors **10** (R^2 = aryl) by reductive coupling.

Reaction of **7c** with HBr (from TMSBr and MeOH) in dichloromethane gave alkenyl bromide **12** (100%), which was used in carbonylative couplings to form **10j**–**l** (Scheme 2).[11] Initial attempts to couple **12** to boronic acids under standard carbonylative Suzuki–Miyaura reaction conditions failed.[12] In a systematic investigation of reaction conditions, we developed a carbonylative Suzuki–Miyaura coupling that could be performed at room temperature under just 1 atm of CO(g) using organotrifluoroboronate salts, CsF, and $Pd(dppf)Cl_2$ in THF.[13,14] Under these conditions, ketones **10j** (95%) and **10k** (72%) were obtained in good yield. A carbonylative Stille coupling of **12** to **15** gave **10l** (84%).[15,16]

Nazarov Cyclization. Nazarov cyclizations **10**→**11** were achieved using $MeSO_3H$ in nonpolar solvents (dichloromethane, 1,2-dichoroethane, or toluene) (Table 1).[17] While cyclization of divinyl ketones could be achieved using catalytic quantities of acid (< 10 mol %), this gave a *cis*/*trans*-mixture of isomers. Excess $MeSO_3H$ was employed to ensure complete epimerization of the oxazolidinone to give exclusively the *trans*-isomer. Much to our satisfaction, the cyclization of divinyl ketones **10a**–**f**,**l** produced only one double-bond regioisomer **11a**–**f**,**l**, favoring placement of the double bond distal to the auxiliary. X-ray crystal structure analysis of **11c** and **11d** (entries 3 and 4, Table 1) confirmed the β-stereochemistry of the R^2 substituent, and

(7) Ynamides **7a**–**d** were prepared from the corresponding bromoalkynes and the oxazolidinones using standard methods: Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170. See also the Supporting Information.

(8) For reviews on the synthetic application of ynamides, see: (a) De Korver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840.

(9) For previous reports on the hydrostannylation of ynamides, see: Buissonneaud, D.; Cintrat, J.-C. *Tetrahedron Lett.* **2006**, *47*, 3139.

(10) The ratio of regioisomers in the hydrostannylation of **7c** and **7d** is 3:1 and 6:1, respectively; see the Supporting Information.

(11) For an alternative hydrobromination of ynamides using $MgBr_2$ in CH_2Cl_2, see: (a) Rodriguez, D.; Martinez-Esperon, M. F.; Castedo, L.; Saa, C. *Synlett* **2007**, 1963. (b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H.; Frederick, M. O.; Shen, L.; Zificsak, C. A. *Org. Lett.* **2003**, *5*, 1547.

(12) See, for example: Couve-Bonnaire, S.; Carpentier, J.-F.; Mortreux, A.; Castanet, Y. *Tetrahedron* **2003**, *59*, 2793.

(13) For carbonylative Suzuki–Miyaura couplings using BF_3 salts under more forcing conditions, see: Wu, X.-F.; Neumann, H.; Beller, M. *Adv. Synth. Catal.* **2011**, *353*, 788 and references cited therein.

(14) A fuller account of the scope and limitations of this reaction will be reported elsewhere.

(15) Compound **15** was formed by *syn*-hydrostannylation of the corresponding arylalkyne; see: Xu, G.; Loftus, T. L.; Wargo, H.; Turpin, J. A.; Buckheit, R. W., Jr.; Cushman, M. *J. Org. Chem.* **2001**, *66*, 5958.

(16) Cu(I) salts facilitate carbonylative Stille reactions: Mazzola, R. D., Jr.; Giese, S.; Benson, C. L.; West, F. G. *J. Org. Chem.* **2010**, *69*, 220.

(17) Cyclization of the resistant substrate **11i** required 2 equiv of TfOH in CH_2Cl_2 at 40 °C.

(18) See the Supporting Information.

(19) Evidence for H-bonding in **TS-I** comes from ^{1}H NMR of **11f**, which is very similar in structure to **TS-I**. The enolic OH in **11f** appears as a sharp singlet at 8.55 ppm, indicative of intramolecular H-bonding.

(20) (a) Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 168. (b) Koltunov, K. Yu.; Walspurger, S.; Sommer, J. *Tetrahedron Lett.* **2005**, *46*, 8391. (b) Malona, J. A.; Colbourne, J. M.; Frontier, A. J. *Org. Lett.* **2006**, *8*, 5661. (c) Vaidya, T.; Manbeck, G. F.; Chen, S.; Frontier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 3300. (d) Malona, J. A.; Colbourne, J. M.; Frontier, A. J. *Org. Lett.* **2006**, *8*, 5661. (e) Vaidya, T.; Manbeck, G. F.; Chen, S.; Frontier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 3300.

we have tentatively assigned all other Nazarov products this stereochemistry.[18] This observed sense of induction can be rationalized by evoking the transition-state structure **TS-I**/**II** (Figure 1). A combination of intramolecular H-bonding and overlap between nitrogen electron-lone-pair and cationic π-system in **TS-I** direct R^1 toward R^2, sterically favoring **TS-I** over **TS-II**.[19]

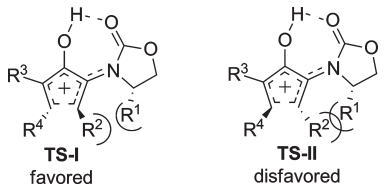
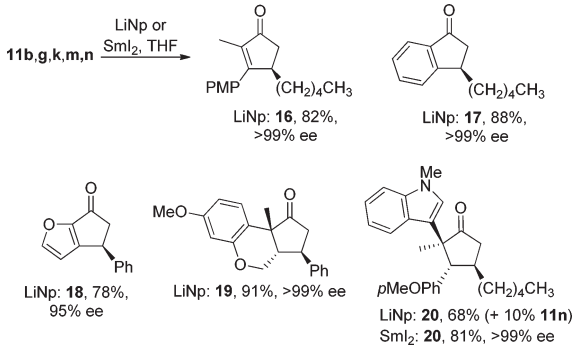


Figure 1. Proposed transition state of Nazarov cyclization.

This new, oxazolidinone-mediated Nazarov reaction accommodates a large variety of substrate classes, including sterically hindered and aryl fused substrates, which generally require high acid concentrations in order to cyclize and are unsuitable for chiral catalysis. Cyclization of the sterically hindered substrate **10f** to **11f** proceeded smoothly with good induction, enabling two stereocenters to be generated torquoselectively (99%, dr $>$20:1) (entry 6, Table 1). While the cyclization of aryl vinyl ketones **10g**–**k** required moderate heating (40–80 °C) in some cases, all products **11g**–**k** were obtained in good yield (76–97%) and in excellent diastereoselectivity (dr $>$20:1) (entries 7–11, Table 1). These are much milder conditions then are generally required to cyclize aryl vinyl ketones.[20] In fact, all previous attempts to cyclize furan-2-yl vinyl ketones have failed.[20a,b,c] Thus, the efficient formation of **11i** (79%) and **11k** (82%), the latter at room temperature, indicate that the oxazolidinone is a powerful promoter of Nazarov cyclization.[17] Both intra- and intermolecular trapping reactions were attempted and both proceed in good yield with excellent regio- and stereochemical control, **10m** → **11m** (85%, dr $>$20:1) and **10b** + *N*-methylindole → **11n** (93%, dr = 18:1). This is notable, as previous attempts to use related substrates **1** (R^a = Me) in similar trapping reactions have been frustrated by competitive proton elimination.[21]

Auxiliary Cleavage. The oxazolidinone auxiliary was cleaved from a sample set of Nazarov cyclization products **11** using either lithium naphthalenide (LiNp) or SmI_2, giving the products (**16**–**20**) in good yield and enantiomeric excess (Scheme 3).[22] Oxazolidinones can also be ring-cleaved to produce an NH_2 groups, but we have not yet evaluated this for products **11**.[23]

Scheme 3. Auxiliary Cleavage



In summary, the stereoselective *syn*-hydrostannylation and *syn*-hydrobromination of readily accessible ynamides **7** provides concise access to a range of aryl vinyl and divinyl ketones **10** through a variety of different palladium-mediated coupling techniques. In the course of these studies, a new carbonylative Suzuki–Miyaura coupling, which operates at room temperature and 1 atm of CO(g) (balloon), has been developed. Oxazolidinones have emerged as highly effective multifunctional auxiliaries in Nazarov cyclization, enabling access to a broad range of cyclopentanoid structures. In addition to affording high levels of torquoselective control in the Nazarov cyclization, the oxazolidinones also exerts excellent regiochemical control in the placement of the double-bond in **4** and of the nucleophile in **5**. As an activating group, the oxazolidinone auxiliary has enabled the cyclization of conventionally resistant substrates to be achieved, torquoselectively. Finally, this auxiliary can be conveniently cleaved using reductants, such as LiNp or SmI_2.

Supporting Information Available. X-ray crystal structure data for **11c** and **11d**, preparative procedures and spectroscopic data for all compounds, and chiral HPLC traces for **16**–**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(21) Rieder, R. J.; Fradette, C. J.; West, F. G. *Heterocycles* **2010**, *80*, 1413.

(22) The enantiomeric excesses are based on a combination of chiral HPLC and ^{1}H NMR of the oxazolidinone substituted substrates. Note that the enantiomeric excesses are not a reflection of the level of induction in cases **17**, **19**, and **20** since the major diastereomer was further purified by chromatography prior to auxiliary cleavage.

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