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Expedient Synthesis of Chiral Oxazolidinone Scaffolds via Rhodium-Catalyzed Asymmetric Ring-Opening with Sodium Cyanate

Gavin Chit Tsui, Nina M. Ninnemann, Akihito Hosotani, and Mark Lautens*

Davenport Research Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario, Canada M5S 3H6

mlautens@chem.utoronto.ca

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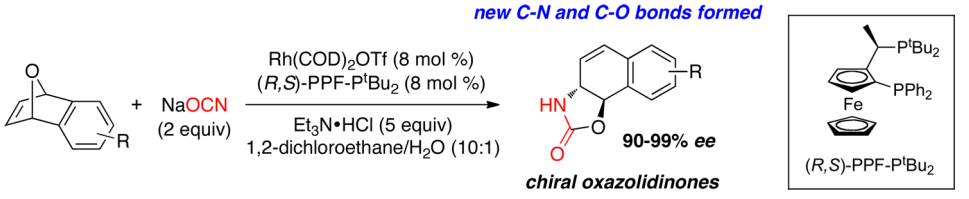
ABSTRACT



A method for synthesizing chiral oxazolidinone scaffolds from readily available oxabicyclic alkenes is described. The reaction utilizes a domino sequence of Rh(I)-catalyzed asymmetric ring-opening (ARO) with sodium cyanate as a novel nucleophile followed by intramolecular cyclization to generate oxazolidinone products in excellent enantioselectivities (*trans* stereochemistry).

The use of the cyanate anion in transition-metal-catalyzed processes has attracted increasing attention. To date, there have only been a few reports on Ni-,[1a] Cu-[1b] and Pd[1c]-catalyzed reactions with metal cyanates. For example, Buchwald recently reported an efficient cross-coupling of aryl chlorides and triflates with sodium cyanate to generate aryl isocyanate intermediates toward the synthesis of unsymmetrical ureas.[1c] Isocyanates are versatile intermediates in organic synthesis. They are precursors to carbamates and ureas by nucleophilic additions with alcohols and amines. They also participate in various cycloadditions to generate heterocycles.[2] The synthesis of isocyanates is usually difficult and involves the use of highly toxic and hazardous reagents.[3] However, transition-metal-catalyzed C−N bond formation with metal cyanates offers more efficient and safe synthetic routes to isocyanate products. To the best of our knowledge, there has been no example of using cyanates as reagents in rhodium-catalyzed reactions, particularly in asymmetric transformations.

We decided to explore the possibility of using metal cyanate as a nucleophile in Rh(I)-catalyzed asymmetric ring-opening (ARO) reactions. Over the past decade, Rh(I)-catalyzed ARO of oxa- and azabicyclic alkenes with heteroatom nucleophiles has stood out as a selective and reliable process to generate chiral functionalized hydronaphthalene cores and biologically active compounds.[4−6] A mechanistic working model has been established to account for the formation of the ring-opened products by an S_N2' nucleophilic displacement of the bridgehead

(1) (a) Tkatchenko, I.; Jaouhari, R.; Bonnet, M.; Dawkins, G.; Lecolier, S. France Patent FR2575467, 1986; U.S. Patent 4,749,806, 1988. (b) Kianmehr, E.; Baghersad, M. H. *Adv. Synth. Catal.* **2011**, *353*, 2599. (c) Vinogradova, E. V.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 11132.

(2) For selected recent examples of applications of isocyanates, see: (a) Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 11430. (b) Oberg, K. M.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 4785. (c) Komine, Y.; Tanaka, K. *Org. Lett.* **2010**, *12*, 1312.

(3) For reviews on the synthesis of isocyanates, see: (a) Ozaki, S. *Chem. Rev.* **1972**, *72*, 457. (b) Pal, P. *Synlett* **2012**, *23*, 2291.

(4) For reviews, see: (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (b) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (d) Rayabarapu, D. K.; Cheng, C.-H. *Acc. Chem. Res.* **2007**, *40*, 971. (e) *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005.

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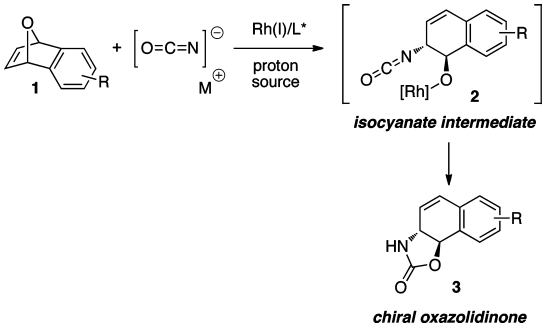
leaving group with inversion to give the 1,2-*trans* products as a single regio- and diastereomer.[7]

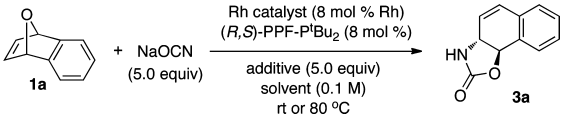
We envisioned that by using the cyanate anion as a nucleophile in Rh(I)-catalyzed ARO with oxabicyclic alkene **1**, chiral oxazolidinone product **3** would be obtained enantioselectively in a domino ARO/cyclization sequence via the formation of the isocyanate intermediate **2** (Scheme 1). Chiral oxazolidinones have been widely used as chiral auxiliaries in asymmetric transformations (Evans' chiral auxiliaries) and successfully employed in stereoselective syntheses of natural products and biologically active compounds.[8]

Scheme 1. Using Metal Cyanate in a Domino Rh(I)-catalyzed ARO/Cyclization Sequence to Synthesize Chiral Oxazolidinone



Some potential challenges included finding suitable catalytic conditions due to the requirement of a protic additive for catalyst turnover and solubility issues of the metal cyanate salt in organic solvents. The relative stereochemistry of the product that would be formed was also not easily predicted since the interaction between the cyanate anion and Rh in the ring-opening process was unknown.[9] We began our studies by reacting oxabenzonorbornadiene **1a** with excess sodium cyanate in THF or THF/H_2O at 80 °C using catalytic $[Rh(COD)Cl]_2$/(*R*,*S*)-PPF-P^{t}Bu$_2$[10] and triethylamine hydrochloride as a proton source (Table 1).[11]

Table 1. Optimization of Rh(I)-catalyzed ARO of Oxabenzonorbornadiene **1a** with Sodium Cyanate[a]



entry	Rh catalyst	solvent	additive	yield[b] (%)	ee[c] (%)
1[e]	$[Rh(COD)Cl]_2$	THF	$Et_3N\cdot HCl$	17[d]	
2[e]	$[Rh(COD)Cl]_2$	THF/H_2O	$Et_3N\cdot HCl$	42	40
3[e]	$[Rh(COD)Cl]_2$	dioxane/H_2O	$Et_3N\cdot HCl$	33	41
4[e]	$[Rh(COD)Cl]_2$	toluene/H_2O	$Et_3N\cdot HCl$	25	70
5	$[Rh(COD)Cl]_2$	MeCN/H_2O	$Et_3N\cdot HCl$	30	95
6[e]	$[Rh(COD)Cl]_2$	DCE[g]/H_2O	$Et_3N\cdot HCl$	28	93
7[e]	$[Rh(COD)I]_2$	DCE/H_2O	$Et_3N\cdot HCl$	40	95
8[e]	$[Rh(COD)OH]_2$	DCE/H_2O	$Et_3N\cdot HCl$	44	91
9[e]	$Rh(COD)_2OTf$	DCE/H_2O	$Et_3N\cdot HCl$	62	92
10[f]	$Rh(COD)_2OTf$	DCE/H_2O	$Et_3N\cdot HCl$	66	97
11[f,h]	$Rh(COD)_2OTf$	DCE/H_2O	$Et_3N\cdot HCl$	69	98
12[f]	$Rh(COD)_2OTf$	DCE	$Et_3N\cdot HCl$	57	99
13[f]	$Rh(COD)_2OTf$	DCE/H_2O	none	28	99
14[f]	$Rh(COD)_2OTf$	DCE/H_2O	TFE[i]	<5[d]	
15[f]	$Rh(COD)_2OTf$	DCE/H_2O	CSA[j]	38[d]	
16[f]	$Rh(COD)_2OTf$	DCE/H_2O	^{t}BuOH	14[d]	
17[f,k]	none	DCE/H_2O	$Et_3N\cdot HCl$	<5[d]	

[a] Unless specified otherwise, reactions were run with **1a** (0.2 mmol), Rh catalyst (8 mol % Rh), (*R*,*S*)-PPF-P^{t}Bu$_2$ (8 mol %), sodium cyanate (5.0 equiv), additive (5.0 equiv), in organic solvent/H_2O (10:1) (0.1 M), at 80 °C for 1−4 h or at rt for 17 h, under argon atmosphere. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Determined by ^{1}H NMR spectroscopy of the crude material. [e] Reaction was run at 80 °C. [f] Reaction was run at rt. [g] DCE = 1,2-dichloroethane. [h] Used 2.3 equiv of sodium cyanate. [i] TFE = 2,2,2-trifluoroethanol. [j] CSA = camphorsulfonic acid. [k] Reaction was run without the catalyst and ligand, only starting material was recovered.

A reaction in aqueous THF (10:1 ratio of THF:H_2O) gave the desired product **3a** in 42% isolated yield (>90% conversion) along with 26% of 1-naphthol from the decomposition of substrate **1a** (entry 2). Using potassium cyanate gave a similar yield (38%). Added water enhanced the yield (cf. entry 1). However, the enantioselectivity of the product was disappointingly low (40% *ee*). Subsequent screening of solvents showed a strong influence of the nature of the solvent on enantioselectivity in the following order: THF ≈ dioxane < toluene < MeCN ≈ 1,2-dichloroethane (DCE) (entries 3−6). Very high enantioselectivities (93−95% *ee*) could now be achieved when reactions were run in MeCN/H_2O or DCE/H_2O. The chemical yields were still poor (25−33%), but by varying the Rh(I) source we could significantly improve the yield while maintaining high *ee* using aqueous DCE as the solvent (entries 7−9).[12] In particular, the more reactive cationic $Rh(COD)_2OTf$

(5) Rh(I)-catalyzed ARO with alcohols and amines: (a) Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* **2000**, *122*, 5650. (b) Lautens, M.; Fagnou, K.; Taylor, M.; Rovis, T. *J. Organomet. Chem.* **2001**, *624*, 259. (c) Lautens, M.; Fagnou, K. *J. Am. Chem. Soc.* **2001**, *123*, 7170. (d) Lautens, M.; Fagnou, K.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 14884. Phenols: (e) Lautens, M.; Fagnou, K.; Taylor, M. *Org. Lett.* **2000**, *2*, 1677. Carboxylates: (f) Lautens, M.; Fagnou, K. *Tetrahedron* **2001**, *57*, 5067. Thiols: (g) Leong, P.; Lautens, M. *J. Org. Chem.* **2004**, *69*, 2194. Water: (h) Tsui, G. C.; Lautens, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 5400. Triethylamine trihydrofluoride: (i) Zhu, J.; Tsui, G. C.; Lautens, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 12353.

(6) Application of Rh(I)-catalyzed ARO in the synthesis of analgesic compounds: (a) Lautens, M.; Fagnou, K.; Zunic, V. *Org. Lett.* **2002**, *4*, 3465. Rotigotine and (*S*)-8-OH-DPAT: (b) Webster, R.; Boyer, A.; Fleming, M. J.; Lautens, M. *Org. Lett.* **2010**, *12*, 5418.

(7) Lautens, M.; Fagnou, K. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5455.

(8) For reviews, see: (a) Ager, D. J.; Prakash, J.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (b) Ager, D. J.; Prakash, J.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3.

(9) Presumably the *cis* product would arise if Rh(I) transmetallates with the metal cyanate followed by *syn*-insertion to the double bond of **1**. Buchwald's report proposed such a type of transmetalation with Pd(II), see ref 1c. The *trans* product would arise if the reaction follows the above-mentioned S_N2' pathway where Rh(I) does not transmetallate with metal cyanate, see ref 7.

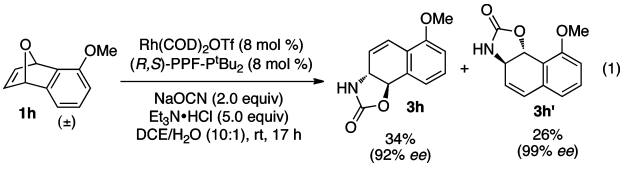
(10) (*R*,*S*)-PPF-P^{t}Bu$_2$ = (*R*)-1-[(*S*)-2-(Diphenylphosphino)-ferrocenyl]-ethyl-di-*tert*-butylphosphine, a Josiphos family ligand.

(11) We have previously found that $Et_3N\cdot HCl$ was a crucial proton source in Rh(I)-catalyzed ARO with sodium acetate salt, see reference 5f.

catalyst gave the highest yield (62%) and good enantioselectivity (92% *ee*).[13] A reaction run at room temperature gave improved yield and enantioselectivity (entry 10). In fact, only 2.3 equiv of sodium cyanate were needed to give complete conversion at room temperature to furnish the desired product in 69% yield and 98% *ee* (entry 11). Under these conditions, the formation of the 1-naphthol side product was also suppressed. Further reduction of the NaOCN equivalents (1.2 equiv) gave a lower yield (60%). Using anhydrous DCE caused a considerable decrease in yield (entry 12).[14] The effects of the proton source were also investigated. In the absence of $Et_3N\cdot HCl$ (i.e., water as the proton source), reaction was incomplete and gave a poor yield (entry 13). Using trifluoroethanol (TFE) did not afford **3a** but yielded 70% of the TFE-induced ring-opened product,[15] and using camphorsulfonic acid (CSA) and *tert*-butanol gave low yields (entries 15–16). It was found that 5.0 equiv of $Et_3N\cdot HCl$ was optimal. Reaction was not complete at 4 mol % Rh loading, and DPPF was not an effective ligand in this transformation. The control experiment showed no background ring-opening process (entry 17).[16]

The scope of oxabicyclic alkenes was studied under the optimized conditions (Table 2). The electron-rich substrates **1b**, **1c**, **1d** and **1f** gave moderate yields and excellent enantioselectivities (entries 1–3 and 5). The elctron-poor **1g** gave much lower yield and a diminished *ee* (entry 6). The more hindered substrate **1e** required a higher reaction temperature to reach complete conversion though maintaining satisfactory yield and *ee* (entry 4). The bromo-functional group was tolerated and did not prevent catalyst turnover considering the reactive cationic Rh could potentially insert into the Ar–Br bond. Unfortunately, less reactive oxabicyclic alkenes such as nonbenzofused, bridgehead-substituted substrates and azabicyclic alkenes did not afford the desired products.

By using regiodivergent resolution of the racemic unsymmetrical oxabicyclic alkene **1h**, the two regioisomeric products **3h** and **3h′** were obtained in a total yield of 60% with >90% *ee* in each product (eq 1).[17]



The absolute configuration of the oxazolidinone product was unambiguously confirmed by single-crystal X-ray analysis of compound **3b** (Figure 1). The structure clearly showed a *trans* stereochemistry at the ring junction.

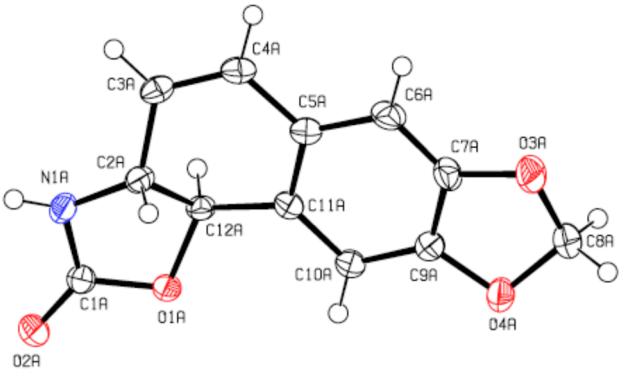
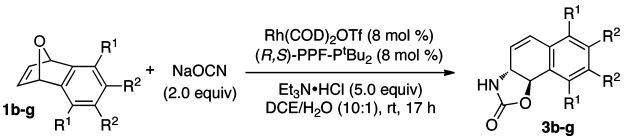


Figure 1. Molecular structure of **3b** showing 30% displacement ellipsoids.

The double bond of oxazolidinone **3a** can be reduced under mild hydrogenation conditions to afford **4**

Table 2. Scope of Oxabicyclic Alkenes **1b–g** in Rh(I)-catalyzed ARO with Sodium Cyanate[a]



entry	R^1	R^2	yield[b] (%)	*ee*[c] (%)	product
1	H	-OCH_2O-	52	98	**3b**
2	H	OMe	53	96	**3c**
3	H	Me	65	97	**3d**
4[d]	Me	Br	62	94	**3e**
5	OMe	H	73	96[f]	**3f**
6[e]	H	F	35	90	**3g**

[a] Unless specified otherwise, reactions were run with **1b–g** (0.2 mmol), $Rh(COD)_2OTf$ (8 mol %), (*R,S*)-PPF-P^tBu_2 (8 mol %), sodium cyanate (2.0 equiv), $Et_3N\cdot HCl$ (5.0 equiv), DCE/H_2O (10:1) (0.1 M), at rt for 17 h, under argon atmosphere. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Reaction was run at 80 °C, 1.5 h. [e] Reaction was run at 30 °C, 17 h. [f] The *ee* was measured from the *N*-Ts derivative of **3f**.

(12) We have previously demonstrated strong halide effects in Rh(I)-catalyzed ARO reactions, see refs 5c, 5d, 5f, and a review: Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26. The use of a Rh iodide catalyst (generated *in situ* using tetrabutylammonium iodide) often gave drastically improved yields and enantioselectivites. In this case, the effects were moderate (cf. Table 1, entries 6 and 7).

(13) For examples of the superior reactivity of cationic Rh catalyst over Rh halide catalysts in ARO reactions, see: (a) Webster, R.; Böing, C.; Lautens, M. *J. Am. Chem. Soc.* **2009**, *131*, 444. (b) Preetz, A.; Kohrt, C.; Drexler, H. -J.; Torrens, A.; Buschmann, H.; Lopez, M. G.; Heller, D. *Adv. Synth. Catal.* **2010**, *352*, 2073.

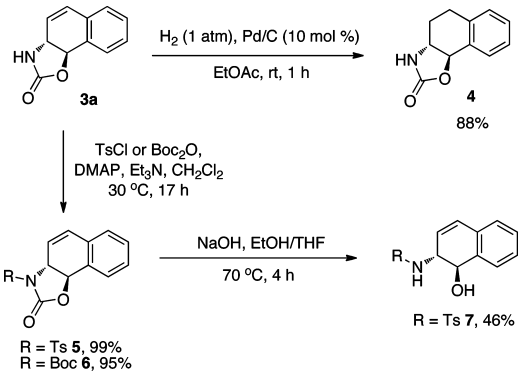
(14) We observed improved solubility of NaOCN and $Et_3N\cdot HCl$ when water was added to the reaction at room temperature. Dissolving NaOCN and $Et_3N\cdot HCl$ in water then adding to the reaction did not improve the yield. The reaction mixture was biphasic.

(15) TFE was a known nucleophile in the ARO reaction, see ref 5a.

(16) See Supporting Information for full details of the optimization including the screening of various chiral ligands. We have also found that polar solvents such as DMSO and DMF were ineffective. Other chlorinated solvents such as dichloromethane was effective (62% yield, 94% *ee*, rt, 17 h) but chloroform gave no conversion. Using cationic Rh catalyst in aqueous DCE gave a higher yield compared to MeCN. At a higher temperature (80 °C), reactions tend to give lower yields over prolonged reaction times. Increasing concentration (0.2 M) led to lower yields. Adding more water (DCE/H_2O = 1:1) resulted in a decreased yield. We have also used NaSCN and CuSCN as the nucleophile but observed no reaction.

(17) For applications of regiodivergent resolution in Rh(I)-catalyzed ARO reactions, see refs 6b, 13 and Nguyen, T. D.; Webster, R.; Lautens, M. *Org. Lett.* **2011**, *13*, 1370.

Scheme 2. Further Transformations of Product **3a**



containing the tetrahydronaphthalene core (Scheme 2). The nitrogen can be protected with Ts and Boc groups in high yields. Subsequent hydrolysis of the cyclic carbamate moiety of **5** offered the amino alcohol product **7**. We observed no deterioration of *ee* in these operations.

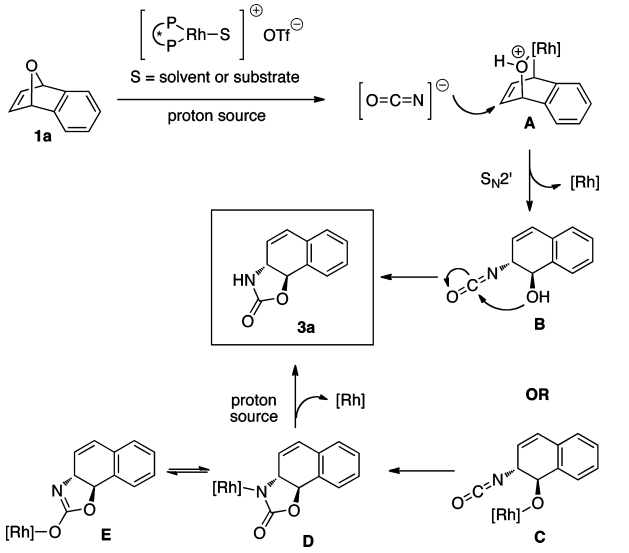
Based on the X-ray structure of the product and the previously established mechanistic model,[7] we proposed the following pathway for the formation of oxazolidinone **3a** (Scheme 3). The *trans* stereochemistry of the product implied an S_N2' pathway that is common with heteroatom nucleophile and ruled out the possibility of transmetalation between Rh and sodium cyanate. The key event is the enantioselective formation of the highly reactive cationic Rh complex **A**, facilitated by protonation from the proton source.[18] Nucleophilic attack by the cyanate anion in an S_N2' fashion leads to the *trans* isocyanate intermediate **B**, which is susceptible to cyclization furnishing **3a**. Alternatively, a Rh-alkoxide species **C** can be generated after the ring-opening. Insertion of Rh−O bond to the isocyanate moiety leads to *N*-bound and/or *O*-bound Rh complexes **D** and/or **E**.[19] Finally, protonolysis gives product **3a** and regenerates the catalyst.[20]

(18) Since the pK_a of the conjugate acid of cyanate is lower than the conjugate acid of Et_3N, sodium cyanate will remain deprotonated in the presence of $Et_3N\cdot HCl$. In the absence of $Et_3N\cdot HCl$, water can also act as the proton source albeit less effectively (cf. Table 1, entry 13). In the absence of both $Et_3N\cdot HCl$ and water, no reaction occurred (see Supporting Information).

(19) A similar mechanism has been proposed in Rh(I)-catalyzed addition reactions of isocyanates, see: (a) Miura, T.; Takahashi, Y.; Murakami, M. *Chem. Commun.* **2007**, 3577. (b) Hoshino, Y.; Shibata, Y.; Tanaka, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 9407.

(20) Attempts to trap the isocyanate intermediates **B** or **C** with an external nucleophile such as phenol, ^{t}BuOH or aniline failed to give the corresponding noncyclized carbamate or urea products. Only **3a** and the competing nucleophile-induced ARO products were observed, which showed that the intramolecular cyclization is a much faster process than intermolecular nucleophilic addition.

Scheme 3. Proposed Mechanism for Rh(I)-catalyzed ARO with Cyanate Anion and Intramolecular Cyclization



In conclusion, we have developed a highly enantioselective cationic Rh(I)-catalyzed ARO reaction using sodium cyanate as the nucleophile. Chiral oxazolidinone scaffolds with well-defined stereocenters can be synthesized in one step from readily available oxabicyclic alkenes via a domino ARO/cyclization sequence. We are currently investigating the potential of using other metal salts to generate novel chiral building blocks *via* ARO technology.

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Supporting Information Available. Experimental procedures, full characterization for all compounds and crystallographic data for **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.