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Chemoselectivity of the Ru-Catalyzed Cycloisomerization Reaction for the Synthesis of Dihydropyrans; Application to the Synthesis of L-Forosamine

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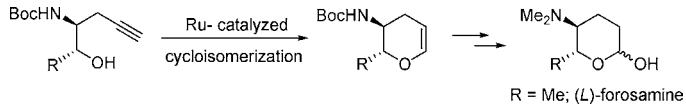
ABSTRACT



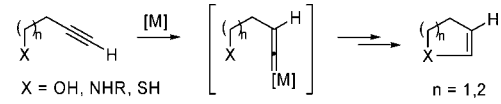
The chemoselectivity of a Ru-catalyzed cycloisomerization reaction has been established. The preference for *O*- capture of the vinylidene intermediate allows for the synthesis of 4-aminodihydropyrans that are valuable synthetic intermediates. The synthetic utility of these structures has been demonstrated in the synthesis of L-forosamine.

Vinylidenes generated from the transition metal- catalyzed isomerization of terminal acetylenes are useful synthetic intermediates that can be captured by a variety of functional groups. Intramolecular trapping of these reactive intermediates by *O*,[1] *N*,[2] and *S*[3] moieties provides rapid access to five- and six- membered heterocyclic rings (Scheme 1). Certain cycloisomerization catalyst systems are suitable for both *N*- and *O*- capture of the vinylidene, but this has been demonstrated in cases where only one nucleophile is present.[4]

An interesting case of selectivity arises when two potentially reactive moieties (such as an alcohol and a protected amine) are present in the same substrate, and each could react to afford a different 5- or 6- membered ring product. Chemoselectivity in such instances would open this methodology to the preparation of more diverse products. However, little attention has been paid to this subject. One example was reported where a tungsten-based system showed preference for (carbamate) *N*H- capture of the vinylidene (versus an alcohol *O*H) to form a 5-membered ring pyrroline,[1c] along with one example where a rhodium catalyst demonstrated *O*-selectivity of an alcohol (versus a carbamate protected *N*H) to form a 6-membered ring product.[1d] Interestingly, this question has not been addressed in the case of ruthenium vinylidenes.[5]

Our interest in such chemoselectivity arose from a proposed synthesis of 6-deoxy-4-aminodihydropyrans from

Scheme 1. Cycloisomerization to Form Heterocycles



(1) (a) McDonald, F. E.; Schultz, C. C. *J. Am. Chem. Soc.* **1994**, *116*, 9363. (b) McDonald, F. E.; Gleason, M. M. *J. Am. Chem. Soc.* **1996**, *118*, 6648. (c) McDonald, F. E.; Zhu, Y. H. *Tetrahedron* **1997**, *53*, 11061. (d) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2003**, *125*, 7482. (e) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 2528. For studies that were published during the preparation of our manuscript, see: (f) Verela-Fernández, A.; González-Rodríguez, C.; Varela, J. A.; Castedo, L.; Sáa, C. *Org. Lett.* **2009**, *11*, 5350.

(2) (a) McDonald, F. E.; Chatterjee, A. K. *Tetrahedron Lett.* **1997**, *44*, 7687. (b) Motamed, M.; Brunelle, E. M.; Singarem, S. W.; Sarpong, R. *Org. Lett.* **2007**, *9*, 2167. (c) Smith, C. R.; Brunelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169.

(3) McDonald, F. E.; Burova, S. A.; Huffman, L. G. *Synthesis* **2000**, 970.

(4) (a) Trost, B. M.; McClory, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 2074. (b) Although not presented in the same study, refs 1c and 2a overlap in demonstration of this compatibility.

(5) Intermolecular selectivity (for the carboxylic OH) has been reported in the case of N-carbamate protected amino acids: Doucet, H.; Martin-Vaca, B.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1995**, *60*, 7247.

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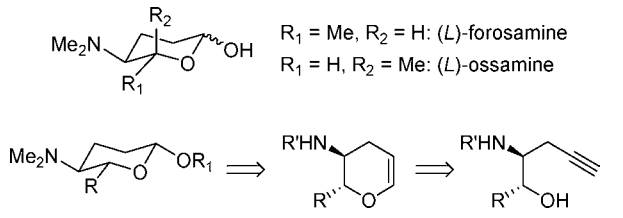
the cycloisomerization of amino- substituted bis-homopropargylic alcohols (Scheme 2). Such dihydropyran products

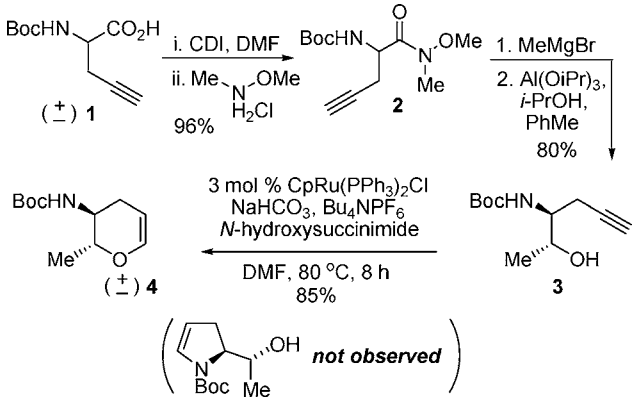
Scheme 2. Retrosynthetic Analysis



are useful reagents for the selective installation of the biologically important[6] forosamine and ossamine glycosides favoring the desired equatorial[7] (β in the case of L- sugars) isomer.[6a,8,9] Among the known cycloisomerization catalysts, we were initially attracted to Trost's ruthenium system[1e] due to its demonstrated efficiency of forming dihydropyrans. Although we required the selective cycloisomerization of the alcohol moiety, in principle either a dihydropyran or a 2-pyrroline product could form (via *O*- or *N*- cyclization, respectively). In this communication, we report the discovery of *O*- selectivity in this reaction as part of an efficient synthetic route to amino-substituted dihydropyrans, and demonstrate the utility of these products in a concise total synthesis of L-forosamine.

We began by securing a suitably functionalized amino alcohol, targeting the synthesis of a forosaminide dihydropyran as a means to validate the proposed strategy. *N*-Carbamate protection was selected for compatibility of the dihydropyran with glycosylation conditions.[1d,6,8] Hence, commercially available racemic *N*-Boc-propargyl glycine (**1**) was converted to the Weinreb amide **2** using CDI and (MeO)MeNH$_2$Cl in DMF in 96% yield (Scheme 3). MeMgBr

Scheme 3. Cycloisomerization of Amino Alcohol **3**

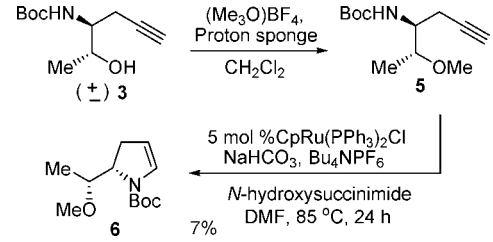


was then added to **2** to form a methyl ketone that was directly subjected to a diastereoselective reduction[10] to afford **3** as a 95:5 mixture of diastereomers. Following separation of the minor diastereomer, the desired alcohol was obtained in 80% over two steps. Aminoalcohol **3** was then exposed to the Ru- catalyzed cycloisomerization reaction conditions: CpRu(PPh$_3$)$_2$Cl, NaHCO$_3$, *N*-hydroxysuccinimide, and Bu$_4$NPF$_6$ in DMF at 80 °C for 8 h. To our delight, dihydropyran **4** was obtained in 85% isolated yield.[11] Furthermore, no products arising from *N*- cyclization were detected.

As a means of comparison, **3** was subjected to other catalytic systems reported for the formation of dihydropyrans. The use of McDonald's tungsten- catalyzed cycloisomerization conditions[1c,12] resulted in the formation of a product which was consistent with the *N*-Boc-pyrroline (see Scheme 3).[13] In this case, **4** was not observed as part of the reaction mixture. By contrast, the use of Trost's more expensive rhodium- based catalytic system[1d] led to the exclusive formation of **4**. Nonetheless, we deemed the ruthenium system optimal for the rest of our studies due to cost and to ease of operation. Furthermore, we were interested in expanding upon the identification of selectivity with ruthenium vinylidenes.

The observed selectivity was further examined by subjection of the methyl ether **5** to the reaction conditions. In the event, *N*-Boc-pyrroline **6** was obtained in 7% yield after 24 h at 85 °C (Scheme 4). The remainder of the crude reaction

Scheme 4. Cycloisomerization of Ether **5**



mixture consisted of unreacted **5**, as determined by ^{1}H NMR spectroscopy. On the basis of this result, we conclude that (carbamate) *N*H- capture of the ruthenium vinylidene to form

(6) (a) Graupner, P. R.; Martynow, J.; Anzeveno, P. B. *J. Org. Chem.* **2005**, *70*, 2154. (b) Zongbao, Z.; Hong, L. Liu, H-w. *J. Am. Chem. Soc.* **2005**, *127*, 7692. (c) He, X.; Liu, H.-w. *Annu. Rev. Biochem.* **2002**, *71*, 701. (d) Weymouth-Wilson, A. C. *Nat. Prod. Rep.* **1997**, *14*, 99.

(7) The known natural products incorporating these 2,3,6-trideoxy-4-dimethylamino glycosides (such as the spiramycins, spinosyns, ossamycin and dunaimycin D2S) bear β linkages to a macrocyclic core.

(8) Suhara, Y.; Sasaki, F.; Koyama, G.; Maeda, K.; Umezawa, H.; Ohno, M. *J. Am. Chem. Soc.* **1972**, *94*, 6501. Chloronitration of a dihydropyran demonstrated a high equatorial selectivity for the Cl atom. As the mechanism is considered to be stepwise (see Rasmussen, J. K.; Hassner, A. *J. Org. Chem.* **1974**, *39*, 2558) equatorial selectivity is expected in the coupling of an alcohol moiety.

(9) By contrast, imidate and glycosyl bromide derivatives of these sugars give predominantly a coupling products. For example, (a) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497. . (b) Paquette, L. A.; Collado, I.; Purdie, M. *J. Am. Chem. Soc.* **1998**, *120*, 2553.

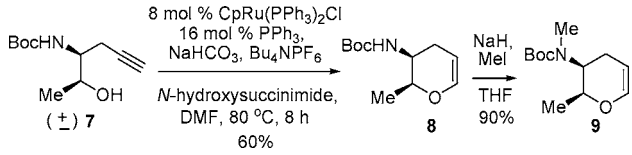
(10) Yin, J.; Huffman, M. A.; Conrad, K. M.; Armstrong, J. D., III. *J. Org. Chem.* **2006**, *71*, 840.

(11) The analytical yield was 95% based on HPLC assay of the crude reaction mixture. The lower isolated yield is associated with the volatility of **4**.

a 5-membered ring is possible, but inefficient compared to *O*H capture that forms a 6-membered ring.[14]

Cycloisomerization of the threo substrate **7**[15] was less efficient than that of **3**, requiring 10 mol % of $CpRu(PPh_3)_2Cl$ to achieve full conversion and furnishing dihydropyran **8** in only 30% yield under otherwise identical conditions. After extensive experimentation we discovered that the combination of 8 mol % $CpRu(PPh_3)_2Cl$ and 16 mol % PPh_3 improved the yield to 60% (Scheme 5). The pyrroline product

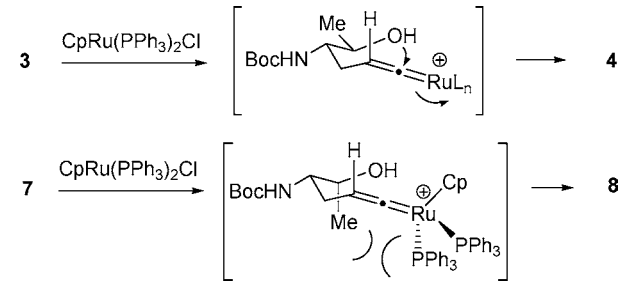
Scheme 5. Cycloisomerization of Amino Alcohol **7**



obtained from from *N*- capture of the vinylidene was not observed under either set of conditions. Methylation of **8** afforded **9**, which is a carbamate analogue (*N*-Boc vs *N*-Troc) of the dihydropyran used to install the ossaminide moiety in the synthesis of spinosyn G.[6]

The difference in reactivity profiles between **3** and **7** is not fully understood but may result from steric congestion in the vinylidene transition state (Scheme 6). The vinylidene

Scheme 6. Proposed Vinylidene Intermediates

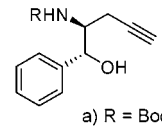
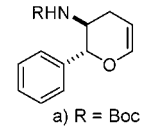
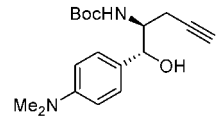
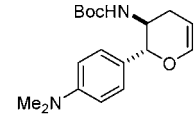
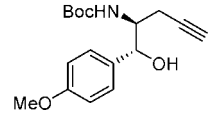
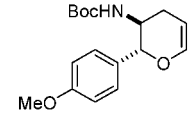
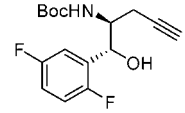
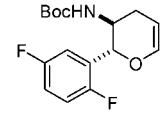
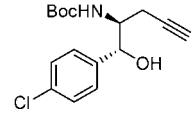
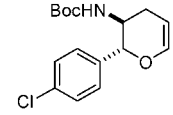


formed from **3** can adopt a pseudo chairlike formation with equatorial substituents. In this conformation, the *O*H moiety is proximate to the electrophilic carbon of the vinylidene.

In the case of **7**, the likely pseudo chairlike conformation (with an axial methyl group) may suffer from steric repulsion between the methyl group and the extended ligand sphere of the metal. The vinylidene species may avoid this destabilization by undergoing conformational adjustment that decreases the distance between the *O*H and the electrophilic center, which would account for the slower reaction rate.[16] The beneficial role of excess PPh_3 is believed to result from stabilization of the vinylidene species against competing nonproductive pathways,[17] which require ligand dissociation prior to engagement.[18]

Given the superior reactivity of **3**, the scope of this cycloisomerization process was broadened through various erythro substrates decorated with an aromatic moiety (Table 1). The reaction tolerated both electron- rich and electron-

Table 1. Cycloisomerization of Erythro Analogs[a]

entry	substrate	dihydropyran	yield (%)[b]
1			
	a) R = Boc	a) R = Boc	87%
	b) R = CBz	b) R = CBz	80%
	c) R = CO_2Me	c) R = CO_2Me	75%
2			86%
3			84%
4			89%
5			85%

[a] Conditions: 5 mol % $CpRu(PPh_3)_2Cl$, 0.5 equiv of $NaHCO_3$, 0.5 equiv of *N*-hydroxysuccinimide, 0.13 equiv of Bu_4NPF_6, DMF, 80 °C. [b] Isolated yield.

poor benzene rings, and in each case only one product diastereomer was observed. Products arising from *N*- capture of the vinylidene intermediate were not observed in any case. Entries 1a−c demonstrate the tolerance for various carbamate protecting groups, and further highlight the preference for *O*- cyclization. While there is no apparent reason why Boc

(12) Koo, B.-S.; McDonald, F. E. *Org. Lett.* **2007**, *9*, 1737.

(13) Based on ^{1}H NMR. This product was obtained in ~25% yield as part of a complex reaction mixture.

(14) The preferential formation of an N-Boc-pyrroline in related systems (i.e., tungesten vinylidenes in refs 1c, 13) suggests that factors other than product ring size contribute to the observed rate difference.

(15) Prepared as a racemate by reduction of Weinreb amide 2 followed by the addition of Me_2CuLi according to the procedure of Reetz Reetz, M. F.; Rolfing, K.; Griebenow, N. *Tetrahedron Lett.* **1994**, *35*, 1969. See Supporting Information.

(16) Alternatively the reaction may proceed through a higher energy boat-like transition state that minimizes steric repulsions.

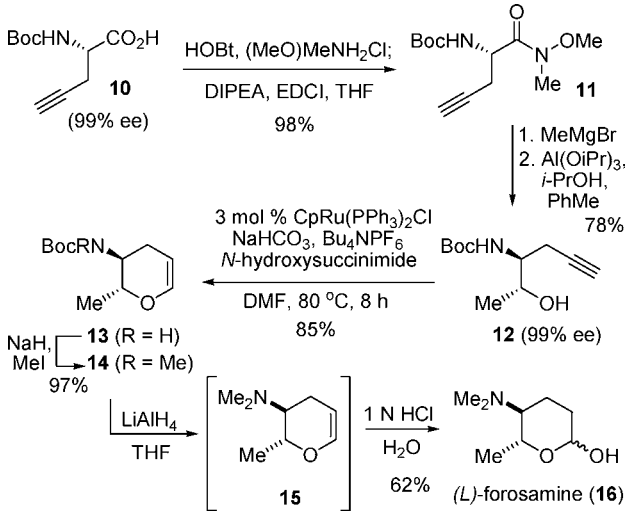
(17) Such as alkyne dimerization, which was observed without sufficient ligand in the related rhodium catalyzed cycloisomerization (ref 1d). For a recent example of dimerization using a closely related ruthenium catalyst, see: Daniels, M.; Kirss, R. U. *J. Organomet. Chem.* **2007**, *692*, 1716.

(18) The desired pathway, by contrast, does not require dissociation of a PPh_3 ligand prior to nucleophilic attack by oxygen. For relevant discussions see reference 1e and Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 5579.

protection gave slightly higher yields in entries 1a−c, these examples demonstrate that the steric bulk of the *N*-Boc group does not play a significant factor in the observed chemoselectivity since no other products were observed. This observation is consistent with the steric argument outlined in Scheme 6. All of these substrates were prepared following the route in Scheme 3; thus, further variation of the Grignard reagent should allow access to a large number of analogs.[19]

To demonstrate the utility of the dihydropyrans obtained from this cycloisomerization, we completed a short enantioselective total synthesis of L-forosamine (Scheme 7).

Scheme 7. Enantioselective Synthesis of L-Forosamine



Enantiopure (*S*)-*N*-Boc-propargyl glycine (**10**)[20] was treated with (MeO)MeNH$_2$Cl, *i*Pr$_2$NEt, EDCI, and HOBt to afford **11** in 95% yield without any detectable epimerization.[21] The sequence employed in Scheme 3 (namely, MeMgBr addition followed by the Al(O*i*Pr)$_3$- mediated Meerwein-Pondorf-Verley reduction) was then implemented to afford **12** in 78% yield after purification, as a single diastereomer in >99% e.e. Cycloisomerization provided **13**, which was then alkylated with MeI to give **14**. The *N*-Boc moiety was reduced with LiAlH$_4$ to afford a volatile intermediate **15** that was not isolated, but was identified by ^{1}H NMR spectroscopy. By incorporating an acidic aqueous quench after the LiAlH$_4$ reaction, **15** was obtained in 62% over two steps (from **13**). We believe that the mass balance was accounted for by losses due to the difficult isolation of **16** from an aqueous system.[22] Spectroscopic data from compound **16** matched the known data for L-forosamine.[23]

In conclusion, we have demonstrated the chemoselectivity for the Ru-catalyzed cyclization of carbamate protected 4-amino-bis-homopropargylic alcohols. The observed preference for *O*- capture of the vinylidene intermediate allows for the synthesis of amino- substituted dihydropyrans. The synthetic utility of these dihydropyrans has been demonstrated by the synthesis of L-forosamine.

Acknowledgment. We gratefully acknowledge Robert A. Reamer and Peter G. Dormer (Merck and Co., Inc.) for NMR assistance. Kate Vaynshteyn and Stephen M. Marcinko (Merck and Co., Inc.) are also acknowledged for assistance with high resolution mass spectroscopy.

Supporting Information Available: Experimental procedures, characterization data, and stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9026667

(19) For medicinal chemistry studies of forosamides, see: (a) Uesato, S.; Tokunaga, T.; Takeuchi, K. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1969. (b) US patent US600 1981, 1999. (c) US patent US541 2081. 1995. (d) Eur. Pat. Appl. EP457215, 1991.

(20) Purchased from Acros Organics.

(21) Determined by chiral HPLC analysis. See Supporting Information.

(22) Although the conversion of **14** to **16** appeared to be efficient, the extraction of **16** into organic solvents was difficult. Upon concentration of the aqueous phase in order to improve the extraction efficiency, glycal **16** was observed to partially dehydrate back to the volatile **15**.

(23) For a recent synthesis of forosamine, see: (a) Tietze, L. F.; Bönke, N.; Dietz, S. *Org. Lett.* **2009**, *11*, 2948. For a sample of previous syntheses, see: (b) Ono, M.; Saotome, C.; Akita, H. *Hetereocycles* **1999**, *51*, 1503. (c) Malik, A.; Afza, N.; Voelter, W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2103.