Advanced Synthesis & Catalysis

Accepted Article

Title: Iridium-Catalyzed Dynamic Kinetic Stereoselective Allylic Etherification of Achmatowicz Rearrangement Products

Authors: Zhongpeng Zhu, Haoyuan Wang, CHRISTOPHER SIMMONS, Po-Sen Tseng, Xiang Qiu, Yu Zhang, XIYAN DUAN, Jing-Kui Yang, and Weiping Tang

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201700950

Link to VoR: http://dx.doi.org/10.1002/adsc.201700950

10.1002/adsc.201700950

UPDATE

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Iridium-Catalyzed Dynamic Kinetic Stereoselective Allylic Etherification of Achmatowicz Rearrangement Products

Zhongpeng Zhu,#[a,b] Hao-Yuan Wang,#[b] Christopher Simmons,[c] Po-Sen Tseng,[b] Xiang Qiu,[b] Yu Zhang,[b] Xiyan Duan,[b] Jing-Kui Yang,[a] and Weiping Tang[b,c]*

[a] School of Chemistry and Chemical Engineering, University of Chinese Academy of Sciences, Beijing, P. R. China
[b] School of Pharmacy, University of Wisconsin-Madison, Madison, WI 53705, USA
Phone: (608) 890-1846, Fax: (608) 262-5345, Email: wtang@pharmacy.wisc.edu
[c] Department of Chemistry, University of Wisconsin-Madison, Madison, WI 53705, USA
# These two authors contributed equally.

Received: ((will be filled in by the editorial staff))

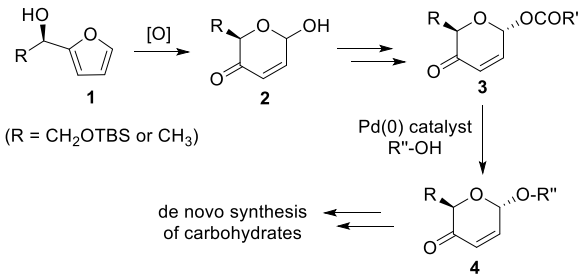
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

Abstract. We recently developed a novel Ir-catalyzed dynamic kinetic isomerization reaction for Achmatowicz rearrangement products. In this update, we show that products derived from the Achmatowicz rearrangement can also undergo Ir-catalyzed dynamic kinetic allylic etherification in the presence of an appropriate ligand and additive to afford useful intermediates for the synthesis of carbohydrates. The addition of the triphenyl phosphite ligand shuts down the isomerization pathway and promotes the allylic etherification pathway. The addition of diphenyl phosphate improved the diastereoselectivity for the addition reaction. Interestingly, opposite diastereoselectivity was observed for sterically demanding alcohol nucleophiles compared to less sterically demanding alcohol nucleophiles. The method was also applied to the synthesis of several 2,3-dideoxypyranosides.

Keywords: iridium; homogenous catalysis; carbohydrates; allylic substitution; etherification

The Achmatowicz rearrangement[1] converts feedstock furan derivatives (e.g. **1**, Scheme 1) to much more structurally complex dihydropyranones, such as **2**, efficiently, and it is one of the most useful reactions in carbohydrate synthesis.[2] Among the strategies for the *de novo* synthesis of carbohydrates, the most notable one is the Pd-catalyzed stereospecific allylic alkylation of esters or carbonates **3** derived from the acylation of **2**.[3] Numerous *de novo* syntheses of natural and unnatural sugars have been reported using this method.[4]

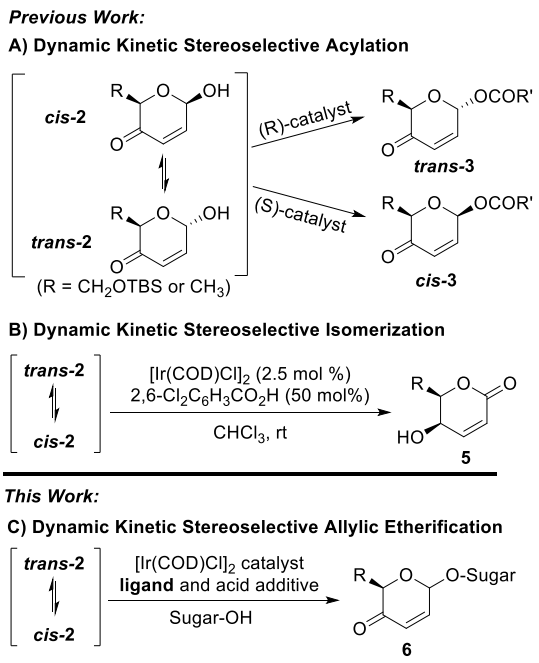
The desired stereoisomers of esters or carbonates **3** were often prepared by resolution or separation of two isomers by column chromatography. We[5] and others[6] recently used chiral organocatalysts to promote the dynamic kinetic stereoselective acylation of lactols derived from the Achmatowicz rearrangement through a stereoconvergent process (Scheme 2A).[7] We also found that a dynamic kinetic stereoselective isomerization of the same lactol could be realized in the presence of an iridium catalyst and acid additives (Scheme 2B).[8] This stereoselective isomerization was recently applied to the total synthesis of natural product angiopteralactone B.[9] In this update, we will describe a new type of dynamic kinetic stereoselective process - an Ir-catalyzed allylic etherification reaction, which is shown in Scheme 2C. The addition of an appropriate ligand is essential for suppressing the isomerization.



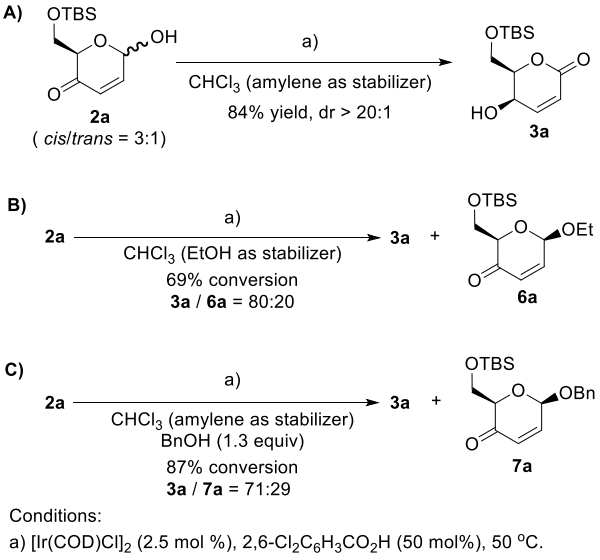
Scheme 1. Achmatowicz Rearrangement and Pd-catalyzed Allylic Alkylation

We have reported previously that isomerization product **3a** can be prepared from **2a** in high yield and high diastereoselectivity using chloroform as the solvent (Scheme 3A).[8] The commercially available chloroform is stabilized by trace amounts of amylene or ethanol. When we accidentally used chloroform that contained ethanol as stabilizer, we obtained a mixture of isomerization product **3a** and allylic etherification product **6a** (Scheme 3B). Since the amount of ethanol stabilizer varied among different batches of chloroform, we examined the reaction using benzyl alcohol as the nucleophile and chloroform that contained an amylene stabilizer (Scheme 3C). Slightly more allylic etherification product **7a** was obtained in this case. However, isomerization was still the dominant pathway under these conditions. In both cases, the *cis*-isomer was major product.

10.1002/adsc.201700950



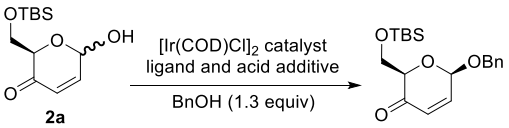
Scheme 2. Dynamic Kinetic Transformations of Lactols Derived from the Achmatowicz Rearrangement



Scheme 3. Initial Discovery of Dynamic Kinetic Allylic Etherification of Lactols Derived from the Achmatowicz Rearrangement

Substrate **2a** could be prepared from commercially available 2-acetyl furan as reported previously.[5, 8] The optimization for the dynamic kinetic stereoselective allylic etherification is shown in Table 1. Under conditions shown in Scheme 3C, **3a** was formed as the major product (**3a**/**7a** = 71:29) and **7a** was isolated in 25% yield (entry 1). Lowering the reaction temperature led to the formation of only trace amounts of **7a**, and no **3a** was observed (entry 2). The addition of phosphine ligand completely shut down the reaction (entries 3 and 4). Interestingly, phosphite ligands completely suppressed the isomerization reaction and led to the formation of **7a** as the major product (entries 5-11). Further optimization by varying the ligands and acids led to a 75% yield of **7a** with a 10:1 dr favoring the *cis*-isomer (entry 9). Compared with other acids, diphenyl phosphate provided the best results in terms of yield and dr. Other solvents, such as dichloroethane or methylene chloride, gave either a lower yield or dr (entries 10 and 11).

Table 1. Screening Conditions for Dynamic Kinetic Stereoselective Allylic Etherification



entry	conditions	yield[a]	dr[b]
1	2,6-Dichlorobenzoic acid, $CHCl_3$, 50 °C	25%	10:1
2	2,6-Dichlorobenzoic acid, $CHCl_3$, rt	trace	
3	PPh_3, 2,6-Dichlorobenzoic acid, $CHCl_3$, rt	NR	
4	$P(C_6F_5)_3$, 2,6-Dichlorobenzoic acid, $CHCl_3$, rt	NR	
5	2,2'-Biphenyl phenyl phosphite 2,6-Dichlorobenzoic acid, $CHCl_3$, rt	46%	3:1
6	$P(PhO)_3$, 2,6-Dichlorobenzoic acid, $CHCl_3$, rt	41%	20:1
7	$P(PhO)_3$, 3-Nitrobenzoic acid, $CHCl_3$, rt	trace	
8	$P(PhO)_3$, 4-(Trifluoromethyl)benzoic acid, $CHCl_3$, rt	55%	8:1
9	**$P(PhO)_3$, Diphenyl phosphate, $CHCl_3$, rt**	**75%**	**10:1**
10	$P(PhO)_3$, Diphenyl phosphate, DCE, rt	35%	10:1
11	$P(PhO)_3$, Diphenyl phosphate, CH_2Cl_2, rt	85%	1:1

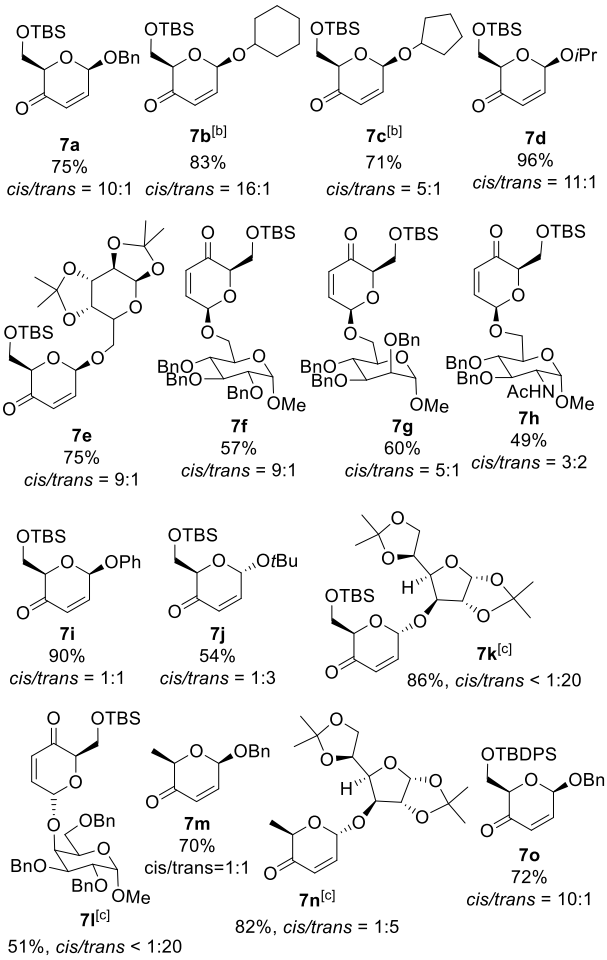
a) Isolated yield of **7a**. NR = no reaction. Chloroform containing amylene stabilizer was used. b) Diastereomeric ratios (*cis/trans*) were calculated based on ^{1}H NMR of the crude product.

The scope of the iridium-catalyzed dynamic kinetic allylic etherification was then explored (Scheme 4). Glycosyl acceptors including primary alcohols, secondary alcohols, and even tertiary alcohols, such as *t*-BuOH were tolerated. Sterically less hindered acceptors yielded the *cis*-isomers or β-anomers as the major isomers. The *cis/trans* or β/α ratio ranged from 5:1 to 16:1 (e.g. **7a - 7g**). Low selectivity was observed for products **7h** and **7i** derived from GlcNAc and phenol acceptors. Interestingly, sterically hindered acceptors such as *t*-BuOH afforded the *trans*-isomers or α-anomers as the major product. The *trans/cis* or α/β ratios ranged from 3:1 to more than 20:1 (e.g. **7j - 7l**). The *trans*- and *cis*-isomers of products **7a** and **7j** have been reported in the literature.[3a, 10] Comparison of coupling constants of these products with the literature values confirmed the structural assignment as shown in the supporting information. Surprisingly, when we tried to prepare product **7m**, the dr dropped to 1:1. A more sterically hindered acceptor yielded product **7n** with a higher dr, which is consistent with the result for product **7k**. We also examined a more hindered

10.1002/adsc.201700950

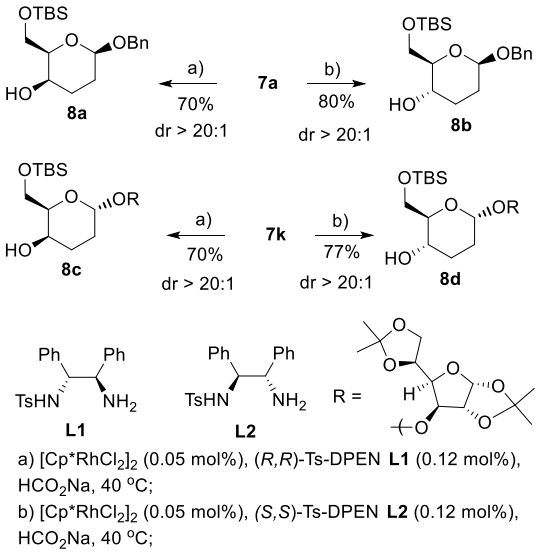
TBDPS protecting group shown in product **7o** and did not observe any difference compared to product **7a**.

Products in Scheme 4 can be further elaborated to natural and unnatural carbohydrates according to literature procedures.[4] We have previously reported a reagent-controlled reduction of product **4** (R = Me) for the synthesis of all possible stereoisomers of 2,3,6-trideoxypyranosides.[11] We then investigated the possibility of reducing enones **7a** and **7k** for the synthesis of 2,3-dideoxypyranosides based on the same protocol (Scheme 5). Products **8a** - **8d** were prepared highly efficiently, and the diastereomeric ratios were more than 20:1 for the two pairs of products.



a) conditions: $[Ir(COD)Cl]_2$ (2.5 mol %), $(PhO)_3P$ (10 mol%), $CHCl_3$, Diphenyl phosphate (50 mol%), rt. All yields were isolated yields. b) using $[Ir(COD)Cl]_2$ (5 mol %), $(PhO)_3P$ (20 mol%), 6h, others are the same as a). c) using $[Ir(COD)Cl]_2$ (5 mol %), $(PhO)_3P$ (20 mol%), 24h, others are the same as a).

Scheme 4. Scope of Ir-Catalyzed Dynamic Kinetic Allylic Etherification[a]

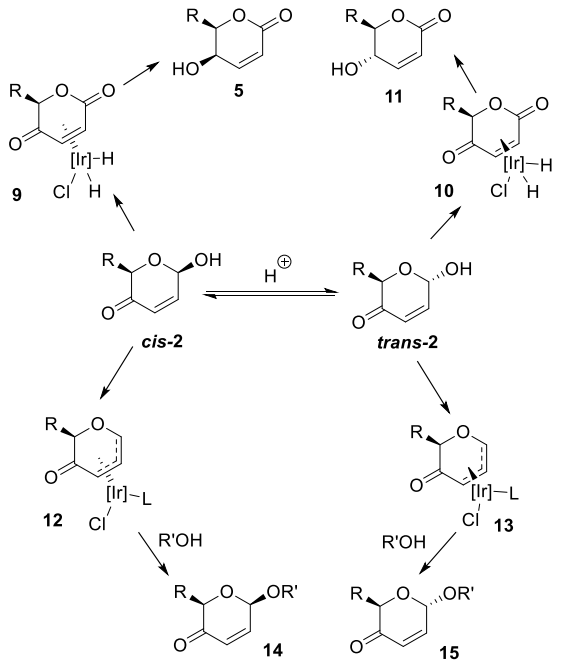


a) $[Cp^*RhCl_2]_2$ (0.05 mol%), (*R,R*)-Ts-DPEN **L1** (0.12 mol%), HCO_2Na, 40 °C;
b) $[Cp^*RhCl_2]_2$ (0.05 mol%), (*S,S*)-Ts-DPEN **L2** (0.12 mol%), HCO_2Na, 40 °C;

Scheme 5. Stereodivergent Synthesis of Deoxy Sugars *via* Reagent-controlled Reduction

Based on the mechanism previously proposed for Ir-catalyzed dynamic kinetic isomerization of **2** to **5**,[8] the mechanism for the Ir-catalyzed dynamic kinetic allylic etherification is proposed in Scheme 6. As proposed previously,[8] the Brønsted acid can promote the rate of equilibration between epimers *cis*-**2** and *trans*-**2**. The addition of a phosphite ligand, such as $(PhO)_3P$, clearly suppresses the formation of iridium hydride species **9**/**10** and favors the formation of iridium-π-allyl species **12**/**13**.

It is well known that either the ionization or nucleophilic addition step can be the rate- and stereo-determining step in transition metal-catalyzed allylic alkylation reactions.[12] The iridium catalyst tends to approach the olefin from the face opposite of the R-group to avoid steric interactions and form intermediate **12** for nucleophilic addition to afford product **14**. On the other hand, nucleophile R'OH prefers to attack iridium-π-allyl intermediate **13** to avoid steric interactions with the R-group. When sterically less hindered alcohol nucleophiles are employed, the ionization step is likely the rate- and stereo-determining step, and the formation of product **14** is the major pathway via intermediate **12**. When sterically more hindered alcohol nucleophiles are employed, the nucleophilic attack step is likely the rate- and stereo-determining step, and the formation of product **15** is the major pathway via intermediate **13**. Our experimental observations for substrate **2a** are indeed consistent with this mechanistic analysis.



Scheme 6. Proposed Mechanism for Ir-Catalyzed Dynamic Kinetic Allylic Etherification

In conclusion, we have developed a novel Ir-catalyzed dynamic kinetic stereoselective etherification reaction. Products derived from this reaction can be applied to the *de novo* synthesis of deoxysugars. High chemoselectivity and diastereoselectivity could be obtained by judicious selection of ligands and acid additives.

Experimental Section

General procedure for Ir-catalyzed dynamic kinetic allylic etherification

To a solution of $[Ir(COD)Cl]_2$ (1.7 mg, 2.5 mol %) in chloroform (2 mL, with amylene as stabilizer) at room temperature was added $P(PhO)_3$ (3 mg, 10 mol %) under argon atmosphere. After the reaction mixture was stirred for 5 min, **2a** (25.8 mg, 0.1mmol), BnOH (14 mg, 130 mol %), and diphenyl phosphate (12.5mg, 50 mol %) were added into the mixture. The reaction solution was then stirred at room temperature for 12h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel to afford the corresponding product.

Acknowledgements

We thank the University of Wisconsin-Madison for funding. Z.Z. thanks the *University of Chinese Academy of Sciences for financial support.*

References

[1] O. Achmatowicz, P. Bukowski, B. Szechner, Z. Zwierzch, A. Zamojski, *Tetrahedron* **1971**, *27*, 1973.

[2] a) O. Achmatowicz, P. Bukowski, *Can. J. Chem.* **1975**, *53*, 2524; b) O. Achmatowicz, B. Szechner, *Carbohydr. Res.* **1976**, *50*, 23; c) R. Bognar, P. Herczegh, *Carbohydr. Res.* **1976**, *52*, 11; d) N. L. Holder, *Chem. Rev.* **1982**, *82*, 287; e) M. Takeuchi, T. Taniguchi, K. Ogasawara, *Synthesis* **1999**, *2*, 341; f) A. K. Ghosh, M. Brindisi, *RSC Adv.* **2016**, *6*, 111564.

[3] a) R. S. Babu, G. A. O'Doherty, *J. Am. Chem. Soc.* **2003**, *125*, 12406; b) R. S. Babu, M. Zhou, G. A. O'Doherty, *J. Am. Chem. Soc.* **2004**, *126*, 3428; c) A. C. Comely, R. Eelkema, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2003**, *125*, 8714.

[4] For selected reviews, see: a) X. Li, J. Zhu, *J. Carbohydr. Chem.* **2012**, *31*, 284; b) M. J. McKay, H. M. Nguyen, *ACS Catal.* **2012**, *2*, 1563; c) M. F. Cuccarese, J. J. Li, G. A. O'Doherty, in *Modern Synthetic Methods in Carbohydrate Chemistry: From Monosaccharides to Complex Glycoconjugates* (Eds.: D. B. Werz, S. Vidal), 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2014**, pp. 1; d) A. Z. Aljahdali, P. Shi, Y. S. Zhong, G. A. O'Doherty, in *Advances in Carbohydrate Chemistry and Biochemistry, Vol 69, Vol. 69* (Ed.: D. Horton), **2013**, pp. 55; e) W. Song, S. Wang, W. Tang, *Chem. Asian J.* **2017**, *12*, 1027.

[5] H.-Y. Wang, K. Yang, D. Yin, C. Liu, D. A. Glazier, W. Tang, *Org. Lett.* **2015**, *17*, 5272.

[6] a) A. Ortiz, T. Benkovics, G. L. Beutner, Z. Shi, M. Bultman, J. Nye, C. Sfouggatakis, D. R. Kronenthal, *Angew. Chem. Int. Ed.*, **2015**, *54*, 7185; b) C. Zhao, F. Li, J. Wang, *Angew. Chem. Int. Ed.* **2016**, *55*, 1820.

[7] V. Bhat, E. R. Welin, X. L. Guo, B. M. Stoltz, *Chem Rev.* **2017**, *117*, 4528.

[8] H.-y. Wang, K. Yang, S. R. Bennett, S.-r. Guo, W. Tang, *Angew. Chem. Int. Ed.* **2015**, *54*, 8756.

[9] M. I. Thomson, G. S. Nichol, A. L. Lawrence, *Org. Lett.* **2017**, *19*, 2199.

[10] M. Zhou, G. A. O'Doherty, *J. Org. Chem.* **2007**, *72*, 2485.

[11] W. Song, Y. Zhao, J. C. Lynch, H. Kim, W. Tang, *Chem. Commun.* **2015**, *51*, 17475.

[12] B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921.

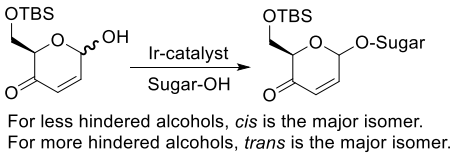
10.1002/adsc.201700950

UPDATE

Iridium-Catalyzed Dynamic Kinetic Stereoselective Allylic Etherification of Achmatowicz Rearrangement Products

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Zhongpeng Zhu, Hao-Yuan Wang, Christopher Simmons, Po-Sen Tseng, Xiang Qiu, Yu Zhang, Xiyan Duan, Jing-Kui Yang, and Weiping Tang*



For less hindered alcohols, *cis* is the major isomer.
For more hindered alcohols, *trans* is the major isomer.