

UC Irvine

UC Irvine Previously Published Works

Title

Catalyzed Claisen rearrangements of O-allyl kojates

Permalink

<https://escholarship.org/uc/item/2th8c6ct>

Journal

Tetrahedron Letters, 54(29)

ISSN

0040-4039

Authors

Pirrung, Michael C

Nalbandian, Jenifer N

Publication Date

2013-07-01

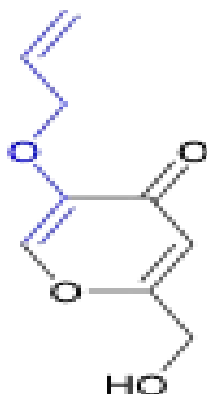
DOI

10.1016/j.tetlet.2013.05.002

Peer reviewed

Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.



Catalyzed Claisen rearrangements of *O*-allyl kojates

Michael C. Pirrung^{a*} and Jenifer N. Nalbandian^a

^aDepartment of Chemistry, University of California, Riverside, CA 92521 USA

ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

Keywords:

Claisen rearrangement;

microwave-assisted synthesis;

Lewis acid catalysis;

zinc triflate

ABSTRACT

Allylic ethers of kojic acid undergo Claisen rearrangement with catalysis by zinc triflate to give the corresponding *C*-allylated kojic acids in moderate to good yields.

© 2009 Elsevier Ltd. All rights reserved.

The Claisen rearrangement of allylic ethers of the pyrone natural product kojic acid[1] has provided access to interesting bioactive compounds. Such reactions are key to the preparation of early intermediates in syntheses of phorbol and related compounds,[2] and our lab has used the aromatic version of this process to access heterocyclic biaryls.[3] Typical conditions for these Claisen rearrangements are demanding, requiring long reaction times or temperatures exceeding 150 °C. The ability to catalyze them would expand the range of functionalities that could be tolerated. In some cases, these reactions create asymmetric centers, so the possibility of chiral catalysis is also tantalizing.

There is significant structural similarity between allylic ethers of kojic acid and the (allyloxy)acrylates that have proved to be one of the most successful reactants in catalyzed Claisen rearrangements, including asymmetric versions.[4] Further, kojates are locked into a conformation that permits chelation between the two oxygens (Chart 1); such a chelate is used as a model to explain asymmetric catalysis in reactions of (allyloxy)acrylates, which by contrast to kojates are conformationally flexible. We hypothesized that it should be possible to promote the Claisen rearrangement of *O*-allyl kojates using catalysts similar to those that succeed with (allyloxy)acrylates. The range of catalysts examined here is wide, including Lewis and Brønsted-Lowry acids as well as a hydrogen bonding catalyst. We find that zinc triflate is the most efficient of the catalysts examined for the Claisen rearrangement of a prenyl kojate, and that classical metal box-based asymmetric catalysts do not provide rate enhancement. The rate acceleration was determined and the scope of the reaction was examined.

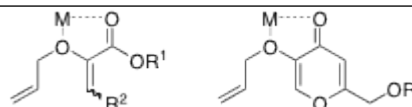
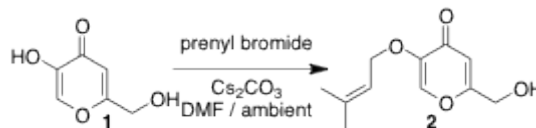


Chart 1. Putative reactant-catalyst complexes for catalyzed Claisen rearrangements of (allyloxy)acrylates and allyl kojates.

To evaluate catalysts for the allyl kojate Claisen rearrangement, starting with kojic acid (**1**) a prototype reactant **2** can be prepared in 84% yield (Scheme 1). Its purely thermal rearrangement could be conducted at 160 °C (neat, open flask, 1 h) to give the product **3** in 94% yield. Under conditions reported by Wender[2b] (78 °C, ethanol, 60 h), it is produced in 79% yield.



Scheme 1. Preparation of prenyl kojate **2**.

Catalysts for the rearrangement of **2** were screened at 10 mol % under a standard set of conditions: 0.028 M in toluene, microwave heating at 100 °C, 1 h. It is simple to determine reaction progress by ¹H NMR spectroscopy using the integration of the vinylic hydrogens in the crude reaction product. These reactions are clean and in all cases the product was isolated in pure form. All reactions were performed in duplicate, and the

* Corresponding author. fax: +1-951-827-2749; e-mail: michael.pirrung@ucr.edu

outcome of the study of a selection of catalysts is summarized in Table 1.

For comparison to catalyzed processes, the thermal reaction was conducted at 100 °C, where it gives very little product. The conventional Lewis acid Claisen catalyst[5] boron trifluoride etherate gives only a trace of **3**, and in fact is an inhibitor. Palladium(II) catalysis[4d] is likewise ineffective. While gold(I) catalysts have been used for the aryl allyl Claisen rearrangement[6] and the propargyl Claisen rearrangement,[7] neither gold catalyst that we examined is effective for this reaction. Metal triflates have also been investigated previously, Yb(III) and Cu(II) for the (allyloxy)acrylates[4a] and Yb(III) for aryl allyl ethers.[8] While complete conversion of **2** is seen with both, the isolated yield of **3** is low. With a milder Lewis acid, Ag(I), no catalysis is observed. Trost reported the use of lanthanide NMR shift reagents to promote an aromatic Claisen rearrangement,[9] and this method was used in natural product synthesis for the introduction of *C*-prenyl groups.[10] The europium complex was examined here, with the result that the rearrangement product could be obtained only in low yield.

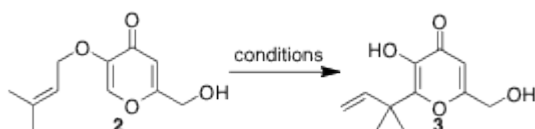


Table 1. Catalysis of the conversion of **2** to **3** under various conditions at 100 °C for 1 h.

Catalyst	Conversion (%)	Yield of 3 (%)
none	7	4
BF ₃ •OEt ₂	<1	<1
PdCl ₂ (ACN) ₂	<1	<1
Ph ₃ PAuCl	1	<1
Ph ₃ PAuOTf	8	5
AgOTf	9	5
Yb(OTf) ₃	100	15
Cu(OTf) ₂	100	12
Eu(fod) ₃	a	8
Ph ₂ GuanBARf	10	14
Zn(OTf) ₂	100	31
Zn(OTf) ₂ b	100	39
HOTf	1	<1

a Eu salts prevented NMR analysis of the crude reaction. b 10 mol % *t*Bu₂Py added as an acid scavenger.

Jacobsen has reported hydrogen-bonding guanidinium catalysts for Claisen rearrangements of (allyloxy)acrylates, including asymmetric versions.[11] In the case of **2**, Jacobsen's simple guanidinium salt (Chart 2) results in no catalysis.

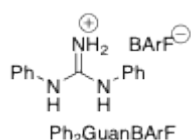


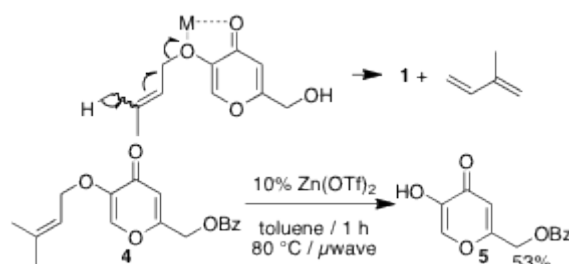
Chart 2. Organocatalyst investigated for the kojic acid Claisen rearrangement.

The best of these reactions are catalyzed with zinc triflate, which completely consumes **2** and gives **3** in 31% isolated yield. To establish that this reaction is not catalyzed by triflic acid produced by adventitious hydrolysis of the triflate, 2,6-di-*tert*-butylpyridine was added. A slight improvement in yield occurs, and the lack of product formation when triflic acid itself is used shows that protons do not catalyze this process.

Further experimental variations in the superior Zn(OTf)₂-catalyzed reaction were examined. A mild solvent effect is observed, as reaction in dichloroethane causes a drop in the product yield (23%), but a mixed solvent of 1:1 toluene:dichloroethane provides a slight yield enhancement (38%). Dropping the temperature to 80 °C increases the isolated yield of **3** to 48%, but reaction is incomplete; extending the reaction time to 2 h provides **3** in 54% yield.

Kinetic studies were performed on the zinc triflate-catalyzed rearrangement of **2** to determine the rate acceleration compared to the uncatalyzed process. Reactions were performed in triplicate at 80 °C and monitored by NMR for >3 half-lives. Percent conversion data were fitted to a standard first-order kinetic equation. Rate constants are 0.035 s⁻¹ and 0.001 s⁻¹, respectively, making the catalytic rate acceleration at 80 °C a reasonable 35-fold.

The low yields of purified product and the seeming inconsistency of conversions and yields with some catalysts in Table 2 was puzzling. One hypothesis was formed that an elimination reaction was occurring in competition with the rearrangement (Scheme 2). This would give isoprene and kojic acid, neither of which would be isolated after chromatography. To provide evidence for the elimination pathway, benzoate **4** was prepared and examined under the milder reaction conditions. The rearrangement product is obtained in only 20% yield, and **5** accounts for more than half of the converted **4**. While this process affects the production of **3**, other reactants can have different tendencies toward elimination and therefore give higher yields at full conversion (vide infra). The proportion of elimination also depends on conditions (vide supra).



Scheme 2. Support for a possible elimination pathway in reducing the yield of Claisen rearrangement products.

The combination of metal salts with ditopic or tritopic C₂-symmetric donor ligands (box, pybox, etc.) have been among the most successful catalysts for the asymmetric aliphatic Claisen rearrangement, and they show ligand-accelerated catalysis. We examined the combination of 10 mol % each of pybox ligand and zinc triflate for the **2** to **3** conversion (80 °C, 2 h). There is a negligible increase in product formation. Aiming for evidence that ligand-accelerated catalysis of this rearrangement is possible

(to encourage investigation of this catalyst with reactants that generate stereochemistry), the amount of pybox ligand was doubled to maximize the proportion of metal-ligand complex at equilibrium. However, catalysis decreases and only 18% of **3** is obtained. The addition of excess ligand evidently competes substrate away from the Lewis acid. Interestingly, it was reported (in a footnote)[12] that a $\text{Zn}(\text{OTf})_2 \cdot \text{pybox}$ complex catalyzes the asymmetric Claisen rearrangement of a substituted allyl kojate in a 74:26 *er*, which is at odds with the observations here.

The breadth of the zinc triflate-catalyzed Claisen rearrangement was examined with the reactants given in Table 2. Most (**6a-d**) were prepared from kojic acid by allylic bromide alkylations analogous to Scheme 1. The remainder (**6e** and **6f**) were prepared by semi-hydrogenation of the corresponding alkynes, themselves synthesized via alkylation with the mesylate made from 3-butyn-2-ol (20%), or Sonogashira coupling of iodobenzene with propargyl kojic acid (50%), respectively. Variations in reaction time and temperature were used to optimize yields of the rearrangement products **7**. *O*-Propargyl kojic acid (not shown) was also examined, but it gives no reaction under these conditions. Control experiments show that these reactants undergo no rearrangements at the reported temperatures in the absence of $\text{Zn}(\text{OTf})_2$. The more stringent conditions required for **a**, **d**, and **e** show that greater α' -substitution on the allyl fragment facilitates rearrangement. The superior yield observed with **6c**, which cannot eliminate, supports the idea that elimination is an important yield-limiting side reaction. Yet, other reactants also cannot eliminate, but their yields of rearrangement products are only moderate. The only reactant that creates stereochemistry, **6e**, gives a single geometric isomer.

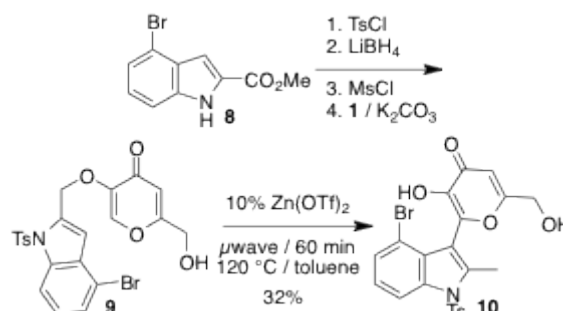
Table 2. Catalyzed Claisen rearrangement of *O*-allyl kojates.

	conditions	reactant	product	yield
a	120 °C / 200 min			49
b	80 °C / 120 min			46
c	80 °C / 120 min			84
d	120 °C / 200 min			33
e	120 °C / 200 min			59
f	120 °C / 60 min			41

Interestingly, we found that, among all reactants in Table 2, **6b** uniquely undergoes thermal Claisen rearrangement somewhat easily, upon evaporation of solvent with heating or storage neat at ambient temperature. Care had to be taken in handling it to ensure that the reported conversion was due only to the catalyzed reaction. Heating it at 45 °C for 3 d gives 8% of the rearrangement product. In contrast, **6c** is completely stable under these conditions. Since **6b** has the same alkene substitution as the reactant earlier reported to be subject to asymmetric catalysis, [12] it may have been a fortunate selection for that work.

Recognition that elimination was an important side reaction suggested that we could have missed valuable catalysts in our initial screen by using **2** as the reactant. We therefore reinvestigated some catalysts using **6c**, owing to its lack of elimination pathways and high yield. Since Yb(III) and Cu(II) triflates both provide full conversion of **2**, they were examined with **6c**. The isolated yields of **7c** are only 64% and 60%, respectively, confirming zinc triflate as the superior catalyst.

One purpose in examining catalysis of kojic acid Claisen rearrangements was to apply the method to the heterobiaryl synthesis we have developed based on this reaction.[3] Reactant **9** was assembled for this purpose (Scheme 3). Known indole **8** was *N*-protected and the ester was reduced to the alcohol (55%, 2 steps). It was converted to the chloride, which was used to alkylate kojic acid, giving **9** (54%, 2 steps). Its treatment under catalyzed rearrangement conditions gives 85% conversion, with an isolated yield of **10** of 32%. The uncatalyzed version of this reaction, performed neat, requires 7 h at 150 °C (96%).



Scheme 3. Catalyzed kojic acid Claisen rearrangement to prepare an (indolyl)kojic acid.

In summary, zinc triflate has been identified as a good catalyst for the Claisen rearrangement of *O*-allyl kojic acid ethers. Surprisingly, most catalysts that accelerate the rearrangement of the closely related (allyloxy)acrylates are not effective for these reactants. Zinc triflate provides a significant rate acceleration over purely thermal reactions with far milder conditions, but ligand-accelerated catalysis is not observed.

Acknowledgments

Fellowship support from NIH (GM086130, JNN) is appreciated. Mass spectra were obtained on an instrument purchased with NSF grant CHE0541848. We thank Andrew Carlson for preparing starting materials.

References and notes

- McLamore, W. M.; Gelblum, E.; Bavley, A. *J. Am. Chem. Soc.* **1956**, *78*, 2816-18.
- a) Wender, P. A.; McDonald, F. E. *J. Am. Chem. Soc.* **1990**, *112*, 4956-8. b) Wender, P. A.; Mascarenas, J. L. *J. Org. Chem.* **1991**, *56*, 6267-9. c) Wender, P. A.; Buschmann, N.; Cardin, N.B.;

- Jones, L.R.; Kan, C.; Kee, J.M.; Kowalski, J.A.; Longcore, K.E. *Nat. Chem.* **2011**, *3*, 615-9.
- Xiong, X.; Pirrung, M.C. *Org. Lett.* **2008**, *10*, 1151.
 - a) Hiersemann, M.; Abraham, L. *Org. Lett.* **2001**, *3*, 49-52. b) Abraham, L.; Czerwonka, R.; Hiersemann, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 4700-3. c) Abraham, L.; Körner, M.; Hiersemann, M. *Tetrahedron Lett.* **2004**, *45*, 3647-3650. d) Hiersemann, M. *Synlett* **1999**, 1823.
 - a) Cairns, N.; Harwood, L. M.; Astles, D. P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3101-3107. b) Cairns, N.; Harwood, L. M.; Astles, D. P.; Orr, A. *J. Chem. Soc., Chem. Commun.* **1986**, 182-183.
 - Reich, N. W.; Yang, C.-G.; Shi, Z.; He, C. *Synlett* **2006**, 1278.
 - Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978-9.
 - Sharma, G. V. M.; Ilangovan, A.; Sreenivas, P.; Mahalingam, A. K. *Synlett* **2000**, 615.
 - Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815.
 - a) Gester, S.; Metz, P.; Zieran, O.; Vollmer, G. *Tetrahedron* **2001**, *57*, 1015. b) Tischer, S.; Metz, P. *Adv. Synth. Catal.* **2007**, *349*, 147-151. c) Poerwono, H.; Sasaki, S.; Hattori, Y.; Higashiyama, K. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2086-2089.
 - Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 9228-9229.
 - Wender, P. A.; D'Angelo, N.; Elitzin, V. I.; Ernst, M.; Jackson-Ugueto, E. E.; Kowalski, J. A.; McKendry, S.; Rehfeuter, M.; Sun, R.; Voigtlaender, D. *Org. Lett.* **2007**, *9*, 1829-1832.