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Highly Diastereoselective Synthesis of *vicinal* Quaternary and Tertiary Stereocenters Using the Iodo-aldol Cyclization

Frederic Douelle, Amy S. Capes, and Michael F. Greaney*

University of Edinburgh, School of Chemistry, Joseph Black Building, King's Buildings, West Mains Rd., Edinburgh EH9 3JJ, U.K.

michael.greaney@ed.ac.uk

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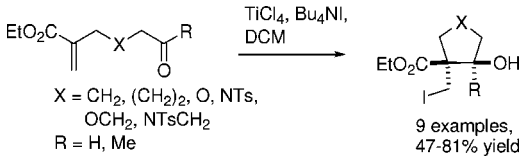
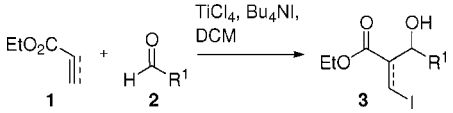
ABSTRACT



The intramolecular iodo-aldol cyclization of α-substituted enoate aldehydes and ketones is described. Using prochiral starting materials, the reaction produces hetero- and carbocycles containing quaternary centers adjacent to secondary or tertiary centers. The reactions occur in good yields and are highly selective for the *trans*-products, having the hydroxyl and iodomethyl groups on opposite faces of the ring system.

The iodo-aldol reaction,[1,2] part of the Morita−Baylis−Hillman (MBH) family of tandem conjugate addition/aldol processes,[3] has become an increasingly well-developed strategy for C−C bond formation in recent years.[4−8] A generalized reaction is shown in Scheme 1, whereby a Michael acceptor such as an enoate or ynoate, **1**, undergoes conjugate addition with iodide followed by intermolecular aldol reaction with an aldehyde, **2**.

Scheme 1. Intermolecular Iodo-aldol Reaction



When sp^2 Michael acceptors are employed, the reagent combination $TiCl_4/Bu_4NI$ is particularly effective at producing the *β*-iodo carbonyl products, **3**, rather than the eliminated MBH products.[4b] As with the reductive aldol reaction, the nucleophile is thus incorporated into the product and a chiral center is installed adjacent to the carbonyl group. The iodo-aldol features several strengths inherent to all MBH-type reactions: it provides excellent atom economy and complex-

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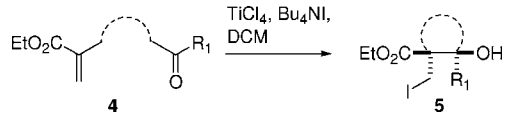
ity generation, generating 1, 2, or 3 chiral centers from often simple starting materials in a single step, it enables enolate chemistry without the requirement of a strong base, and it is amenable to (asymmetric) catalysis.

A current limitation of the iodo-aldol reaction and tandem aldol processes in general is their relative lack of application to the construction of quaternary centers.[9] Given the value and challenge associated with quaternary center generation in complex molecule synthesis, we were interested in examining the scope of the iodo-aldol process for the synthesis of hindered γ-iodoalcohols. The vast majority of tandem aldol procedures in the literature use mono- or 1,2-substituted Michael acceptors as substrates, whereas quaternary center construction will require an α-substituted Michael acceptor such as **4** (Scheme 2).

Scheme 2. Intramolecular Iodo-aldol Reaction for Quaternary Center Construction

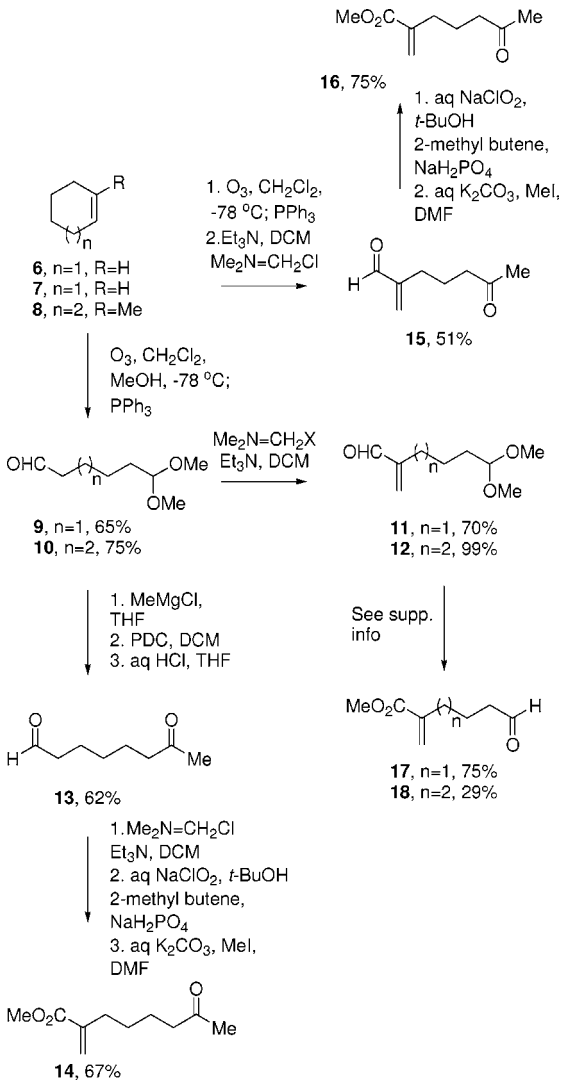


4 **5**

We elected to study the intramolecular iodo-aldol reaction as our method for quaternary center generation, as this potentially powerful variant has been the subject of only one previous report.[4e] Enoate aldehydes **17** and **18** were chosen as carbocylization substrates and synthesized as shown in Scheme 3. Ozonolysis of cyclohexene or cycloheptene in methanol afforded the acetal-aldehydes **9** and **10**. Methylenation via Böhme or Eschenomser's salt using Et_3N as base installed the enal functionality in a single step, which could be oxidized and deprotected to give **17** and **18**. It was also of interest to prepare the enoate-ketones **14** and **16**; **14** could be accessed from cycloheptene using a similar synthetic sequence, whereas **16** was synthesized via ozonolysis of 2-methyl cyclohexene and subsequent methylenation and oxidation.

The iodo-aldol cyclization of enoate-aldehyde **17** was carried out using $TiCl_4$ (1.2 equiv) and Bu_4NI (1.2 equiv) in DCM at 0 °C, with slow addition of the substrate (Scheme 4). We were pleased to observe smooth cyclization to afford the 1,1-disubstituted cyclopentane in 1 h. ^1H NMR analysis of the crude reaction mixture indicated an 9:1 mixture of diastereoisomers, which could be purified by chromatography to give the major compound in 81% isolated yield. The stereochemistry was assigned as *trans* on the basis of

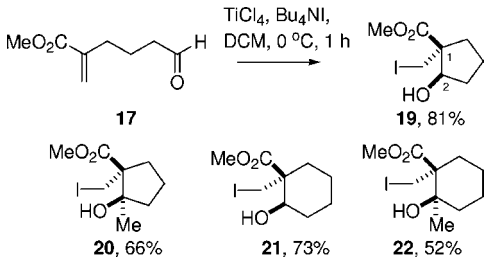
Scheme 3. Synthesis of Iodo-aldol Carbocyclization Substrates **14** and **16**−**18**



NOESY data showing enhancements between the C2 tertiary proton and the iodomethyl group, indicating that the hydroxyl and iodomethyl groups were on opposite faces of the cyclopentane ring.

The cyclization was similarly effective for the enoate ketone **16**, forming the cyclopentane **20** as a single diastereoisomer featuring *vicinal* tertiary and quaternary carbon

Scheme 4. Iodo-aldol Carbocyclization

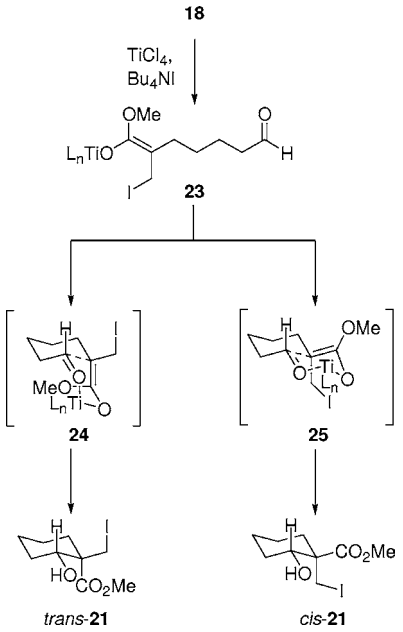


(9) Recent examples of tandem conjugate addition/aldol processes for quaternary center construction: (a) Nishiyama, H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* **2005**, *127*, 6972−6973. (b) Zhao, G.-L.; Shi, Y.-L.; Shi, M. *Org. Lett.* **2005**, *7*, 4527−4530. (c) Hayashi, M.; Matsuura, Y.; Watanabe, Y. *Tetrahedron Lett.* **2005**, *46*, 5135−5138. (d) Lee, C. A.; Floreancig, P. E. *Tetrahedron Lett.* **2004**, *45*, 7193−7196. (e) Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811−4814. (f) Lipshutz, B. H.; Papa, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 4580−4582. (g) Shibata, K.; Kimura, M.; Shimizu, M.; Tamaru, Y. *Org. Lett.* **2001**, *3*, 2181−2183. (h) Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F. *Org. Lett.* **2001**, *3*, 1901−1903. (i) Kamimura, A.; Mitsudera, H.; Asano, S.; Kidera, S.; Kakehi, A. *J. Org. Chem.* **1999**, *64*, 6353−6360.

centers, in a slightly attenuated 66% yield. Enoate-aldehyde **18** and ketone **14** were likewise competent substrates for diastereoselective 6-*exo* iodo-aldol cyclization, forming the neopentyl iodides **21** (73% yield) and **22** (52% yield) as single diastereoisomers. As previously observed for the cyclopentannulation of **16**, some erosion of yield was observed for the construction of the hindered *vicinal* tertiary and quaternary carbon centers in **22**. Stereochemistry was assigned as *trans* in all cases by analogy with **19**, and in light of subsequent X-ray data (vide infra).

The observed stereoselectivity can be explained using the model shown in Scheme 5 for substrate **18**, which is based

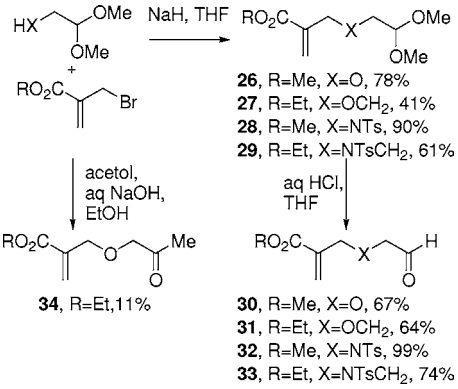
Scheme 5. Stereochemical Model for Iodo-aldol Cyclization



upon the twin requirements of initial conjugate addition of iodide giving the (*Z*)-enolate **23** and subsequent aldol reaction taking place via a six-membered chelated chair transition state that has been observed in previous iodo-aldol studies.[4] Two chair−chair transition states, **24** and **25**, are consistent with a chelated (*Z*)-enolate, with the observed stereoselectivity arising from the *cis*-decalin-type structure **24**. Discrimination between **24** and **25** is likely due to the orientation of the bulky CH_2I group, which is placed in the least hindered equatorial position in **24**, with the small H (or Me) group occupying the axial position. The *trans*-decalin-type structure **25**, by contrast, has the CH_2I group occupying the more-hindered axial position, accounting for the lack of *cis*-**21** product observed in the iodo-aldol cyclization.

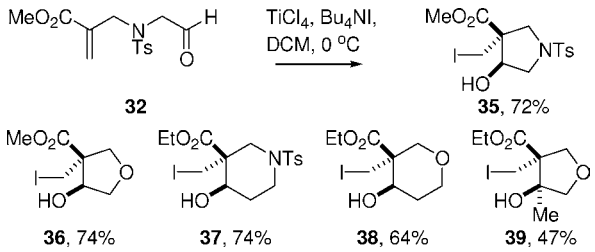
We next looked to extend the cyclization to heterocycle synthesis, an area that has received little attention in previous iodo-aldol studies.[10] Using ethyl or methyl bromomethylacrylate as a starting material,[11] we could prepare the O- and NTs-linked enoate hexanals **30** and **32** and the heptanals **31** and **33** in two steps. The methyl ketone **34** was prepared in one step by reaction of ethyl bromoacrylate with acetol (Scheme 6).

Scheme 6. Synthesis of Iodo-aldol Heterocyclization Substrates



Iodo-cyclization was again successful, with good isolated yields of the pyrrolidine **35**, furan **36**, piperidine **37**, and pyran **38** being recorded (Scheme 7). As previously, the

Scheme 7. Iodo-aldol Heterocyclization



reaction displayed high levels of stereoselectivity for each substrate, with ^{1}H NMR showing a single diastereoisomer being formed in each case. A single crystal of the 3,5-dinitrobenzoate derivatives of the five- and six-membered ring structures **35** and **37** could be grown, and the X-ray data supported the *trans*-stereochemistry originally assigned on the basis of NOESY data (Figure 1). The reaction could be successfully extended to the enoate-ketone substrate **34**, but as with the analogous carbocyclization the yield of the furan **39** was attenuated somewhat in the construction of the extremely hindered tertiary center.

Li has recently reported the first iodo-aldol reactions that employ catalytic amounts of Lewis acid for the intermolecular allenoate iodo-aldol reaction.[5f] We were interested in exploring the possibility of lowering the amounts of $TiCl_4$ employed in our own system, with a view to future developments in asymmetric catalysis. In analogous Mukaiyama aldol systems this is usually achieved through the addition of a silylating agent that can facilitate turnover of the Lewis acid.[12] Preliminary experiments indicate that this

(10) One example of a pyran-forming iodo-aldol cyclization has been reported in ref 4e.

(11) Hediger, M. E. *Bioorg. Med. Chem.* **2004**, *12*, 4995−5010.

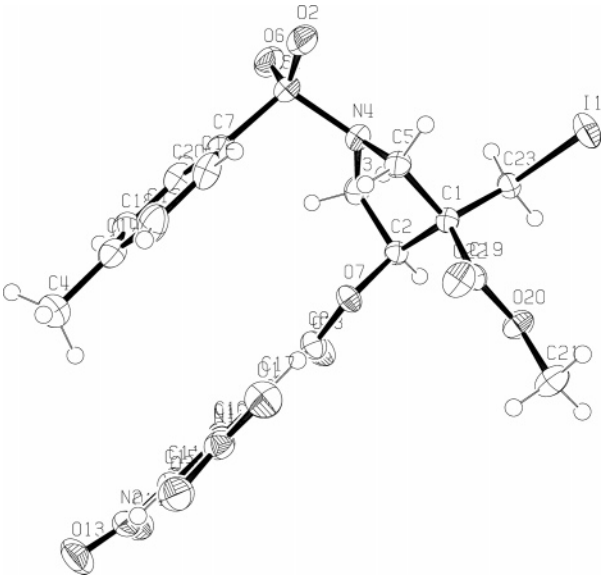


Figure 1. X-ray structure of the 3,5-dinitrobenzoate derivative of pyrrolidine **35**.

strategy is effective for our system: Using the O-linked compound **34** as substrate, we were pleased to see that a protocol of $TiCl_4$ (0.2 equiv) and TMSI (2.4 equiv) in DCM at −78 °C was catalytically fit for purpose, producing furan **39** in a slightly higher 53% yield. A similar protocol afforded the pyran **38** in the slightly attenuated yield of 49%.

In conclusion, we have developed the intramolecular iodo-aldol cyclization of enoate-aldehydes and ketones to afford hetero- and carbocycles containing quaternary centers. The reaction transforms simple, prochiral starting materials into cyclic alcohols containing *vicinal* quaternary and secondary/tertiary stereocenters, in good yields with excellent stereoselectivity. In addition, the products display a collection of orthogonal functional groups that may be further elaborated in the synthesis of complex natural product targets, which will be the focus of our future work in the area.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds, including files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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