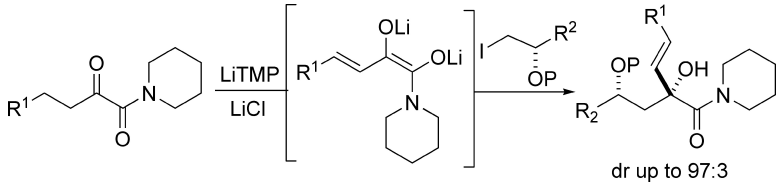
Communication

Electrophile-Directed Diastereoselective Alkylation of Prochiral Enediolates

Stephen P. Marsden, and Rebecca Newton

J. Am. Chem. Soc., **2007**, 129 (42), 12600-12601• DOI: 10.1021/ja073624e • Publication Date (Web): 03 October 2007



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 10/03/2007

Electrophile-Directed Diastereoselective Alkylation of Prochiral Enediolates

Stephen P. Marsden* and Rebecca Newton

School of Chemistry, University of Leeds, Leeds LS2 9JT, United Kingdom

Received May 21, 2007; E-mail: s.p.marsden@leeds.ac.uk

The construction of asymmetric centers by alkylation of non-stabilized enolates of simple esters and amides is a process of enormous significance in both academic and industrial target synthesis.[1] Control of stereochemistry in asymmetric alkylations is almost always achieved by temporary covalent attachment of chiral auxiliaries to prochiral carboxyl substrates,[2] or by self-regeneration of chirality approaches utilizing α-chiral carboxylate derivatives.[3] While progress has been made in the catalytic asymmetric alkylation of the more acidic ketone enolates,[4] work in the carboxyl series is still limited to substrates bearing additional acidifying substituents.[5] An alternative but little used strategy is to exploit chirality in the electrophile to control the facial selectivity of attack on a prochiral enolate.[6−9] We report herein a new approach to the construction of quaternary α-hydroxy carboxylic derivatives utilizing such a strategy.

We recently reported an efficient method for the synthesis of quaternary α-hydroxy-α-alkylbut-3-enamides by regiospecific alkylation of dienediolates prepared by double deprotonation of α-ketoamides.[10] In a proposed application to the synthesis of the phospholipase A_2 inhibitor cinatrin B[11] we aimed to install a key quaternary asymmetric center by alkylation of a dienediolate with a β-hydroxyalkyl cation equivalent. In the event, alkylation of the prochiral dienediolate **1** (derived from ketoamide **2a**) with protected iodohydrin **3** gave the desired alkylation product **4** as a 90:10 mixture of diastereoisomers (Scheme 1). The identity of the major isomer was confirmed by X-ray crystallographic analysis of the derived lactone **5**.

This represents a rare example of the diastereoselective alkylation of a prochiral enolate directed by a β-stereogenic center in a primary alkyl electrophile. To our knowledge, the only previous examples of this phenomenon are the pioneering studies on the alkylation of 3-substituted oxindole enolates by Overman[6] and of metalated hydroxyfurans by Tadano and Hale.[7] We therefore undertook further studies based on our preliminary observation to better define the scope and generality of the transformation. Pleasingly, this novel diastereoselective alkylation protocol appears to be general, with good to excellent (up to 32:1) stereoselectivities observed with a range of dienediolates and electrophiles (Table 1).[12]

The degree of asymmetric induction is essentially unaltered by variation in the dienediolate side chain R^1 (dr ≈ 90:10, entries 1−3). With regard to the electrophile, the nature of the R^2 group was found to be influential, with a small (methyl) substituent affording lower selectivity (entry 4) but a secondary alkyl group giving very high levels of selectivity (dr = 97:3, entry 5). The presence of an oxygenated R^3 substituent is crucial for asymmetric induction (entry 8), while the nature of the oxygen protecting group also affects the diastereoselectivity, with a methoxy group delivering highest selectivity (dr = 97:3, entry 7).

We next probed the influence of the enolate substituents by examining enediolates derived from substituted glycolic amides. Alkylation of the dianion of 2-hydroxybutanamide **6a**, an analogue of dienediolate **1** bearing a saturated side chain, proceeded in relatively low yield to give a 62:38 mixture of diastereomers (Table 2, entry 1). This suggests that the presence of unsaturation in the enediolate substituent is not an absolute requirement for selectivity, but is beneficial. Diastereoelective alkylation was also observed with an enediolate bearing an aromatic substituent, mandelic amide **6b**, giving a 75:25 mixture of diastereomers in favor of the isomer shown (entry 2).[12] Alkylation of lactic amide **6c**, however, was

Scheme 1. Electrophile-Directed Diastereoselective Alkylation

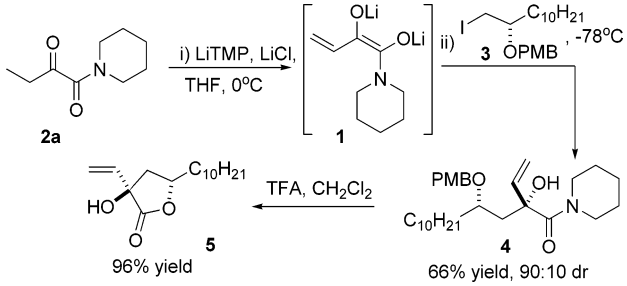
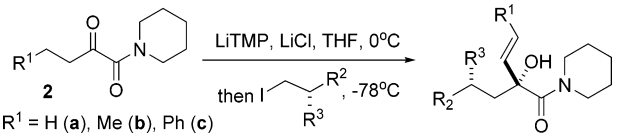


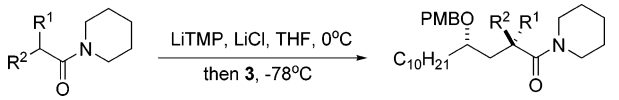
Table 1. Scope of the Electrophile-Directed Diastereoselective Alkylation of Dienediolates



entry	R^1	R^2	R^3	% yield[a]	dr[b]
1	H	$C_{10}H_{21}$	OPMB	66	90:10
2	Me	$C_{10}H_{21}$	OPMB	71	89:11[c]
3	Ph	$C_{10}H_{21}$	OPMB	68	89:11[c]
4	H	Me	OPMB	43	63:37
5	H	^{i}Pr	OPMB	48	97:3
6	H	$C_{10}H_{21}$	OBn	51	91:9
7	H	$C_{10}H_{21}$	OMe	37	97:3
8	H	$C_{10}H_{21}$	Me	51	50:50

[a] Isolated yield. [b] Determined by analysis of ^{1}H NMR of product. [c] (*E*)-Alkene obtained exclusively.

Table 2. Influence of Enolate Substituents on the Electrophile-Directed Diastereoselective Alkylation



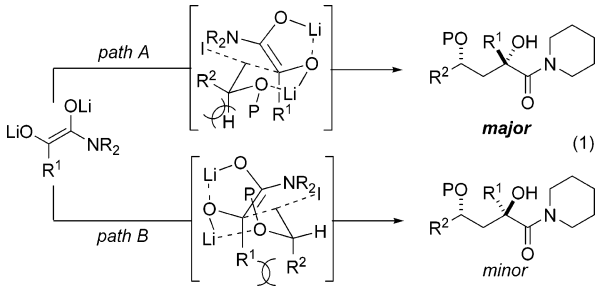
entry	substrate	R^1	R^2	% yield[a]	dr[b]
1	**6a**	OH	Et	18	62:38
2	**6b**	OH	Ph	46	75:25
3	**6c**	OH	Me	41	50:50
4	**6d**	OH	(*E*)-styryl	71	88:12
5	**7**	OMe	(*E*)-styryl	10	50:50
6	**8**	Me	CH_2=CH−	60	50:50
7	**9**	Me	Ph	28	50:50

[a] Isolated yield. [b] Determined by analysis of ^{1}H NMR of product.

10.1021/ja073624e CCC: $37.00

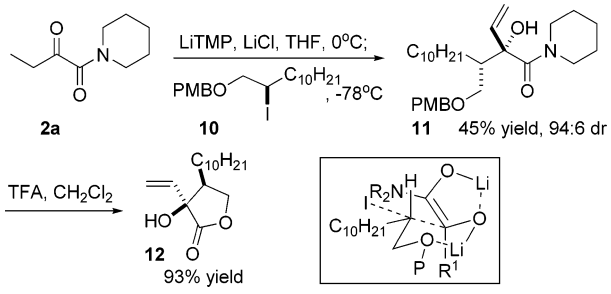
nonselective (entry 3), demonstrating that the size of the substituent is influential. Alkylation of hydroxyamide **6d**, which generates the same dienediolate intermediate as substrate **2c**, returned product with the same dr as before, confirming that the method of dienediolate generation is not a determining factor (entry 4, cf. Table 1, entry 3). Finally, we probed the necessity for the presence of an α-lithioalkoxy enolate substituent. The alkylation reactions of the monoenolates of substrates **7**−**9** (where the lithioalkoxy group is replaced by a methoxy or methyl group) were found to be both low yielding and nonstereoselective in all cases (entries 5−7).

The substituents necessary for the attainment of high diastereoselectivities were therefore defined. Specifically, the strict requirements for (a) an oxyanion substituent on the enolate and (b) a β-oxygen substituent in the electrophile strongly implicate these elements in a pre-organization of the reactants. On the basis of these observations, we propose that alkylation may proceed through a lithium-coordinated chairlike assembly in which the bulky (*Z*)-(di)enediolate[13] is equatorially disposed (eq 1). The major diastereomeric product results from the equatorial disposition of the electrophile side chain (path A), while the minor isomer arises from diaxial disposition of the R^2 and P groups of the electrophile (relieving torsional strain, path B). The latter assembly would be disfavored as both R^1 and R^2 increase in size, which correlates with the observed increases in selectivity with these changes. Unsaturation in R^1 is also beneficial, possibly due to restriction of conformational flexibility by conjugation with the enolate. This model correctly predicts the identity of the major diastereoisomer in all cases proven to date.



Given the excellent asymmetric inductions attained, we were intrigued by the prospect that highly diastereoselective alkylations might be feasible using regioisomeric secondary iodohydrin derivatives, in which the nucleofugal iodine is attached to the asymmetric center and the alkoxy substituent to the primary carbon. If successful, this would lead to the efficient construction of contiguous quaternary and tertiary asymmetric centers, a synthetically highly demanding operation.[9] In the event, we were gratified to observe that alkylation of dienediolate **1** (derived from ketoamide **2a**) with iodide **10** gave the alkylated product **11** as a 94:6 mixture of diastereomers in 45% yield (Scheme 2). The identity of the major isomer was elucidated by NOE studies on the derived lactone **12**. This outcome is again consistent with a lithium-coordinated chairlike transition-state assembly, with equatorial disposition of enolate and electrophile substituents.

Scheme 2. Highly Stereoselective Construction of Adjacent Quaternary/Tertiary Asymmetric Centers



In summary, we have developed a novel methodology for the synthesis of quaternary α-hydroxycarboxyl derivatives by employing electrophile-directed diastereoselective alkylation of prochiral enolates with chiral primary and secondary protected iodohydrins. The determination of the exact scope of this transformation and its application toward the synthesis of cinatrin B are in progress.

Acknowledgment. We thank Mr. Simon Barrett and Mr. Colin Kilner (Leeds) for the NOE experiments and X-ray determinations. GlaxoSmithKline are thanked for unrestricted research funding.

Supporting Information Available: Experimental protocols, compound data, and NMR spectra for key reactions. This material is available free of charge via the Internet at http://pubs.acs.org

References

(1) (a) Santelli, M.; Ollivier, C. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005; Vol. 1, p 121. (b) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734.

(2) Gawley, R. E.; Aube, J. *Principles of Asymmetric Synthesis*; Elsevier: Oxford, 1996.

(3) Self-regeneration of chirality: Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *35*, 2708. Memory of chirality: Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, 1.

(4) For recent examples of metal-catalyzed asymmetric ketone allylation, see: (a) Graening, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 17192. (b) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180. Alkylation of lithium enolates with oligoamine catalysts: Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *Tetrahedron* **2000**, *56*, 179 and refs therein. Chromium-catalyzed alkylation of tin enolates: Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62. Phase-transfer catalyzed ketone alkylation: Andrus, M. B.; Hicken, E. J.; Stephens, J. C.; Bedke, D. K. *J. Org. Chem.* **2005**, *70*, 9470. For intramolecular organocatalyzed alkylation of aldehydes, see: Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450.

(5) Review of asymmetric phase-transfer catalyzed alkylations of acidified carboxyl derivatives: Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.

(6) Oxindole enolates and β-chiral primary triflates: (a) Overman, L. E.; Larrow, J. F.; Stearns, B. A.; Vance, J. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 213. (b) Hoyt, S. B.; Overman, L. E. *Org. Lett.* **2000**, *2*, 3241. (c) Overman, L. E.; Peterson, E. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 2525. (d) Overman, L. E.; Peterson, E. A. *Tetrahedron* **2003**, *59*, 6905. (e) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043.

(7) Metallated hydroxyfurans and β-chiral primary triflates: (a) Takao, K.; Ochiai, H.; Hashizuki, T.; Koshimura, H.; Tadano, K.; Ogawa, S. *Tetrahedron Lett.* **1995**, *36*, 1487. (b) Takao, K.; Ochiai, H.; Yoshida, K.; Hashizuki, T.; Koshimura, H.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1995**, *60*, 8179. (c) Li, Y.; Hale, K. J. *Org. Lett.* **2007**, *9*, 1267.

(8) Oxindole enolates and primary electrophiles bearing a remote chiral auxiliary: (a) Emura, T.; Esaki, T.; Tachibana, K.; Shimizu, M. *J. Org. Chem.* **2006**, *71*, 8559. (b) Pallavicini, M.; Valoti, E.; Villa, L.; Resta, I. *Tetrahedron: Asymmetry* **1994**, *5*, 363.

(9) Prochiral enolates and secondary alkyl triflates: (a) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813. (b) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **2003**, *125*, 4166.

(10) (a) Marsden, S. P.; Newton, R. *Synthesis* **2005**, 3263. (b) Koft, E. R.; Williams, M. D. *Tetrahedron Lett.* **1986**, *27*, 2227.

(11) Itazaki, H.; Nagashima, K.; Kawamura, Y.; Matsumoto, K.; Nakai, H.; Terui, Y. *J. Antibiot.* **1992**, *45*, 38.

(12) Stereochemistry of alkylation has been unambiguously assigned in four cases by deprotection/lactonization, followed by X-ray (Table 1, entries 1 and 3) or NOE (Table 1, entry 5 and Table 2, entry 2) analysis.

(13) Enediolates of tetrasubstituted glycolic esters have (*Z*)-stereochemistry: Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3941. We have verified that dienediolates derived from ketoamides **1a**−**c** are single isomers, with **1a** shown (NOE) to have (*Z*)-stereochemistry.

JA073624E