Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

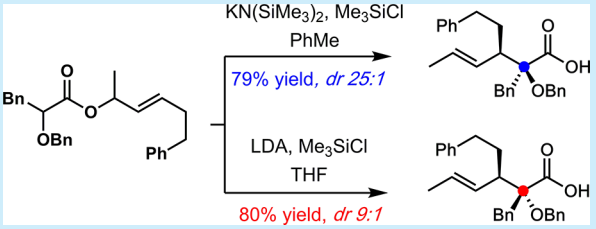
Stereodivergence in the Ireland−Claisen Rearrangement of α-Alkoxy Esters

Maša Podunavac, Jacob J. Lacharity, Kerry E. Jones, and Armen Zakarian*

Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States

Supporting Information

ABSTRACT: A systematic investigation into the Ireland−Claisen rearrangement of α-alkoxy esters is reported. In all cases, the use of $KN(SiMe_3)_2$ in toluene gave rearrangement products corresponding to a *Z*-enolate intermediate with excellent diastereoselectivity, presumably because of chelation control. On the other hand, chelation-controlled enolate formation could be overcome for most substrates through the use of lithium diisopropylamide (LDA) in tetrahydrofuran (THF).



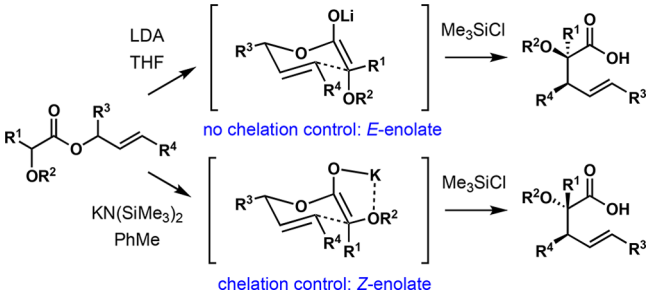
Downloaded via UNIV OF GOTHENBURG on August 3, 2018 at 01:48:09 (UTC).
See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.

The Ireland−Claisen rearrangement has represented a powerful tool in chemical synthesis for over 40 years.[1] The utility of this method is underscored by the ease of preparation of the requisite allylic esters and the predictable stereochemical outcome of the reaction.[2] The stereochemistry of the alcohol fragment is reliably transferred to the α and β positions of the carboxylic acid product with high enantioselectivity and diastereoselectivity, usually via a chairlike transition state, providing a powerful approach to the construction of sterically congested vicinal stereocenters.[3] Furthermore, the carboxy group formed in the reaction can serve as an effective proxy to a wide variety of other functional groups.[4]

Efficient transmission of chirality during the Ireland−Claisen rearrangement is critically dependent on the stereoselective formation of an *E*- or *Z*-enolate. In the case of α-alkoxy esters, it is widely expected that formation of the *Z*-enolate is kinetically favored, because of chelation of the alkoxy and carbonyl oxygen atoms with the metal cation of the base. Indeed, selective *Z*-enolate formation in the Ireland−Claisen rearrangement of esters derived from glycolic and lactic acid has been observed in numerous cases.[5−9] Therefore, we were surprised to find a report from Langlois and co-workers that described selective *E*-enolate formation in the Ireland−Claisen rearrangement of an α-OPMB ester when LDA was used as the base in tetrahydrofuran (THF).[10] In this single reported example, a 3:1 ratio of products arising from the *E*- and *Z*-enolates, respectively, was observed. This selectivity was reversed when Et_2O or toluene were used as the solvent, when HMPA was employed as an additive, or when $KN(SiMe_3)_2$ was used as the base.

To the best of our knowledge, this work represents the only case of nonchelation-controlled, *E*-selective enolization of an α-alkoxy ester. It is an important observation because it is generally presumed that only one diastereomer is accessible by the Ireland−Claisen rearrangement of α-alkoxy esters attributed to the overwhelming preference for the *Z*-enolate via chelation-controlled enolization (see Scheme 1).[11] Thus,

Scheme 1. Proposed Stereodivergent Access to Both Diastereomeric Ireland−Claisen Rearrangement Products of α-Alkoxy Esters



no systematic studies on the divergence in the diastereoselectivity in the Ireland−Claisen rearrangement, based on the choice of the enolization reagent, has been reported for this class of substrates. If it is indeed possible to achieve selective *E*- or *Z*-enolate formation from the same substrate, facile access to both diasteromeric Ireland−Claisen products could be realized.

We became interested in exploring whether the effect of the base used for the enolization of α-alkoxy esters on the diastereochemical outcome of the Ireland−Claisen rearrangement is general. If so, practical levels of diastereomer ratios (dr) can be achieved for both isomers from the same substrate simply by the choice of base (see Scheme 2). To this end, we prepared a library of these compounds to examine the effects of the reaction conditions and the structure of the ester on the diastereoselectivity of the rearrangement.

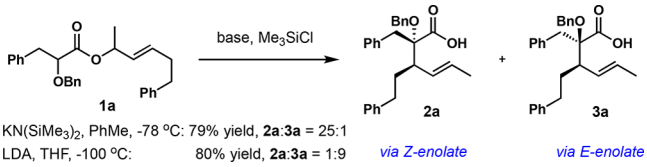
Using α-benzyloxy hydrocinnamate **1** as a representative α-alkoxy ester, initial studies focused on identifying suitable reaction conditions capable of selectively delivering both diastereomeric products based on the choice of base. The

Received: June 27, 2018

© XXXX American Chemical Society

DOI: 10.1021/acs.orglett.8b02011
Org. Lett. XXXX, XXX, XXX−XXX

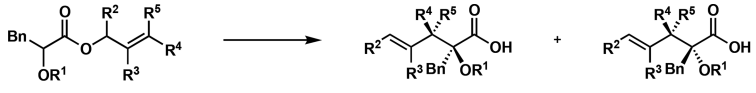
Scheme 2

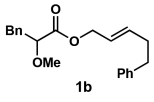
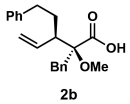
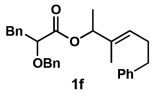
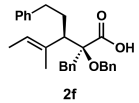
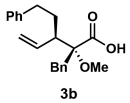
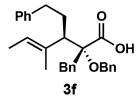
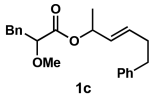
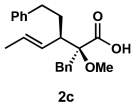
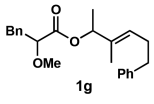
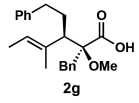
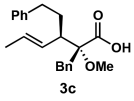
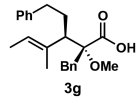
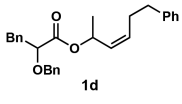
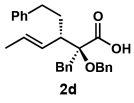
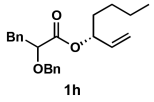
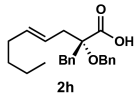
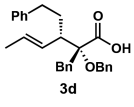
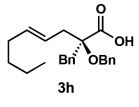
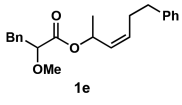
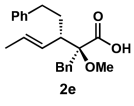
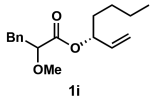
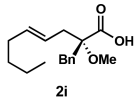
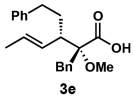
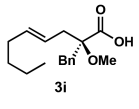


screening of several different bases in different solvents revealed that $KN(SiMe_3)_2$ in PhMe is optimal for the formation of the chelation-controlled diastereomer. Remarkably, LDA in THF proved most effective for the formation of the opposite diastereomeric product (see Scheme 1). Furthermore, the temperature and time of enolization also proved to be critical parameters influencing diastereocontrol (see the Supporting Information (SI) for full details of optimization experiments).

A series of α-alkoxy esters were prepared and subjected to the optimal [3,3] sigmatropic rearrangement protocols in the presence of bases $KN(SiMe_3)_2$ or LDA (see Table 1). We began by screening a variety of α-alkoxy hydrocinnamic acid esters bearing distinct R^2/R^3 substituents, in addition to different R^1 alkoxy substituents. $KN(SiMe_3)_2$ as a base afforded acids via a *Z* enolate in moderate to excellent yields (79%–90%) with diastereoselectivities as high as 25:1. In all examples, a slight decrease in dr was observed when the alkoxy substituent R^1 was changed from Bn to a methyl group. It was found that the nature of the R^1 substituent had little effect on the reaction in terms of yield. In contrast, using LDA as the base led to the rearrangement via an *E* enolate in comparable yields (72%–92%), but with noticeably smaller dr (17:1 being the highest). A substantial decrease in yield was observed for esters derived from primary alcohols compared with secondary (R^2 = H instead of Me). This result is due to competitive lithiation of the allylic methylene, leading to the formation of C-silylated byproducts (see the SI). Although yields were similar for acids with $R^2 = CH_3$, in most cases, α-benzyloxy esters gave products with higher dr.

Table 1. Substrate Scope in the α-Alkoxy Hydrocinnamic Ester Series[a]

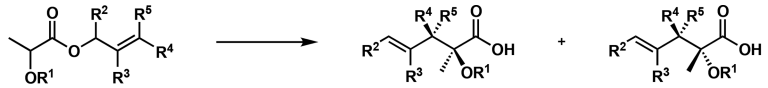


entry	substrate	major isomer	base	yield 2:3	entry	substrate	major isomer	base	yield 2:3
1	 1b	 2b	$KN(SiMe_3)_2$	85% 14:1	9	 1f	 2f	$KN(SiMe_3)_2$	79% 25:1
2	**1b**	 3b	LDA	45% 1:2	10	**1f**	 3f	LDA	72% 1:17
3	 1c	 2c	$KN(SiMe_3)_2$	82% 17:1	11	 1g	 2g	$KN(SiMe_3)_2$	80% 25:1
4	**1c**	 3c	LDA	85% 1:5	12	**1g**	 3g	LDA	76% 1:6
5	 1d	 2d	$KN(SiMe_3)_2$	87% 25:1	13	 1h	 2h	$KN(SiMe_3)_2$	87% 10:1
6	**1d**	 3d	LDA	79% 1:17	14	**1h**	 3h	LDA	92% 1:7
7	 1e	 2e	$KN(SiMe_3)_2$	90% 17:1	15	 1i	 2i	$KN(SiMe_3)_2$	73% 10:1
8	**1e**	 3e	LDA	85% 1:8	16	**1i**	 3i	LDA	95% 1:7

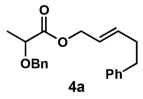
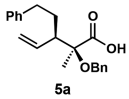
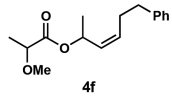
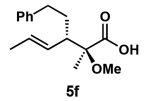
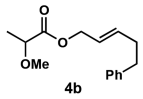
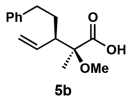
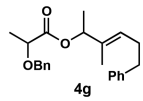
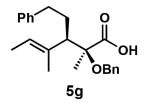
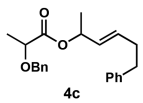
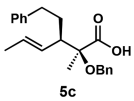
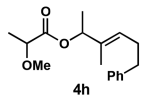
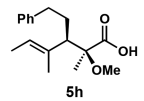
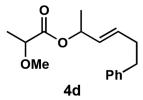
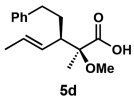
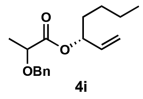
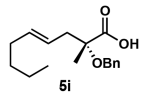
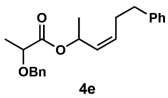
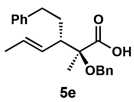
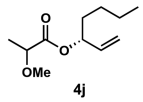
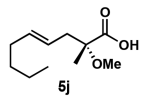
[a]The substrate was treated with the indicated base at −78 °C ($KN(SiMe_3)_2$) or −100 °C (LDA). Internal quench with Me_3SiCl was used for LDA. Isomer ratio determined by ^1H NMR spectroscopy. See the SI for details.

DOI: 10.1021/acs.orglett.8b02011
Org. Lett. XXXX, XXX, XXX–XXX

Table 2. Substrate Scope in the Lactic Ester Series[a]



4 5 (via *Z*-enolate) 6 (via *E*-enolate)

entry	substrate	major isomer	base	yield, 5:6	entry	substrate	major isomer	base	yield, 5:6
1	 4a	 5a	$KN(SiMe_3)_2$	94% 13:1	11	 4f	 5f	$KN(SiMe_3)_2$	82% 30:1
2	**4a**	**5a**	LDA	77% 2:1	12	**4f**	**6f**	LDA	83% 1:4
3	 4b	 5b	$KN(SiMe_3)_2$	81% 17:1	13	 4g	 5g	$KN(SiMe_3)_2$	72% 25:1
4	**4b**	**5b**	LDA	92% 5:1	14	**4g**	**5g**	LDA	78% 2:1
5	 4c	 5c	$KN(SiMe_3)_2$	82% 20:1	15	 4h	 5h	$KN(SiMe_3)_2$	64% 30:1
6	**4c**	**5c**	LDA	71% 2:1	16	**4h**	**5h**	LDA	82% 5:1
7	 4d	 5d	$KN(SiMe_3)_2$	85% 25:1	17	 4i	 5i	$KN(SiMe_3)_2$	88% 11:1
8	**4d**	**5d**	LDA	88% 6:1	18	**4i**	**5i**	LDA	85% 1.4:1
9	 4e	 5e	$KN(SiMe_3)_2$	81% 7:1	19	 4j	 5j	$KN(SiMe_3)_2$	72% 14:1
10	**4e**	**6e**	LDA	81% 1:2	20	**4j**	**5j**	LDA	91% 8:1

[a]The substrate was treated with the indicated base at −78 °C ($KN(SiMe_3)_2$) or −100 °C (LDA). Internal quench with Me_3SiCl was used for LDA. Isomer ratio determined by ^1H NMR spectroscopy. See the SI for details.

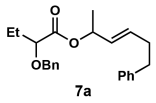
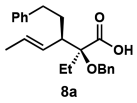
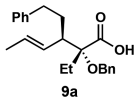
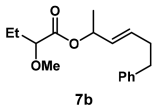
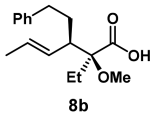
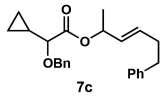
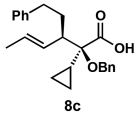
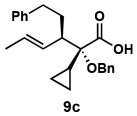
We then examined the Ireland−Claisen rearrangement of α-alkoxy propionic acid esters (see Table 2). Unlike α-alkoxy hydrocinnamic acid esters, the use of LDA as a base generally did not favor formation of an *E* enolate in this class of substrates. Both bases typically gave the same major rearrangement products, corresponding to the *Z*-enolate intermediates, in comparable yields, with $KN(SiMe_3)_2$ giving significantly higher dr. Notable exceptions to this pattern occurred when the alcohol fragment of the allylic ester contained a *Z*-configured olefin (**4e** and **4f**). These substrates were able to overcome chelation-controlled enolization and gave rise to *E*-enolization products (albeit with modest selectivity). Surprisingly, higher dr is achieved when R^1 = Me, compared to R^1= Bn, which is the opposite of what was observed for the esters in Table 1.

To gain insight into the structural constraints required to achieve selective *E*-enolization with LDA, we performed additional experiments, as summarized in Table 3. The optimized conditions for the rearrangement were applied to α-alkoxy butyric acid esters **7a** and **7b**. Remarkably, this simple one-carbon homologation of the carboxylic acid alkyl side chain, relative to the esters in Table 1, once again led to *E*-selective enolization when LDA was used as the base, although a much higher diastereomeric ratio was obtained for α-OBn substrate **7a** (1:6), relative to the corresponding α-OMe ester **7b** (1:1.1), as is consistent with our previous observations. α-Cyclopropyl substrate **7c** proved to be more resistant to *E*-enolization, with a modest diastereoselectivity of 1:1.1 favoring the *E*-enolate-derived product obtained when the rearrangement was performed using LDA as the base. These results seem to suggest that while Z-selective enolization and rearrangement is highly predictable and selective with $KN(SiMe_3)_2$, *E*-selective enolization for α-alkoxy esters is very sensitive to the structure of the alkyl side chains. In addition, greater selectivity is generally observed for larger alkoxy substituents (for example, for OBn versus OMe).

In conclusion, we have conducted a detailed investigation into the Ireland−Claisen rearrangement of α-alkoxy esters. Excellent chelation-controlled selectivity (dr >10:1 in all cases) was observed when the reaction was performed using

DOI: 10.1021/acs.orglett.8b02011
Org. Lett. XXXX, XXX, XXX−XXX

Table 3. Additional Substrate Scope[a]

entry	substrate	major product	base	yield, 8:9
1	 7a	 8a	$KN(SiMe_3)_2$	91% 25:1
2	7a	 9a	LDA	80% 1:6
3	 7b	 8b	$KN(SiMe_3)_2$	88% 25:1
4	7b	8b	LDA	94% 1:1.1
5	 7c	 8c	$KN(SiMe_3)_2$	68% 7:1
6	7c	 9c	LDA	68% 1:1.1

[a]The substrate was treated with the indicated base at −78 °C ($KN(SiMe_3)_2$) or −100 °C (LDA). Internal quench with Me_3SiCl was used for LDA. Isomer ratio determined by ^1H NMR spectroscopy. See the SI for details.

$KN(SiMe_3)_2$ in PhMe for a broad range of substrates. Most importantly, non-chelation-controlled enolization could be achieved in many cases through the use of LDA in THF with an internal quench with Me_3SiCl. Both systems showed greater selectivity in the rearrangement of substrates with large α-alkyl chains on the ester and highly substituted double bonds. However, the selectivity patterns for non-chelation-controlled enolization proved to be quite complex and were far more sensitive to the structure of the ester. α-Alkoxy propionate esters proved to be the most challenging substrates for the LDA−THF system, and high selectivity for non-chelation-controlled enolization products were observed only for allylic esters with *Z*-substituted double bonds. We have shown that, in many cases, both diastereomers of the Ireland−Claisen rearrangement products can be accessed from the same allylic ester simply by the choice of enolization reagent, which is a finding that will prove useful in future synthesis planning.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02011.

Detailed experimental procedures, ^1H and ^{13}C NMR spectra of all new compounds and HPLC trace analysis of enantioenriched compounds (PDF)

Accession Codes

CCDC 1853280 and 1853281 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zakarian@chem.ucsb.edu

ORCID

Armen Zakarian: 0000-0002-9120-1232

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by NSF (No. CHE 1463819). Dr. Hongjun Zhou (UCSB) is acknowledged for assistance with NMR spectroscopy. Dr. Dmitriy Uchenik and the UCSB mass spectroscopy facility are thanked for assistance with mass-spectroscopic analysis. We also thank Dr. Guang Wu (UCSB) for assistance with X-ray crystallography.

■ REFERENCES

(1) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868−2877.

(2) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Chem. Soc. Rev.* **2009**, *38*, 3133−3148.

(3) (a) Kuilya, T. K.; Goswami, R. K. *Org. Lett.* **2017**, *19*, 2366−2369. (b) Stivala, C.; Zakarian, A. *J. Am. Chem. Soc.* **2008**, *130*, 3774−3776. (c) Xiao, Q.; Jackson, J. J.; Basak, A.; Bowler, J. M.; Miller, B. G.; Zakarian, A. *Nat. Chem.* **2013**, *5*, 410−416. (d) He, C.; Zhu, C.; Dai, Z.; Tseng, C.-C.; Ding, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 13256−13260.

(4) (a) Kobayashi, H.; Eickhoff, J. A.; Zakarian, A. *J. Org. Chem.* **2015**, *80*, 9989−9999. (b) Jackson, J. J.; Kobayashi, H.; Steffens, S.; Zakarian, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 9971−9975. (c) Cannon, J. S. *Org. Lett.* **2018**, *20*, 3883−3887. (d) Lacharity, J. J.; Fournier, J.; Lu, P.; Mailyan, A. K.; Herrmann, A. T.; Zakarian, A. *J. Am. Chem. Soc.* **2017**, *139*, 13272−13275. (e) Jamison, C. R.; Overman, L. E. *Acc. Chem. Res.* **2016**, *49*, 1578−1586.

(5) Moore, J. T.; Hanhan, N. V.; Mahoney, M. E.; Cramer, S. P.; Shaw, J. T. *Org. Lett.* **2013**, *15*, 5615−5617.

(6) Whitesell, J. K.; Helbling, A. M. *J. Org. Chem.* **1980**, *45*, 4135−4139. (d) Sato, T.; Tajima, K.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 729−730.

(7) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3941−3945.

(8) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221−5228.

(9) Sato, T.; Tajima, K.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 729−730.

(10) Picoul, W.; Urchegui, R.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 4797−4800.

(11) (a) Feldman, K. S.; Selfridge, B. R. *Tetrahedron Lett.* **2012**, *53*, 825−828. (b) Yang, Y.; Fu, X.; Chen, J.; Zhai, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 9825−9828. (c) Gilbert, J. C.; Selliah, R. D. *J. Org. Chem.* **1993**, *58*, 6255−6265.

DOI: 10.1021/acs.orglett.8b02011
Org. Lett. XXXX, XXX, XXX−XXX