Synthetic Methods

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Acyclic Stereocontrol in the Ireland–Claisen Rearrangement of α-Branched Esters**

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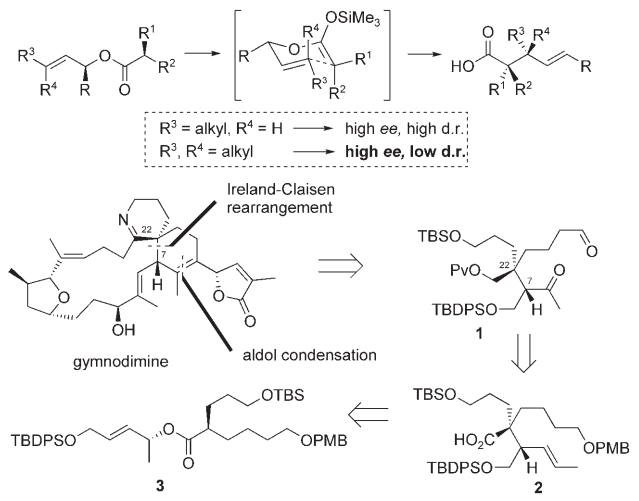
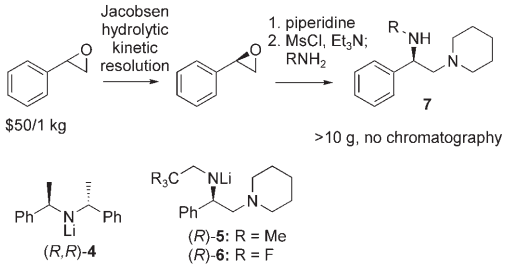
The Ireland–Claisen rearrangement is a powerful synthetic method that has found extensive application in chemical synthesis.[1,2] The substrates for this reaction can be prepared readily and convergently by the coupling of an allylic alcohol with a carboxylic acid, and the chirality of the allylic alcohol is relayed efficiently to the carbon–carbon bond formed in the rearrangement. The absolute configuration of the two stereocenters created in the Ireland–Claisen reaction can be predicted reliably on the basis of a chairlike-transition-state model. The reaction can even be used to assemble two contiguous quaternary stereogenic centers under mild conditions. One of the current deficiencies of the method, however, is the low diastereoselectivity observed in the rearrangement of α-branched esters (Scheme 1). This shortcoming became apparent to us when we chose the Ireland–Claisen rearrangement as an underlying strategy for the synthesis of the spiroimine core of gymnodimine and related natural products:[3,4] We envisaged the efficient formation of the sterically congested C7 and C22 stereocenters through the rearrangement of ester **3** (Scheme 1).



Scheme 1. The Ireland–Claisen rearrangement of α-branched esters as a strategy for the synthesis of the spiroimine core of gymnodimine and related natural products. PMB = *p*-methoxybenzyl, Pv = pivaloyl, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

For efficient chirality transfer to each of the two stereocenters that form upon the rearrangement of α-branched esters such as **3**, *E*/*Z*-selective enolization is required. Herein, we describe the only method developed to date that enables this type of stereoselective enolization,[5] as well as the application of this method to the Ireland–Claisen rearrangement and the enantioselective synthesis of the cyclohexene ring of gymnodimine.

Our initial experiments focused on the selective production of *E* or *Z* enolates from esters in which the difference in the steric and electronic properties of the α substituents R^1 and R^2 is minimal. The chirality of lithium amides **4**–**6** was used to control the stereoselectivity of deprotonation (Scheme 2).[6] The starting amines were selected for their ready availability. O'Brien and co-workers had described a particularly efficient synthesis of amines such as **7**, which can be prepared from inexpensive styrene oxide on a large scale with no chromatographic separation.[7] Importantly, the chiral amines are not consumed in the deprotonation reaction and can be recovered in high yield by simple extraction with aqueous acid.



Scheme 2. Practical synthesis of chiral amines **5** and **6** by the method developed by O'Brien and co-workers.[7] Ms = methanesulfonyl.

Although the stereogenic center at the α position of the ester is destroyed upon deprotonation, it is reintroduced as a quaternary stereogenic center through the [3,3] sigmatropic shift. Ester **8a** derived from commercially available (*S*)-2-methylbutyric acid served as the model substrate for a preliminary study of the deprotonation step (Table 1). In a control experiment, the treatment of **8a** with LDA followed by Me_3SiCl gave the *E* and *Z* isomers of the corresponding enolate with low selectivity (*Z*/*E* 2:1), as expected (Table 1,

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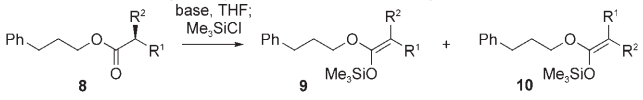
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 1: Preliminary study of the stereoselectivity of enolization.



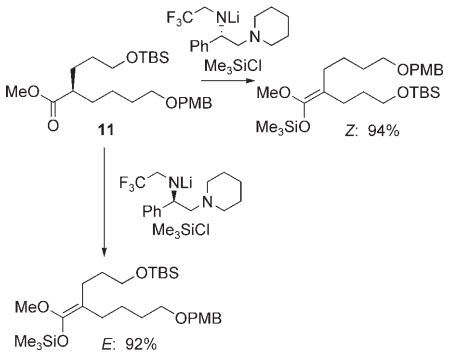
Entry	Ester	R^1	R^2	Base[a]	Z/E[b]
1	**8a**	CH_2CH_3	CH_3	LDA	67:33
2	**8a**	CH_2CH_3	CH_3	(*S*,*S*)-**4**	**95:5**
3	**8a**	CH_2CH_3	CH_3	(*R*,*R*)-**4**	21:79
4	**8a**	CH_2CH_3	CH_3	(*S*)-**5**	24:76
5	**8a**	CH_2CH_3	CH_3	(*R*)-**5**	92:8
6	**8a**	CH_2CH_3	CH_3	(*S*)-**6**	**8:92**
7	**8a**	CH_2CH_3	CH_3	(*R*)-**6**	92:8
8	**8b**	CH_3	CH_2CH_3	(*S*)-**6**	91:9
9	**8b**	CH_3	CH_2CH_3	(*R*)-**6**	8:92
10	**8c**	$(CH_2)_4OPMB$	$CH_2CH(CH_3)_2$	LDE	50:50
11	**8c**	$(CH_2)_4OPMB$	$CH_2CH(CH_3)_2$	LDA	82:18
12	**8c**	$(CH_2)_4OPMB$	$CH_2CH(CH_3)_2$	(*R*,*R*)-**4**	98:2
13	**8c**	$(CH_2)_4OPMB$	$CH_2CH(CH_3)_2$	(*S*,*S*)-**4**	75:25
14	**8c**	$(CH_2)_4OPMB$	$CH_2CH(CH_3)_2$	(*R*)-**5**	50:50
15	**8c**	$(CH_2)_4OPMB$	$CH_2CH(CH_3)_2$	(*S*)-**5**	>95:5
16	**8c**	$(CH_2)_4OPMB$	$CH_2CH(CH_3)_2$	(*R*)-**6**	**29:71**
17	**8c**	$(CH_2)_4OPMB$	$CH_2CH(CH_3)_2$	(*S*)-**6**	**>98:2**
18	**8d**	CH_2CH_3	CH_2Ph	LDA	65:35
19	**8d**	CH_2CH_3	CH_2Ph	(*R*,*R*)-**4**	**>98:2**

[a] LDA = lithium diisopropylamide, LDE = lithium diethylamide. [b] The ratio of isomers was determined by ^{1}H NMR spectroscopy at 500 MHz of the crude mixture of products. The configuration was established by NOE experiments.

entry 1). However, with (*S*,*S*)-**4** as the base, the *Z* silyl ketene acetal **9a** was produced selectively (95:5; Table 1, entry 2). The selectivity was reversed with (*R*,*R*)-**4** to afford predominantly the *E* isomer (79:21; Table 1, entry 3). Next, we explored the reactivity of amides **5** and **6** (Table 1, entries 4–7). Amide **6** exerted a higher degree of diastereoselectivity: Thus, the use of (*S*)-**6** led to the *E* isomer **10a** (91:9) as the major diastereomer, whereas (*R*)-**6** gave predominantly the *Z* silyl ketene acetal (92:8). Other substrates included in the preliminary investigation were esters **8c** and **8d**. Intriguingly, whereas the deprotonation of **8c** with lithium diethylamide (LDE) afforded a 1:1 mixture of **9c** and **10c**, enolization with LDA was relatively selective (82:12; Table 1, entry 11). The matched enantiomers of all three chiral bases showed excellent *Z* selectivity with **8c**, but only (*R*)-**6** was able to overcome the intrinsic selectivity for the *Z* silyl ether to give **9c** as the major isomer (71:29; Table 1, entry 16). The enolization of **8d** with (*R*,*R*)-**4** also proceeded with excellent selectivity to afford the *Z* silyl ether **10d**.

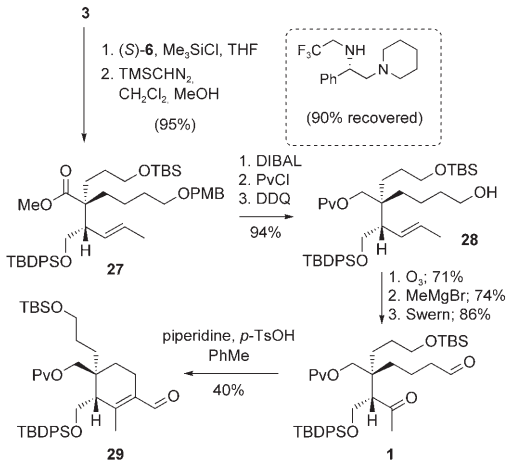
The enolization of ester **11** with (*S*)-**6** and (*R*)-**6** was investigated to evaluate the suitability of the chiral amine **6** as the base for the Ireland–Claisen rearrangement of **3** (Scheme 3). Although there is virtually no difference in the size of the α substituents of this ester, the *E* and *Z* enolates were generated with high stereoselectivity with the appropriate enantiomer of **6**.[8]

We then investigated the utility of the stereoselective enolization in the Ireland–Claisen rearrangement. A series of allylic esters were prepared and subjected to the standard rearrangement protocol in the presence of bases **4**–**6** (Table 2). The stereoselectivity of each reaction could be

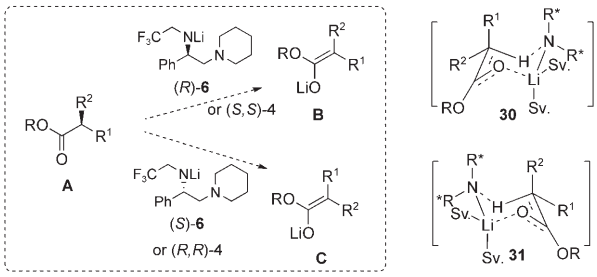


Scheme 3. Enolization of compound **11** as a model for ester **3**.

controlled by an appropriate chiral base. The chiral amines were recovered by extraction with acid in high yield. Thus, the rearrangement of ester **3** to **2** occurred in 95% yield, and (*S*)-**6** was recovered in 90% yield (Table 2, entry 9). Notably, α-branched esters in which the double bond involved in the sigmatropic rearrangement has the substitution pattern found in **14** and **15** give products with two contiguous all-carbon quaternary stereocenters with high diastereoselectivity (Table 2, entries 5–7). Overall, this transformation allows an efficient relay of chirality from readily accessible chiral allylic alcohols and α-branched carboxylic acids to new congested

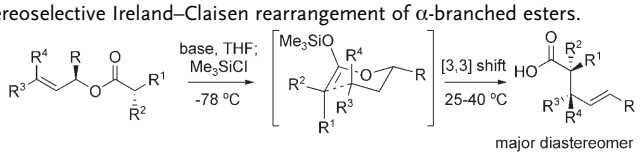


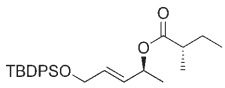
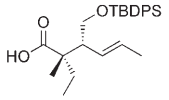
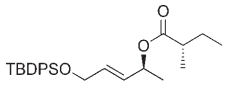
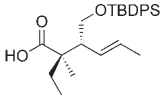
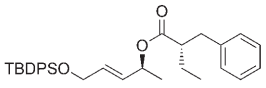
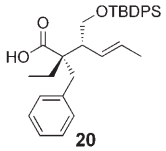
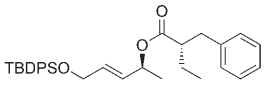
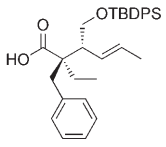
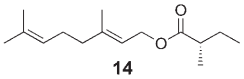
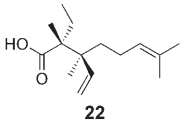
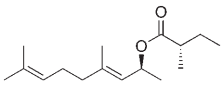
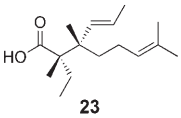
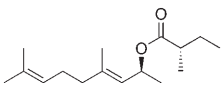
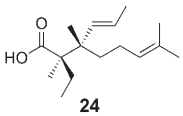
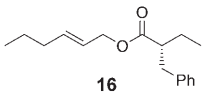
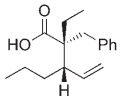
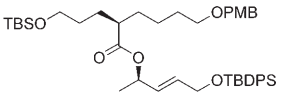
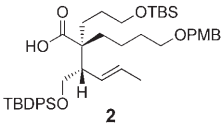
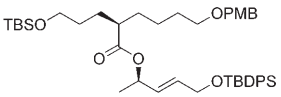
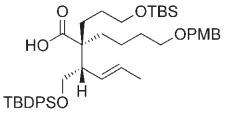
Scheme 4. Construction of the cyclohexene ring of gymnodimine. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBAL = diisobutylaluminum hydride, Ts = toluenesulfonyl, TMS = trimethylsilyl.



Scheme 5. An empirical predictive model for the stereoselective enolization. Sv. = solvent molecule.

Table 2: Diastereoselective Ireland–Claisen rearrangement of α-branched esters.



Entry	Base	Substrate[a]	Product[b]	Yield [%], d.r.[c]
1	(*S*,*S*)-**4**	 **12**	 **18**	85, 16:1
2	(*S*)-**6**	 **12**	 **19**	80, 5:1
3	(*S*,*S*)-**4**	 **13**	 **20**	82, >20:1
4	(*S*)-**6**	 **13**	 **21**	71, 3.5:1
5	(*S*,*S*)-**4**	 **14**	 **22**	95, 13:1
6	(*S*,*S*)-**4**	 **15**	 **23**	100, >20:1
7	(*S*)-**6**	 **15**	 **24**	85, 5:1
8	(*R*,*R*)-**4**	 **16**	 **25**	88, 7:1
9	(*S*)-**6**	 **17**	 **2**	95, 10:1
10	(*R*)-**6**	 **17**	 **26**	95, 5:1

[a] The preparation of the substrates is described in the Supporting Information. [b] The configuration was confirmed by derivatization and NOE experiments for selected compounds. [c] The ratio of isomers was determined by ^{1}H NMR spectroscopy at 500 MHz of the crude mixture of products.

stereocenters through the formation of a carbon–carbon bond.

Next, we applied the methodology to the synthesis of the cyclohexene ring of gymnodimine (Scheme 4). After the key rearrangement of **3**, the resulting acid was converted efficiently into ester **27** by treatment with diazomethane generated in situ. The reduction of **27** followed by protection of the primary alcohol and removal of the PMB group gave **28**.[9] Ozonolysis,[10] the addition of MeMgBr, and oxidation[11] then yielded **1**, which was subjected to an intramolecular aldol condensation: Ketoaldehyde **1** underwent cyclization to give **29** upon treatment with piperidine in the presence of *p*-toluenesulfonic acid in toluene.[12]

On the basis of our observations during this study, we propose an empirical model to predict the stereoselectivity of the enolization step and consequently of the Ireland–Claisen rearrangement (Scheme 5). If the α substituents R^1 and R^2 in the ester are similar alkyl groups and the substrate is drawn as structure **A**, the amide base (*R*)-**6** will produce enolate **B** preferentially, whereas (*S*)-**6** will give enolate **C**. This model is in agreement with all our current results, and further studies are under way to test its validity.

The reasons for the observed selectivity are unclear at present, although the transition structures for enolization proposed by Ireland et al. served as inspiration for the development of this methodology.[1b] We speculated that if the enolate configuration is determined by a highly organized transition structure during the proton transfer, groups R^1 and R^2 would have little influence on whether a structure of type **30** or type **31** is preferred. On the other hand, chiral substituents on the amide nitrogen atom may have a more profound effect on the relative energies of **30** and **31**, and the presence of such substituents may lead to a selective enolization step. The precise interactions responsible for the observed selectivity will be the subject of further studies.

In summary, we have developed a diastereoselective Ireland–Claisen rearrangement of α-branched allylic esters through an unprecedented stereoselective enolization. A high level of selectivity was observed when the chirality of the ester substrates and lithium amide bases were matched. The stereodefined enolates could

potentially serve as intermediates in other asymmetric transformations in which enolate geometry dictates stereoselectivity.

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Keywords: chiral amines · diastereoselectivity · enolization · Ireland–Claisen rearrangement · synthetic methods

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