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Highly diastereoselective Lewis acid promoted Claisen–Ireland rearrangement

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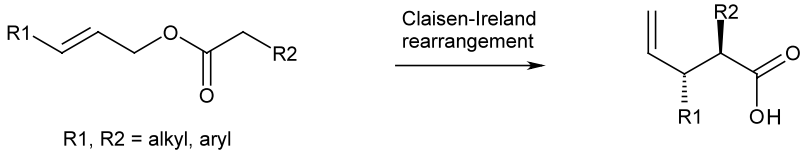
Abstract—In the presence of catalytic amounts of Lewis acids silyl ketene acetals of *trans* allylic esters undergo a highly diastereoselective Claisen–Ireland rearrangement to the corresponding disubstituted γ-δ-unsaturated *erythro* carboxylic acids. Diastereoselectivities of up to 15:1 were achieved when using $TiCl_4$ as catalyst. The uncatalyzed process proceeds slowly and with significantly lower selectivity. A wide range of aryl- and alkyl-substituents are tolerated.

The Ireland ester enolate Claisen rearrangement and variants thereof are powerful carbon–carbon bond forming processes for the control of acyclic stereochemistry. Among the many possible synthetic methodologies available for the construction of vicinal stereocenters, the Claisen rearrangement is one of the most predictable and widely used. In addition, this methodology allows simple introduction of aryl substituents. Our research in the area of matrix metalloproteinase inhibitors has focused on the synthesis of chiral vicinal disubstituted γ-δ-unsaturated carboxylic acid scaffolds **2**. The interest in alkyl- and aryl-substituted derivatives of **2** prompted us to explore the Claisen–Ireland rearrangement of allylic esters **1** as the key step according to Scheme 1.

The allylic esters **1** were synthesized by standard protocols from primary allylic alcohols and carboxylic acids or if commercially available acid chlorides.[1] Initial rearrangement experiments were carried out under standard conditions.[2,3] For allylic esters of phenyl acetic acids long reaction times and high temperatures were required to achieve full conversion. As a result, low selectivities and variable yields were observed. From online FT–IR studies and literature precedence,[4] we concluded that the moderate conversion could be the result of thermic decomposition of the silyl ketene acetal intermediate. A related problem was addressed by Kazmeier et al.[5] by using zinc or magnesium salts to stabilize the enolates of amino acid-derived substrates through chelation.

Corey and Lee have demonstrated that the use of stoichiometric amounts of chiral bromoborane controller reagents results in a highly enantioselective rearrangement of allylic esters.[6] We closely investigated the application of Lewis acid catalysis to optimize the Claisen–Ireland rearrangement (Scheme 2).

Indeed, the addition of catalytic amounts of Lewis acids to the silyl ketene acetal of **3** turned out to be beneficial in terms of both yield and selectivity. A selection of Lewis acids was initially screened using the model reaction shown in Scheme 2. The results are



R1, R2 = alkyl, aryl

1 **2**

Scheme 1.

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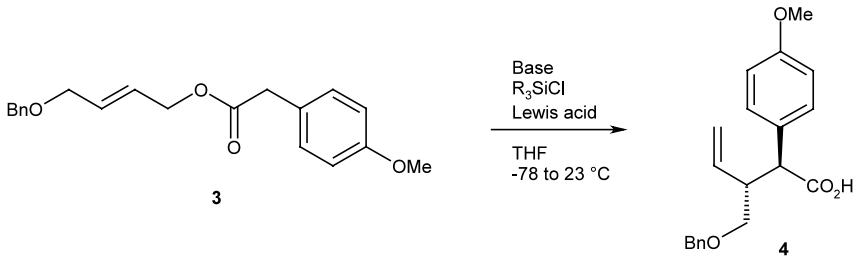


Scheme 2.

summarized in Table 1. The Ireland Claisen rearrangement proceeded smoothly and is reproducible in all cases while allowing the reaction mixture to warm from −78°C to room temperature.

It is known from the literature that the enolate geometry which determines the selectivity of the Ireland–Claisen product is dependent on the nature of the base. Thus, we studied the influence of the deprotonation step on the stereochemistry of the product. The results are summarized in Table 2. The highest yield and *erythro*/*threo* ratio was achieved with lithium bis(trimethylsilyl)amide (LHMDS, entry 2) followed by the lithium salts of 2,2,6,6-tetramethylpiperidine (LTMP, entry 3), isopropylcyclohexylamine (LICA, entry 5) and diisopropylamine (LDA, entry 1). The reaction completely failed when potassium bis(trimethylsilyl)amide (KHMDS, entry 4) was used.

In the next step we looked at the influence of the size of the chlorosilanes (Table 3). Bulky groups e.g. *t*-butyldimethylsilyl (TBS, entry 3) lead to lower diastereoselectivities and lower yields, whereas triethylsilyl (TES, entry 2) gave comparable results to trimethylsilyl (TMS, entry 1). Varying the amounts of base and/or chlorosilane in the range of 1.1–1.5 had no significant effect on the outcome of the reactions (data not presented).

The highest stereoselectivity and excellent yield was observed when LHMDS was used in combination with TMSCl in the presence of catalytic amounts (2%) of $TiCl_4$. These reaction conditions[7] were applied to the synthesis of diverse γ-δ-unsaturated carboxylic acid scaffolds. Representative examples including yields and selectivities are summarized in Table 4.

In summary, the addition of catalytic amounts of Lewis acids vastly accelerates the Claisen–Ireland rearrange-

Table 1. Lewis acids

Entry	Base	[equiv.]	SiR_3Cl	[equiv.]	Catalyst	[mol%]	Yield [%]	*erythro*/*threo*
1[a]	LDA	1.5	TMSCl	1.5	None		75	2:1
2	LDA	1.5	TMSCl	1.5	TMSOTf	10	98	5:1
3	LDA	1.5	TMSCl	1.5	$BF_3{\cdot}OEt_2$	10	78	5:1
4	LHMDS	1.5	TMSCl	1.5	$TiCl_4$	2	95	12:1
5	LHMDS	1.3	TMSCl	1.3	$Ti(O\textit{i}\text{-}Pr)_4$	5	84	7:1
6	LHMDS	1.3	TMSCl	1.3	$ZnCl_2$	5	89	10:1
7	LHMDS	1.3	TMSCl	1.3	$SnCl_4$	5	95	12:1

[a] In the absence of Lewis acids, the reaction required heating to reflux.

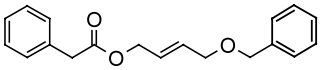
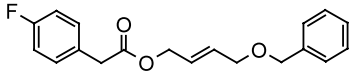
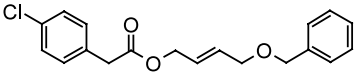
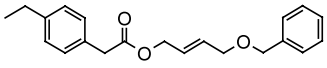
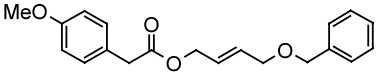
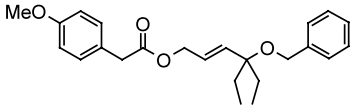
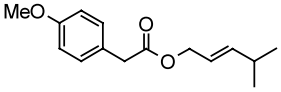
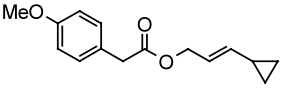
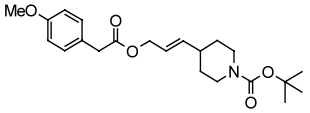
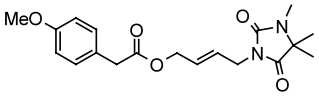
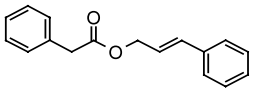
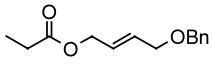
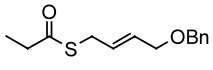
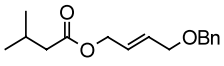
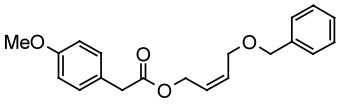
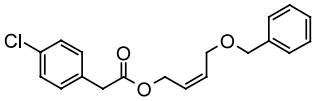
Table 2. Bases

Entry	Base	[equiv.]	SiR_3Cl	[equiv.]	Catalyst	[mol%]	Yield [%]	*erythro*/*threo*
1	LDA	1.1	TMSCl	1.1	$TiCl_4$	2	42	3:1
2	LHMDS	1.5	TMSCl	1.5	$TiCl_4$	2	95	12:1
3	LTMP	1.3	TMSCl	1.3	$TiCl_4$	2	75	8:1
4	KHMDS	1.2	TMSCl	1.2	$TiCl_4$	2	0	Na
5	LICA	1.2	TMSCl	1.2	$TiCl_4$	2	70	5:1

Table 3. Chlorosilanes

Entry	Base	[equiv.]	SiR_3Cl	[equiv.]	Catalyst	[mol%]	Yield [%]	*erythro*/*threo*
1	LHMDS	1.5	TMSCl	1.5	$TiCl_4$	2	95	12:1
2	LHMDS	1.2	TESCl	1.2	$TiCl_4$	2	91	12:1
3	LHMDS	1.2	TBSCl	1.2	$TiCl_4$	2	38	2:1

Table 4. Representative examples

Entry	Ester	Yield [%]	*erythro* /*threo*
1		99	12:1
2		99	11:1
3		85	9.5:1
4		58	10:1
5		99	14:1
6		40	8:1
7		90	5:1
8		77	7:1
9		66	15:1
10		96	10:1
11		92	11:1
12		83	2:1
13		73	>15:1
14		0	
15		68	1:6
16		57	1:4

ment of allylic esters. This new methodology is particularly useful for the rearrangement of aryl acetates and tolerates a variety of aryl substituents (entries 1–5). The reaction is compatible with a wide range of allyl derivatives. Sterically demanding (entries 6–8) as well as heterocyclic (entries 9 and 10) or aromatic substituents (entry 11) are well tolerated. Even a thioester (entry 13) was rearranged with surprisingly high selectivity. However, the isobutyric acetate (entry 14) completely failed to react. The *cis* allylesters (entries 15 and 16) gave the expected *threo* isomers as the main products, although with slightly lower selectivity. Mechanistic investigations using online FT–IR spectroscopy did not allow us to explain the nature of the Lewis acid effect.

Acknowledgements

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References

1. Method A: acid chloride (1.0 equiv.), allylic alcohol (1.0 equiv.), pyridine (1.1 equiv.), CH_2Cl_2, 0°C; Method B: carboxylic acid (1.0 equiv.), allylic alcohol (1.0 equiv.), DCC (1.0 equiv.), DMAP (10 mol%), toluene, 23°C.
2. Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897.
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4. For reviews of these compounds, see (a) Poirier, J. *Org. Prep. Proced. Int.* **1988**, *20*, 319; (b) Brownbridge, P. *Synthesis* **1983**, 85; (c) Rasmussen, J. K. *Synthesis* **1977**, 91.
5. Kazmaier, U.; Maier, S. *Tetrahedron* **1996**, *52*, 941.
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7. Typical experimental procedure: A solution of 38.4 mL (184.3 mmol) 1,1,1,3,3,3-hexamethyldisilazane in 100 mL of THF was treated with *n*-hexyllithium (63.65 g, 184.0 mmol, 26.6% in hexanes) at 0°C over a period of 14 min. The LHMDS solution was stirred for 5 min and cooled to −78°C. Then chlorotrimethylsilane (23.3 mL, 184.0 mmol)

was added over 15 min. To the resulting mixture a solution of ester **3** (50.0 g, 153.2 mmol) in 50 mL of THF was slowly added (43 min). The reaction mixture was treated with 0.31 mL (0.31 mmol) of a $TiCl_4$ solution (1.0 M in toluene), warmed to 23°C over 90 min and stirred at rt for 1 h. The reaction was quenched by the addition of a 1.0 M solution of NaOH (400 mL). The layers were separated and the organic layer was extracted once with 72 mL of 1.0 M NaOH. The combined aqueous solutions were acidified to pH 1.0 by slow addition of 5% HCl (390 mL) at 0°C. Then 286 mL of toluene were added, the layers were separated and organic solution was concentrated in vacuo to afford 38.35 g (77%) of a yellow oil (*anti*/*syn* = 13:1 (HPLC)) of acid **4**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13–3.18 (m, 1H), 3.43 (dd, J = 9.4, 6.2 Hz, 1H), 3.56 (dd, J = 9.4, 5.3 Hz, 1H), 3.72–3.78 (m, 1H), 3.75 (s, 3H), 4.47 (s, 2H), 4.94 (dd, J = 15.5, 12.3 Hz, 2H), 5.48 (ddd, J = 15.5, 12.3, 8.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H), 7.27–7.30 (m, 5H), 8.60–9.80 (s, br, 1H).