Silyl-modified Belluš–Claisen rearrangement†

Donald Craig,*[a] N. Paul King[b] and David M. Mountford[a]

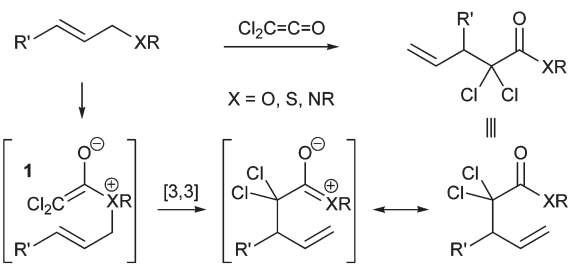
Received (in Cambridge, UK) 6th October 2006, Accepted 9th November 2006
First published as an Advance Article on the web 21st December 2006
DOI: 10.1039/b614535c

A silyl-modified variant of the Belluš–Claisen rearrangement is described; the generality of this rearrangement has been demonstrated with a range of allylic amines and ketenes.

The Claisen rearrangement[1] has found widespread use in synthetic organic chemistry due to the stereospecific and highly stereoselective nature of the [3,3]-sigmatropic carbon–carbon bond-forming process. Modern variants of this rearrangement[2] have ensured the continued prominence of this powerful organic synthesis tool, which allows access to a range of carboxylic acid derivatives, depending on the reaction mode employed.

We have begun a new programme to investigate, in-depth, the effect of stereocentres outside the six-membered pericyclic array upon the stereochemical outcome of Claisen rearrangements.[3] The Belluš–Claisen rearrangement[4,5] was selected as the basis of the new study.[6] In this version of the transformation, the highly reactive electrophile dichloroketene is intercepted by an allylic ether, thioether or tertiary amine, and the resulting zwitterionic intermediate, **1**, undergoes a spontaneous [3,3]-sigmatropic rearrangement to form the corresponding α,α-dichloro-substituted ester, thiol ester or tertiary amide (Scheme 1).

Our initial studies focused on the Lewis acid-assisted version of the Belluš–Claisen rearrangement,[6c,6d,7] in which reactions of less highly activated ketenes with allylic tertiary amines deliver γ,δ-unsaturated tertiary amide products in excellent yields. Whilst our initial findings confirmed that the use of $TiCl_4$ yielded rearranged products for a range of simple allylic tertiary amines and *in situ* generated ketenes,[7] reactions of more complex allylic amines containing protected heteroatoms resulted in either decomposition or recovery of starting material when $TiCl_4$ was used. We ascribed this failure to competing interactions of the Lewis basic groups with the powerful Lewis acid, and an alternative metal-free approach was sought, in which these unwanted interactions might be avoided.



Scheme 1 The Belluš–Claisen rearrangement.

We envisaged combining zwitterion-like motif **2** of the Lewis acid-assisted Belluš–Claisen rearrangement with the silyl ketene acetal moiety of the Ireland–Claisen intermediate **3** to generate a hybrid array **4** (Fig. 1). It was anticipated that silylation of a ketene generated *in situ* with trimethylsilyl triflate (TMSOTf) would sufficiently activate the ketene towards interception by the allylic amine, thereby enabling Claisen rearrangement to take place without the need for a powerful Lewis acid such as Me_3Al[6c,6d] or $TiCl_4$.[7]

Treatment of a mixture of amine **5**,[8] TMSOTf and Hünig's base with phenylacetyl chloride, propionyl chloride or dichloroacetyl chloride using the modified conditions gave, respectively, the rearranged products **7–9** in good yields. It seems likely that the ketenes generated *in situ* are activated by TMSOTf prior to interception by the allylic amine to give intermediates **6**. [3,3]-Sigmatropic rearrangement then gives rise to the unstable iminium species **10**, which readily collapse with concomitant loss of the silyl group to give **7–9** (Scheme 2).‡

For comparison purposes, all three transformations were carried out with TMSOTf, $TiCl_4$ and $TiCl(OTf)_3$[9] as Lewis acidic additives (Table 1). These results show that TMSOTf performs

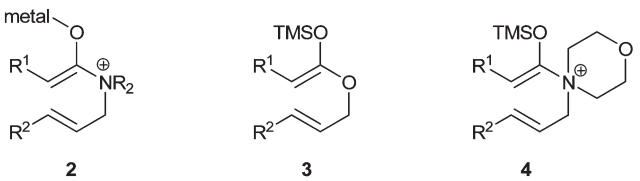
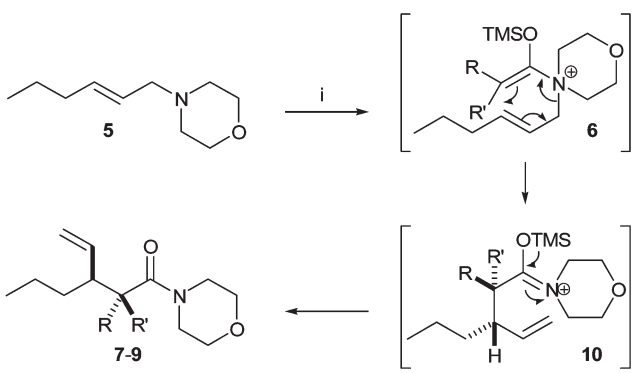


Fig. 1 Claisen rearrangement intermediates.

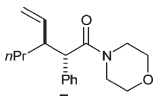
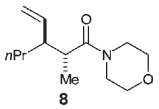
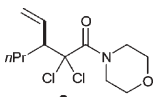


Scheme 2 *Reagents and conditions*: RR′CHCOCl (1.2 equiv.), TMSOTf (1.0 equiv.), iPr_2NEt (1.5 equiv.), CH_2Cl_2, rt, 4.5 h.

[a]*Department of Chemistry, Imperial College London, South Kensington Campus, London, UK SW7 2AZ. E-mail: d.craig@imperial.ac.uk; Fax: +44 (0)20 7594 5868; Tel: +44 (0)20 7594 5771*
[b]*Neurology and GI Centre of Excellence for Drug Discovery, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex, UK CM19 5AW*

† Electronic supplementary information (ESI) available: Experimental details and full spectroscopic data for all allylic amines and rearrangement products. See DOI: 10.1039/b614535c

Table 1 Silyl-modified Belluš–Claisen rearrangement of **5**

	Acid Chloride			Yield (%)[a]		
Entry	R	R′	Product	TMSOTf[b]	$TiCl_4$[c]	$TiCl(OTf)_3$[d]
1	Ph	H	 **7**	74	79	84
2	Me	H	 **8**	83	58	96
3	Cl	Cl	 **9**	57	44	64

[a] Products **7** and **8** were obtained as single diastereoisomers. All reactions were carried out at rt with 1.5 equiv. iPr_2NEt and 1.2 equiv. RR′CHCOCl. [b] 1.0 equiv. TMSOTf, 4.5 h. [c] 0.1 equiv. $TiCl_4$, 1 h. [d] 0.1 equiv. $TiCl(OTf)_3$, 7 h.

similarly to $TiCl(OTf)_3$, and that it gives better yields than $TiCl_4$ in two of the three cases studied.[10] Interestingly, the lowest yields in these reactions were obtained for dichloroketene, which is the least nucleophilic of the three ketenes evaluated. Substitution of TMSOTf with the bulkier TBDMSOTf in the reaction of **5** with phenylacetyl chloride caused a reduction in yield of **7** to 30%, and use of TIPSOTf and TMSCl resulted in the recovery only of **5**. Reducing the amount of TMSOTf used to 0.1 equiv. gave 44% **7** and 48% recovered **5**, suggesting that whilst some turnover of TMSOTf takes place, catalyst decomposition is a significant process. We speculate that this arises through the interception of TMSOTf by chloride ions, which generates rearrangement-inactive TMSCl.

In the case of amide **7**, the assignment of *anti*-stereochemistry followed from X-ray crystallographic analysis (Fig. 2).§[11] The stereochemistry of **8** was inferred from that of **7**. We rationalise the stereochemistry of formation of **7** and **8** in terms of the intermediacy of a *Z*-intermediate **6**, formed by attack of amine **5** on the silylated ketene in an *anti*-sense with respect to the R group. Rearrangement then takes place *via* a chair-like six-membered transition-state (Scheme 3).

The proven *anti*-stereochemistry of amide **7** is in contrast with the findings of Nubbemeyer *et al.*,[6d] who reported that in trimethylaluminium-assisted Belluš–Claisen rearrangements involving pyrrolidine-containing tertiary amines, the use of phenylacetyl chloride gave *syn*-diastereoisomers, whereas propionyl chloride

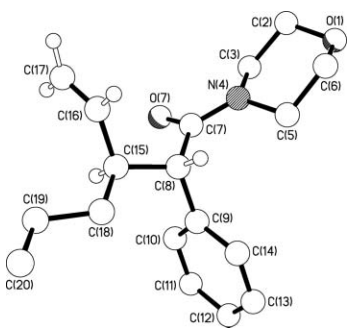
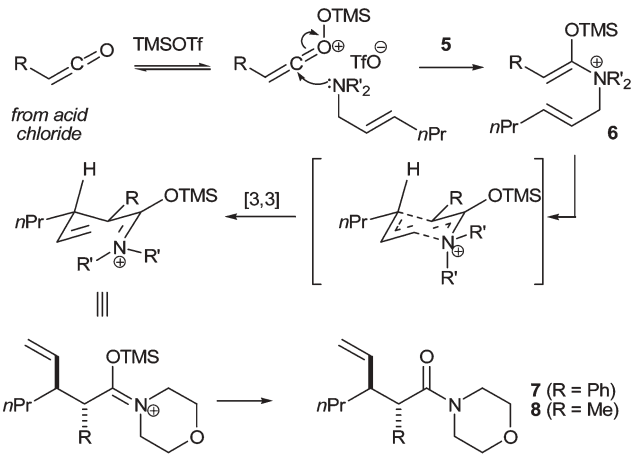


Fig. 2 The molecular structure of **7**.



Scheme 3 Rationale of observed stereoselectivity.

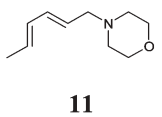
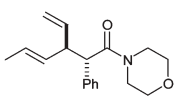
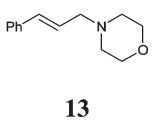
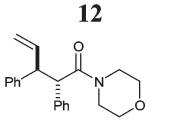
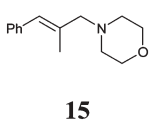
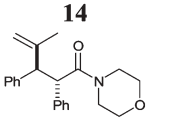
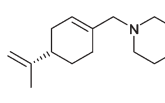
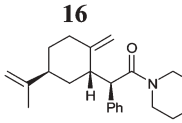
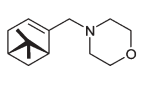
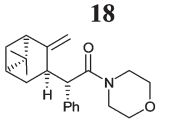
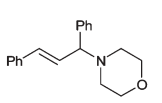
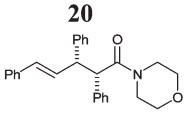
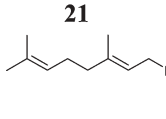
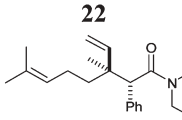
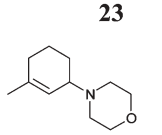
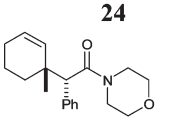
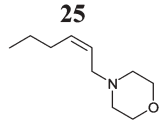
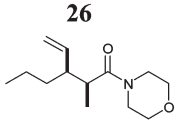
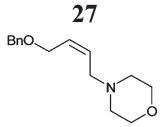
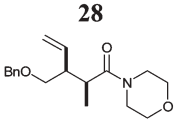
gave the corresponding *anti*-products. Product stereochemistry was assigned indirectly in these two transformations by analysis of the derived α,β-*anti*- and α,β-*syn*-γ-lactones, respectively, made by acid-catalysed cyclisation followed by base-mediated silylation. We speculate that in Nubbemeyer's work, the phenyl-bearing stereocentre may have undergone epimerisation to the sterically more favourable α,β-*anti*-isomer during the ring closure or silyl protection steps.

The new silyl-modified Belluš–Claisen rearrangement conditions were next applied to a range of allylic tertiary amines. The amines were prepared in excellent yields by treatment of the corresponding allylic alcohols with PPh_3–NBS–morpholine as before.[7b] The exposure of mixtures of amine, Hünig's base and TMSOTf to phenylacetyl chloride or propionyl chloride yielded the corresponding rearranged amides in good-to-excellent yields with high and sometimes complete stereoselectivity (Table 2).

Some trends emerge from the data collected in Table 2. The stereochemistry of all of the amide products may be rationalised in terms of the chair-like transition-state model depicted in Scheme 3. The presence of *exo*-pericyclic stereocentres was investigated with allylic amines **17** and **19** (Table 2, entries 4 and 5); both amines successfully underwent rearrangement to yield the corresponding amides **18** and **20** as single diastereomers, which corresponds to delivery of the carboxamide-containing moiety to the less sterically-crowded face of the allylic double bond. The successful rearrangement of substrates **23** and **25** (Table 2, entries 7 and 8) demonstrates that quaternary carbon atoms may be accessed using this chemistry, though the relatively low yield of the conversion of **25** into **26** may reflect the reduced nucleophilicity of the amine on account of steric crowding. In this context, subjection of *Z*-allylic amine **27** to a reaction with phenylacetyl chloride (Table 2, entry 9) gave the phenyl analogue of **28** in only 19% yield. The low yield of the reaction of *Z*-substrate **29** (Table 2, entry 10), even with the more reactive propionyl chloride-derived ketene, may be indicative of the combined effects of the *Z*-double bond and the electron-withdrawing benzyloxy substituent, both of which serve to attenuate amine nucleophilicity. No rearrangement product was obtained when **29** was exposed to phenylacetyl chloride under the standard conditions.

In summary, our investigations have led to the development of a metal-free variant of the Lewis acid-assisted Belluš–Claisen

Table 2 Silyl-modified Belluš–Claisen rearrangement of allylic amines

Entry	Substrate	Product[a,b]	Diastereomer ratio (%)[c]	Yield (%)
1	 **11**	 **12**	100 : 0	79
2	 **13**	 **14**	88 : 12	90
3	 **15**	 **16**	83 : 17	56
4	 **17**	 **18**	100 : 0	76
5	 **19**	 **20**	100 : 0	73
6	 **21**	 **22**	80 : 20	79
7	 **23**	 **24**	97 : 3	89
8	 **25**	 **26**	100 : 0	49
9	 **27**	 **28**	100 : 0	79
10	 **29**	 **30**	100 : 0	39

[a] All reactions were carried out at rt with 1.5 equiv. iPr$_2$NEt, 1.2 equiv. PhCH$_2$COCl or MeCH$_2$COCl and 1.0 equiv. TMSOTf, 4.5 h. [b] Major diastereoisomer shown. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture.

rearrangement. The generality of the rearrangement has been demonstrated with a range of structurally diverse allylic amines and ketenes. Ongoing work is concerned with improving the sub-stoichiometric process and investigating the effect of *exo*-pericyclic stereocentres in acyclic substrates, and the results of these investigations will be reported in due course.

The authors thank EPSRC/GlaxoSmithKline (supported DTA studentship to D. M. M.) for support.

Notes and references

‡ *Typical experimental procedure for the silyl-modified Belluš–Claisen rearrangement of allylic amines:* To a solution of the allylic amine (1.18 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) at rt was added TMSOTf (1.18 mmol, 1.0 equiv.), followed by *N*,*N*-diisopropylethylamine (1.77 mmol, 1.5 equiv.). The solution was stirred for 5 min before a solution of phenylacetyl chloride (1.42 mmol, 1.2 equiv.) in CH_2Cl_2 (5 mL) was added dropwise over 4 h. The resulting mixture was stirred for 30 min. The reaction was then diluted with diethyl ether (10 mL), treated with aqueous NaOH (1 M; 5 mL) and stirred for a further 10 min. The aqueous layer was extracted with diethyl ether (3 × 20 mL), the combined organic layers washed with brine (3 × 10 mL), and dried with Na_2SO_4. Concentration under reduced pressure and chromatography (30% ethyl acetate–petroleum ether) gave the corresponding amide.

§ *Crystal data for* **7**: $C_{18}H_{25}NO_2$, M = 287.39, orthorhombic, a = 6.122(3), b = 15.768(2), c = 17.431(2) Å, β = 90°, U = 1682.7(8) Å^3, T = 293(2) K, $P2_12_12_1$, Z = 4, μ = 0.574 mm^{-1}, R_{int} = 0.0000, $R1$ = 0.0816, w$R2$ = 0.1679 (all data). CCDC 623206. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b614535c

1 (*a*) L. Claisen, *Chem. Ber.*, 1912, **45**, 3157; (*b*) For a recent, comprehensive review of the Claisen rearrangement, see: A. M. M. Castro, *Chem. Rev.*, 2004, **104**, 2939(*c*) See also: *The Claisen Rearrangement: Methods and Applications*, ed. M. Hiersemann and U. Nubbemeyer, Wiley-VCH, Weinheim, 2006.

2 (*a*) A. E. Wick, D. Felix, K. Steen and A. Eschenmoser, *Helv. Chim. Acta*, 1964, **47**, 2425; (*b*) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-T. Li, D. J. Faulkner and M. R. Petersen, *J. Am. Chem. Soc.*, 1970, **92**, 741; (*c*) R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, 1972, **94**, 5897.

3 For examples, see: (*a*) J. K. Cha and S. C. Lewis, *Tetrahedron Lett.*, 1984, **25**, 5263; (*b*) T. Suzuki, E. Sato, S. Kamada, H. Tada, K. Unno and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1986, 387; (*c*) J. R. Hauske and S. M. Julin, *Tetrahedron Lett.*, 1993, **34**, 4909.

4 (*a*) R. Malherbe and D. Belluš, *Helv. Chim. Acta*, 1978, **61**, 3096; (*b*) R. Malherbe, G. Rist and D. Belluš, *J. Org. Chem.*, 1983, **48**, 860.

5 For a review of the Belluš–Claisen rearrangement, see: J. Gonda, *Angew. Chem., Int. Ed.*, 2004, **43**, 3516.

6 For previous examples of 1,2-*exo*-pericyclic stereoselectivity in Belluš–Claisen rearrangement reactions, see: (*a*) U. Nubbemeyer, R. Öhrlein, J. Gonda, B. Ernst and D. Belluš, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1465; (*b*) U. Nubbemeyer, *J. Org. Chem.*, 1995, **60**, 3773; (*c*) U. Nubbemeyer, *J. Org. Chem.*, 1996, **61**, 3677; (*d*) B. Ernst, J. Gonda, R. Jeschke, U. Nubbemeyer, R. Öhrlein and D. Belluš, *Helv. Chim. Acta*, 1997, **80**, 876; (*e*) J. Gonda, M. Martinkova, B. Ernst and D. Belluš, *Tetrahedron*, 2001, **57**, 5607.

7 (*a*) T. P. Yoon, V. M. Dong and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 1999, **121**, 9726; (*b*) T. P. Yoon and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2001, **123**, 2911.

8 Amine **5** was synthesised from (*E*)-2-hexen-1-ol by treatment with morpholine, PPh_3 and *N*-bromosuccinimide. See ref. 7*b*.

9 S. Kobayashi, M. Moriwaki and I. Hachiya, *Bull. Chem. Soc. Jpn.*, 1997, **70**, 267.

10 A recent report describes the failure of TMSOTf, in combination with an unspecified base, to effect an aza-Claisen rearrangement of a prolinol-derived allylic amine. See: Q. Xu and E. Rozners, *Org. Lett.*, 2005, **7**, 2821.

11 We thank Dr. Andrew J. P. White (Department of Chemistry, Imperial College) for the X-ray determinations.