

Asymmetric synthesis of δ -keto esters *via* Michael additions of chiral carbene complexes

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The asymmetric Michael addition of the enolates of chiral imidazolidinone carbene complexes to α,β -unsaturated ketones occur with high induction.

The asymmetric synthesis of δ -keto esters of type **1** could in principle be accomplished either by the Michael addition of a chiral ester enolate equivalent to an enone or by the Michael addition of a chiral ketone equivalent to an enolate.¹ In practice, the only viable and widely applicable method developed to date is that of Enders involving the addition of the enolates of chiral hydrazones to α,β -unsaturated esters.^{2–5} An alternative approach involving the addition of a chiral acetate enolate equivalent to an α,β -unsaturated ketone is not useful, although several groups have described the successful use of the anions of chiral allylic phosphonates and chiral allylic sulfoxides as chiral acetate enolate surrogates.⁶ We report that the enolates of chiral imidazolidinone carbene complexes give high inductions in their additions to α,β -unsaturated ketones and serve as convenient chiral acetate enolate equivalents since the adducts can be easily and efficiently cleaved to give δ -keto esters **1**.[†]

The reaction of the enolate of acetophenone with the *trans*-propenyl imidazolidinone complex **10**[‡] at -20°C gave a 3:1 mixture of the diastereoisomers of **11c** with the 3*R* isomer predominating.[§] This low selectivity was disappointing given the high *syn*-selectivity observed for non-chiral complexes of the type **10**,⁹ but perhaps understandable in terms of structure **6** which is thought to react *via* an *s-cis* conformation. Based on this model it was expected that the enolate **7**, derived from **12**, would have the centre for new carbon–carbon bond formation much closer to the chiral centre and thus provide for greater asymmetric introduction. Indeed the reaction of the enolate of the methyl imidazolidinone carbene complex **12** with *trans*-1-phenylbut-2-enone gives the same product **11c** with $\geq 97:3$ selectivity that is inverted to favour the 3*S* isomer (Table 1, entry 12).¹⁰ Michael addition of the enolate of **12** was examined with a number of enones and as indicated in Table 1 the 3*S* isomer is produced in each case with at least a 96:4 selectivity

with the exception of *trans*-pent-3-en-2-one, where the selectivity was 88:12.[¶] Slight increases in selectivity are seen for enones with increasing size of substituents R^1 and R^2 and loss of reactivity is seen when both substituents are *tert*-butyl. The stereoselectivity of the Michael additions of the enolate of **12** to enones was found to have an inverse temperature dependence and this was investigated in detail for addition to *trans*-4-phenylbut-3-en-2-one. The selectivity for addition to this enone is maximum at -20°C giving a 94:6 selectivity in favour of the 3*S* isomer but drops to 86:14 when carried out at -60°C . This effect appears to be associated with the enolate of **12**¹¹ since the Michael addition to the α,β -unsaturated complex **10** does not exhibit a similar temperature dependence.[§]

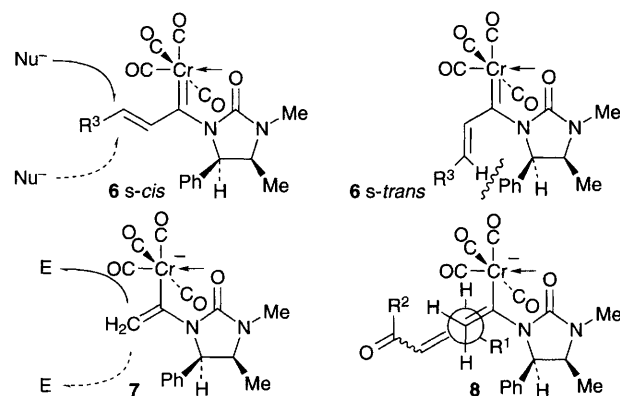


Fig. 1

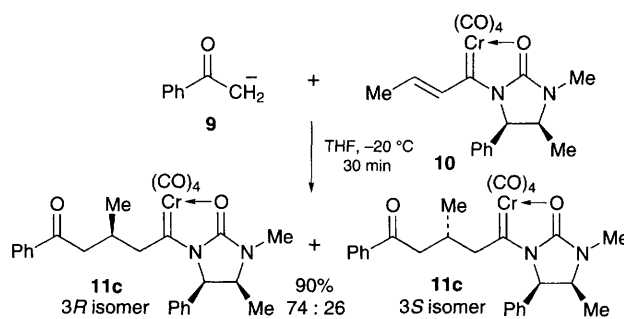
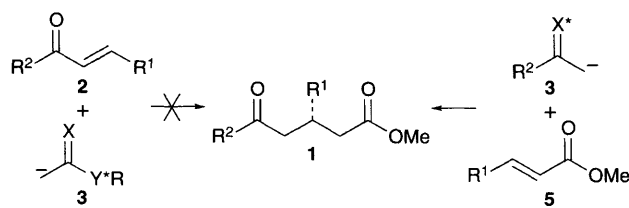
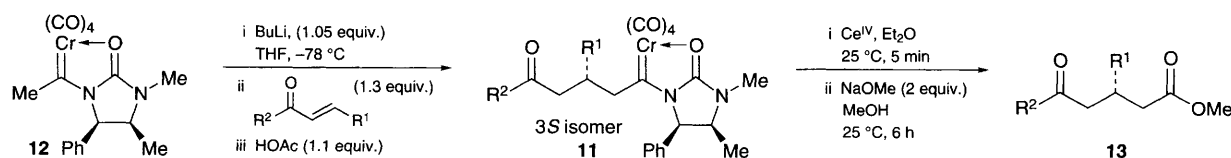


Fig. 2



Scheme 1



Scheme 2

Table 1 Asymmetric synthesis of δ -keto esters^a

R ¹	R ²	Initial temp/°C	Final temp/°C	Time	Additive ^b	Product series	Yield 11 ^c (%)	Ratio ^d S : R	Recovery 12 (%)	Yield 13 ^e (%)	[α] _D of 13
Ph	Me	−78	0	100 min	none	a	93 ^f	92 : 8 (93 : 7)		81	−22.35 ^g
		0	0	10 min			87	88 : 12			
		−20	−20	2 h			91	94 : 6			
		−40	−40	10 h			86	91 : 9			
		−60	−60	24 h			85	86 : 14			
		−20	−20	5 min	MAD ^h		56(76)	87 : 13	26		
		−78	−78	10 min	MAD ^h		64(82)	≥96 : 4 (97 : 3)	22		
		−78	−78	10 min	MAD ⁱ		18(37)	88 : 12 (88 : 12)	51		
Me	Me	−20	−20	30 min	none	b	46(59)	88 : 12	22	72	1.70 ^j
		−78	−78	30 min	MAD ⁱ		87	54 : 46	2		
Me	Ph	−78	−20	2 h	none	c	85	95 : 5 (95 : 5)		83	−5.65 ^k
		−20	−20	10 min			65(87)	> 97 : 3	25		
Me	Pri ^l	−78	0	2 h		d	90	96 : 4 (96 : 4)		83	9.4 ^l
Me	Bu ^l	−78	0	2 h		e	91	97 : 3 (97 : 3)		87	2.97 ^m
Bu ^l	Bu ^l	−78	25	4 h		f	00	—	85		

^a All enones were ≥95% *E*-isomers. ^b 1.3 equiv. methyl aluminium bis(di-2,6-*tert*-butyl-4-methylphenoxide), ref. 11. ^c Isolated yield of 3*S* isomer plus isolated yield of 3*R* isomer except for **11b** where the isomers could not be separated on silica gel. Yields in parentheses based on unrecovered **12**. ^d Ratio determined by ¹³C NMR on crude reaction mixture. Ratios in parentheses are of the isolated 3*S* and 3*R* diastereoisomers. ^e Yield from purified 3*S* isomer except **13b** which was obtained by oxidation of 88 : 12 mixture of **11b**. In each case the chiral auxiliary (4*R*,5*S*)-(−)-1,5-dimethyl-4-phenyl-2-imidazolidinone was isolated with 81–90% recovery. ^f Stereochemistry of 3*S* isomer of **11a** was determined by X-ray analysis. ^g (*c* 2.09, benzene), lit. value −23.1 (benzene), ref. 5(a). ^h Transfer of enolate of **12** (0.07 mol dm^{−3} in THF) to enone–MAD mixture (0.31 mol dm^{−3} in CH₂Cl₂). ⁱ Transfer of enone–MAD mixture (0.05 mol dm^{−3} in CH₂Cl₂) to enolate of **12** (0.07 mol dm^{−3} in THF). ^j (*c* 5.0, Et₂O), rotation taken on material obtained from 88 : 12 mixture of 3*S* and 3*R* isomers; lit. value for 3*R* isomer of **13b**, −2.7 (Et₂O, *c* 30.7), ref. 2(a). ^k (*c* 1.24, benzene), lit. value, +9.25 (neat) for *R*-isomer of **13c**, ref. 2(a). ^l (*c* 0.82, benzene), lit. value −2.92 (neat) for *R*-isomer of **13d**, ref. 2(a). ^m (*c* 1.11, benzene).

The stereochemistry of the addition of the enolate of **12** to enones, determined by an X-ray analysis of the major product obtained from the reaction of **12** with *trans*-4-phenylbut-3-en-2-one, was found to be 3*S* for **11a**. All of the diastereoisomers of the Michael adduct carbene complexes **11** are separable on silica gel except for **11b**. The carbene complex **11** can be converted to the δ -keto ester **13** in excellent yields under mild conditions. Oxidation with ceric ammonium nitrate for a few minutes removes the metal and then hydrolysis of the imide with 2 equiv. of sodium methoxide in MeOH at room temperature gives the methyl ester **13** along with an 81–90% recovery of the chiral auxiliary. In all cases, except **11b**, the cleavage of the metal was carried out on the purified 3*S* isomer to give the δ -keto esters with high optical purity.

While further studies on the mechanism of these reactions are underway we currently favour the open transition state **8** with an *anti* approach of the enone such that the selectivity would be largely independent of the enone conformation.¹² Carbene complex **12** is prepared in a single step from commercially available materials¹⁰ and thus provides a useful method for the asymmetric synthesis of δ -keto esters by the Michael addition of chiral enolates to enones.

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Footnotes

† In previous studies⁷ we have investigated the addition of the enolates of prolinol derived carbene complexes. These complexes suffer as a result of the harsh conditions required to remove the metal and the amine auxiliary and we have since found that they are limited to moderate selectivities for most enones.⁸

‡ Complex **10** was prepared by an aldol condensation of **12** with acetaldehyde in 64% yield in a manner similar to that described for the synthesis of the non-chiral analogue.⁹

§ The reaction of the enolate of the methyl carbene complex derived from 1-menthol with 4-phenylbut-3-en-2-one gave a 1 : 1 mixture of diastereoisomers in 14% yield under conditions where the reaction was initiated at −78 °C and then warmed to 25 °C for 3 h.

§ The reaction of the enolate of acetophenone with **10** at −78 °C for 6 h gave a 76% yield of **11c** (84% based on unrecovered **10**) with a ratio of 3*R* : 3*S* of 78 : 22.

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