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Asymmetric Synthesis of Ketones by SmI_2-Mediated Allylation or Benzylation of Ketenes Followed by Enantioselective Protonation

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SmI_2-mediated allylation or benzylation of alkylarylketenes followed by enantioselective protonation with α,α'-di[(S)-2-hydroxy-2-phenylethyl]-o-xylenedioxide gave the corresponding ketones in 61-91%ee.

Fehr and Galindo reported the asymmetric synthesis of (R)- and (S)-α-damascone by Grignard reaction on the precusor ketene followed by highly enantioselective protonation (84%ee).[1] In this reaction 1 equiv. of lithium alkoxide of a chiral β-aminoalcohol (chiral proton source) must be added prior to the protonation for obtaining the high enantioselectivity. The formation of a mixed lithium-magnesium 1:1 complex between the ketone enolate and the alkoxide brought about a double stereodifferentiation in the protonating transition state by the chiral alcohol.

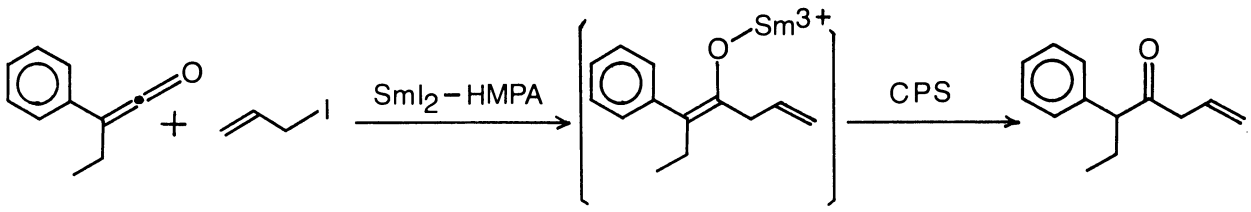
This prompted us to examine the titled reaction in extension of SmI_2-mediated enantioselective prtonation of benzil.[2] In the latter system, samarium 1,2-diphenyl-ethen-1,2-diolate was protonated enantioselectively by quinidine to afford benzoin in 91%ee. Thus we thought that high enantioselectivity should be accomplished also in the case of a samarium enolate without coexistence of other ion such as lithium. In this communication we describe the preliminary results on the enantioselective protonation of the enolate.

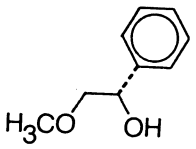
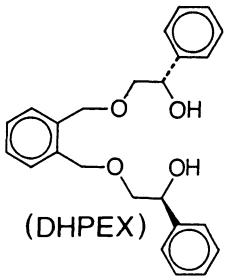
At first, allylation of ethylphenylketene followed by the protonation using several chiral alcohols was carried out in order to find a suitable proton source and an optimal condition for getting high optical yield (Table 1).

As seen from Table 1, rather high enantioselectivity was obtained by using (S)-2-methoxy-1-phenylethanol at low temperature (Entry 4) and α,α'-di[(S)-2-hydroxy-2-phenylethyl]-o-xylenedioxide (DHPEX)[3] which has C_2 symmetric structure gave the best result (84%ee) at -78 °C (Entry 6).

We next examined the allylation and benzylation of some alkylarylketenes using DHPEX as a proton source at -78 °C (Table 2).

Table 1. Enantioselective protonation of the samarium enolate prepared by SmI_2-mediated allylation of ethylphenylketene[a)]

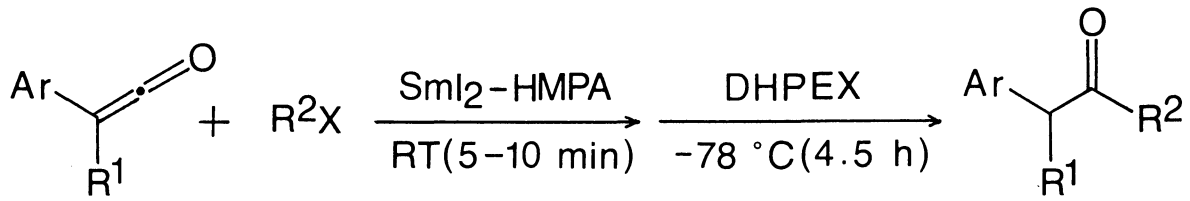


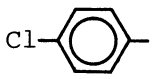
Entry	Chiral proton source (CPS)	Reaction temp/°C	Yield/%	$[\alpha]_D$/°	Confign.	%ee[b)]
1	Quinidine	RT[c)]	30[d)]	+113	S	33
2	Diethyl L(+)-tartrate	RT	70	0	-	0
3		RT	80	-210	R	61
4	"	-45	52	-258	R	75
5		RT	60	-243	R	71
6	"	-78	62	-287	R	84

a) After allylation of the ketene (3-5 min), the chiral proton source was added and the solution was stirred for 30 min (Entries 1-3 and 5) or 4.5h (Entry 6) b) Determined by ^1H NMR and HPLC analyses: See the footnote b of Table 2. c) Room temperature. d) Product whose olefinic double bond was isomerized to α,β-position was obtained.

As seen from Table 2, the enantioselectivities were high in most cases, and allylation of methylphenylketene resulted in 91%ee (Entry 1) which is the highest in the enantioselective protonation reported so far.[4)] p-Chlorophenylisopropylketene gave the ketones of opposite configuration to that in the case of other ketenes. This may be due to the difference of configuration of intermediate samarium enolate. Tidwell reported that Z/E ratio of enolate is more than 95/5 in butylation of methyl- and ethyl-

Table 2. Asymmetric synthesis of ketones by SmI_2-mediated alkylation of ketenes followed by enantioselective protonation with DHPEX



Entry	Ar	R^1	R^2X	Yield/%	$[\alpha]_D$/°[a]	Confign.	%ee[b]
1	Ph	CH_3		51	-283	R	91[c]
2	Ph	CH_3		40	-284	R	88
3	Ph	C_2H_5		62	-287	R	84
4	Ph	C_2H_5		43	-243	R	90
5		i-C_3H_7		68	+210	S[d]	85
6	"	i-C_3H_7		14[e]	+105	S	61

a) Toluene (Entries 1 and 3-6) and benzene (Entry 2) were used as solvent. See Ref. 7 (Entries 1 and 3) and Ref. 8 (Entry 2). b) Determined by ^1H NMR specrta in the presence of $Eu(hfc)_3$ (Entries 1-6) and by HPLC analyses using Chiralcel OB' (Hexane) on the hydrogenated sample of the reaction product (Entries 1 and 3) or Chiralcel OD (Hexane:i-Propanol=9:1) (Entry 3). c) To the solution of methylphenylketene (56.2 mg, 0.425 mmol) and allyliodide (272.9 mg, 1.62 mmol) in THF (2 ml) was added SmI_2 solution (0.1 mol dm^{-3}, 10.3 ml, 1.03 mmol) and HMPA (128.0 mg, 0.714 mmol). The enantioselectivity of the product (37.5 mg, 51%) was determined to be 94%ee and 91.3%ee by ^1H NMR and HPLC analyses, respectively. d) See Ref. 9. e) See Ref 10.

phenylketene by butyllithium and 1/4 in t-butylation of isopropylphenylketene by t-butyllithium.[5] Assuming that Z-enolate is exclucively formed in the case of methyl- and ethylphenylketene and E-enolate is predominantly formed in the case of p-chlorophenylisopropylketene also in the SmI_2-mediated alkylation,[6] it is possible to explain clearly the high enantioselectivity in Entries 1-4 and the reverse enantioselectivity in Entries 5 and 6.

The optimal molar ratios of HMPA and DHPEX to samarium were about 0.67 and 0.60 respectively to get the highest enantioselectivity. The enantioselectivity was lowered when the ratios became smaller or larger than the

corresponding values. For example, the enantioselectivity was 70%ee at DHPEX/Sm=1.0 in the case of allylation of methylphenylketene. Using HMPA at the ratio is also requisite condition to maintain the reaction solution homogeneous at -78 °C. Without HMPA, large amount of precipitates separated out and remained insoluble even by the addition of DHPEX to result in low enantioselectivity ($<$62%ee). From these results, it is deduced that the enolate anion, tetradentate ligand DHPEX, HMPA and solvent THF are co-ordinated to the samarium ion in the protonating transition state to enhance the steric control resulting in the high enantioselectivity. High oxophilicity and high co-ordination number of Sm^{3+} may play an important role in this stage.

DHPEX used in the reaction was recovered quantitatively and can be reused to give the same %ee.

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References

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3) DHPEX was synthesized by the reaction between α,α'-dibromo-o-xylene and (2S)-2-phenyl-2-(2'-tetrahydropyranyloxy)ethanol which was prepared from (S)-(+)-mandelic acid by Stephenson's method: L. M. Stephenson and D. L. Mattern, J. Org. Chem., 41, 3614 (1976). Details will be published elsewhere.
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6) Attempts to isolate the enolates as trimethylsilylate were unsuccessful, because samarium ion catalyzed reaction took place predominantly between trimethylsilylchloride and solvent THF to afford 4-trimethylsilyloxy-1-butylchloride (and -iodide). The isolation of the enolates and the determination of their Z/E ratios are under investigation.
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9) The configuration of the products in Entries 5 and 6 is considered to be S, because the sign of their optical rotations and ^{1}H NMR spectra in the presence of $Eu(hfc)_3$ are different from those in Entries 1-4. The larger one of the two methyl-signals separated by $Eu(hfc)_3$ is observed in higher magnetic field in Entries 1-4 but in lower magnetic field in Entries 5 and 6.
10) The product generated by the reaction at p-position of benzyl radical was also obtained (11% yield; S-configuration; 70%ee).

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