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Asymmetric synthesis of 4,4-disubstituted 2-cyclopentenones from optically active 1-chlorovinyl *p*-tolyl sulfoxides and cyanomethyllithium with formation of a quaternary chiral center

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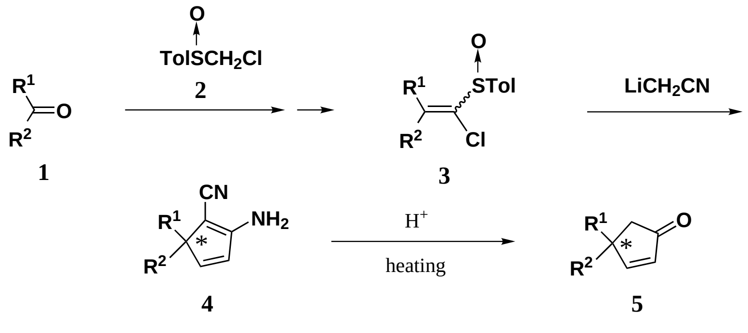
Abstract—Treatment of optically active 1-chlorovinyl *p*-tolyl sulfoxides having two different substituents at the 2-position, which were synthesized from unsymmetrical ketones and (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide in three steps, with cyanomethyllithium gave optically active 2-amino-1-cyano-5,5-disubstituted-1,3-cyclopentadienes with very high asymmetric induction from the sulfoxide chiral center. The products were converted to the enantiomerically pure 4,4-disubstituted 2-cyclopentenones by heating with phosphoric acid in acetic acid. © 2001 Elsevier Science Ltd. All rights reserved.

The cyclopentenone ring system is one of the most abundantly distributed carbon skeletal structure in natural and unnatural organic compounds. Accordingly, novel strategies for the synthesis of cyclopentenones continued to receive considerable attention in the field of synthetic organic chemistry.[1] Two famous recent methods for construction of cyclopentenones are the Nazarov cyclization[2] and Pauson–Khand reaction.[3] Recently, the Pauson–Khand reaction has been developed to a synthesis of optically active cyclopentenones by using, for example, brucine *N*-oxide as a chiral source.[4] On the other hand, construction of the quaternary carbon center has been a formidable work. Especially, the asymmetric synthesis of the quaternary carbon center is a quite interesting challenge in synthetic organic chemistry.[5]

Recently, we reported a novel method for synthesis of 4,4-disubstituted 2-cyclopentenones **5** from 1-chlorovinyl *p*-tolyl sulfoxide **3** (synthesized from ketone **1** and chloromethyl *p*-tolyl sulfoxide **2**) and cyanomethyllithium via the enaminonitrile **4** (Scheme 1).[6a] As shown in Scheme 1, it is expected that if an unsymmetrical ketone (**1**; R^1 and R^2 are different substituents) and chiral sulfoxide **2** were used in this reaction, optically active **4** and **5** could be synthesized. Based on this expectation, we investigated the asymmetric synthesis of 4,4-disubstituted 2-cyclopentenones



Scheme 1.

Keywords: sulfoxides; optically active sulfoxides; 4,4-disubstituted 2-cyclopentenones; asymmetric synthesis; quaternary chiral center.

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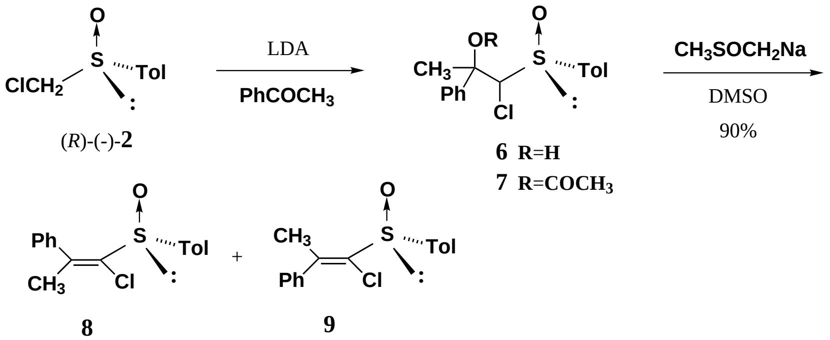
5 starting from optically active (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide (*R*)-**2**[7] with unsymmetrical ketones, and quite interesting results were obtained.

First of all, a synthesis of optically pure 1-chlorovinyl *p*-tolyl sulfoxides (**8** and/or **9**) was investigated (Scheme 2). According to the previous paper,[6] (*R*)-(−)-**2** was treated with LDA at −78°C followed by acetophenone to give the adduct **6** in 99% yield as a mixture of two diastereomers. The adduct **6** was acetylated with acetic anhydride and pyridine in the presence of DMAP to afford the acetate **7** in 96% yield. The acetate **7** was a mixture of two inseparable diastereomers. The mixture was treated with dimsylsodium in DMSO at room temperature to afford the desired optically pure 1-chlorovinyl *p*-tolyl sulfoxides **8** and **9** in 90% yield. The 1-chlorovinyl *p*-tolyl sulfoxides were separable on silica gel flash column chromatography and the ratio of **8** and **9** was found to be 4:1. **8**: $[\alpha]_D^{21}$ +280.5 (*c* 0.4 acetone). **9**: $[\alpha]_D^{27}$ −9.3 (*c* 0.2 acetone). The geometry of the two isomers could be easily determined by ^{1}H NMR.[6b]

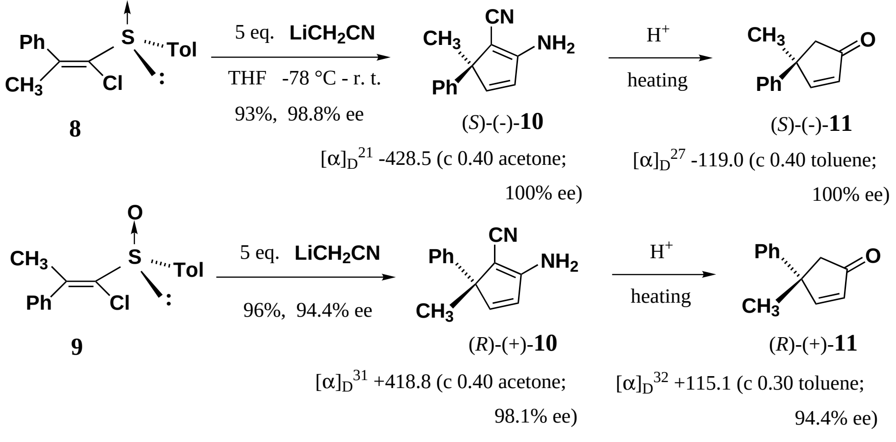
The main product, *E*-vinylsulfoxide **8**, was treated with 5 equiv. of cyanomethyllithium at −78°C to room temperature for 2 h (Scheme 3). The desired enaminonitrile **10** was obtained in 93% yield, which showed a minus sign for the specific rotation. The optical purity was determined by using HPLC with a chiral stationary column,[8] and we were somewhat surprised that the optical purity was 98.8%. One recrystallization of the product from AcOEt–hexane gave us the optically pure (−)-**10** (mp 114–116°C, $[\alpha]_D^{21}$ −428.5 (*c* 0.4 acetone)). The same treatment of *Z*-vinylsulfoxide **9** with cyanomethyllithium gave (+)-**10** in 96% yield with very high ee value (94.4% ee). Obviously, *E*- and *Z*-vinylsulfoxides gave the enantiomers of the enaminonitrile, respectively, in very high ee value.

To ascertain the absolute configuration of the product **10**, (−)-**10** was heated with phosphoric acid in 1,4-dioxane to give (−)-**11** (oil, $[\alpha]_D^{27}$ −119.0 (*c* 0.4 toluene)) in low yield (see Table 1, entry 1). Comparing the sign of the specific rotation of the product with that of the reported optically active **11**,[9] the absolute configuration of the enone was unambiguously determined to be *S*.

As shown in Scheme 4, (*S*)-(−)-**10** is derived from the adduct of the vinyl sulfoxide **8** with acetonitrile, the cyanomethyllithium must be selectively introduced from the *re* face of the vinyl sulfoxide. The observed high selectivity is most conveniently explained by assuming the formation of a chelate with the lithium ion between the oxygen of the sulfoxide and the chlorine, where the cyanomethyl anion approach takes place from the less-hindered *re* face. This is the first example for the asymmetric synthesis by conjugate addition to α,β-unsaturated sulfoxide having a halogen atom on the α-position.[10]

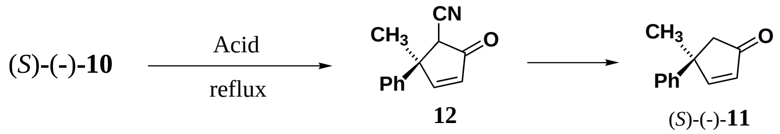


Scheme 2.



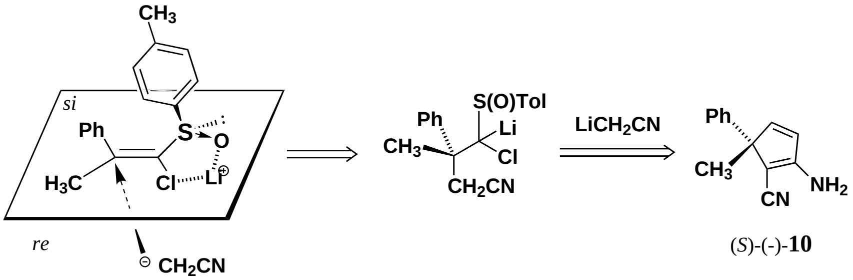
Scheme 3.

Table 1. Hydrolysis and decyanation of (*S*)-(−)-**10** with acids under reflux conditions



Entry	Acid	Solvent	Time (h)	Yield (%)	
				12	(*S*)-(−)-**11**
1	H_3PO_4	1,4-Dioxane	29	59	6
2	H_3PO_4	1,4-Dioxane	77	33	42
3	AcOH, H_3PO_4	1,4-Dioxane	77	78	Trace
4	5% H_2SO_4	1,4-Dioxane	77	65	Trace
5	H_3PO_4	AcOH	16	39	50
6[a]	H_3PO_4	AcOH	44	8	86

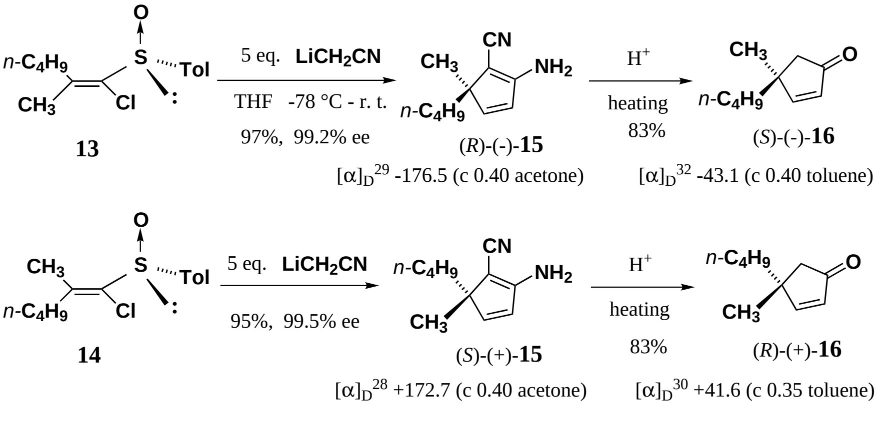
[a] To a solution of (*S*)-(−)-**10** (29 mg, 0.15 mmol) in 10 ml of acetic acid was added phosphoric acid (85%, 4 ml) and water (0.6 ml). The reaction mixture was stirred and heated under reflux for 44 h. The reaction mixture was neutralized with 5% aq. NaOH followed by satd aq. NH_4Cl and the whole was extracted with AcOEt–hexane. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to give an oil, which was purified by silica gel column chromatography to afford 22 mg (86%) of (*S*)-(−)-**11**.



Scheme 4.

Next, we have to establish better conditions for the hydrolysis and decyanation of (*S*)-(−)-**10** to obtain the enone **11** in good yield. The results of the investigation are shown in Table 1. Entry 1 has been mentioned above. Heating **10** with acid rapidly gave hydrolyzed cyanoenone **12**; however, decyanation was quite slow. We finally found that phosphoric acid in acetic acid is the conditions of choice. As shown in entry 6, heating (*S*)-(−)-**10** in acetic acid with phosphoric acid for 44 h gave the desired enone in 86% yield. These conditions seem to be somewhat severe; however, the reaction was rather clean and the mass balance was good.

To investigate the generality of these reactions, we further studied this method starting from 2-hexanone (Scheme 5). The vinyl sulfoxides *E*-**13** and *Z*-**14** were synthesized from 2-hexanone in a similar way as described for the synthesis of **8** and **9**. In the deacetylation step, in this case, the ratio of **13** and **14** was almost 1:1. The vinyl sulfoxide **13** was treated with



Scheme 5.

cyanomethyllithium in the same way as described above to obtain the desired enaminonitrile (–)-**15** in 97% yield with better ee (99.2% ee) than the case of (*S*)-(–)-**10**.

The enaminonitrile (–)-**15** was heated in the solution of phosphoric acid in acetic acid to give the enone (–)-**16** in 83% yield. Comparing the sign of specific rotation of the enone (–)-**16** with that of the reported optically active **16**,[9] the absolute configuration of the enone was determined to be *S*. The result from the vinyl sulfoxide **14** is shown in Scheme 5. Again, the asymmetric induction is explained by the chelated model shown in Scheme 4.

It is worth noting that the asymmetric induction mentioned in this paper is one of the highest in the asymmetric synthesis using chiral sulfoxide. Investigation of the scope and limitation of this asymmetric synthesis and applications to synthesis of natural products are underway in this laboratory.

Acknowledgements

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