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An Improved Asymmetric Nitroolefination of α-Alkyl-γ- and δ-lactones with Modified Nitroenamines

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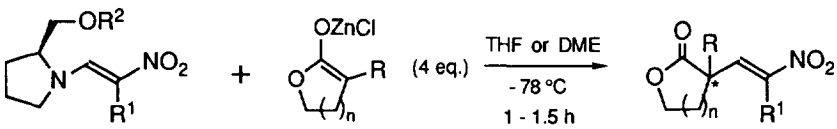
Abstract: New chiral nitroenamines **4a,b** were found to be very effective for asymmetric nitroolefination of α-alkyl-γ- and δ-lactones. The enantiomeric excess of the product ran up to 99 %. A possible chelation model for the transition state of the asymmetric nitroolefination was discussed.

We have been involved in a program on the development of enantioselective carbon-carbon bond forming reactions to create an asymmetric quaternary carbon through an addition-elimination process using readily available chiral nitroenamines (e.g. **1a** and **1b**).[1] (*S*)- or (*R*)-2-Methoxymethylpyrrolidine (SMP or RMP) was an excellent auxiliary for the nitroolefination of δ-lactones and we applied this methodology to the expeditious asymmetric syntheses of indole alkaloids (*Aspidosperma* and *Hunteria* types)[2], Calabar beans alkaloids[3] and diterpenoids[4]. The catalytic property of zinc enolates was observed in this asymmetric nitroolefination.[5] In spite of high enantioselectivities with δ-lactones the enantioselectivities as well as the yields with γ-lactones remained low.[1c] We have found that new chiral nitroenamines **4a,b** having a bulky substituent were excellent in asymmetric nitroolefination (Scheme) with γ-lactones as well as δ-lactones to give high enantioselectivity in excellent chemical yield.

Scheme



1 R^2 = Me
2 R^2 = H
3 R^2 = Tr
4 R^2 = TBS
a : R^1 = H **b** : R^1 = Me
(Tr = Trityl, TBS = *t*-Butyldimethylsilyl)

5a R = Me, n = 1
5b R = Et, n = 1
5c R = allyl, n = 1
6 R = Me, n = 2

n = 1	n = 2
7a R = Me, R^1 = H	**8a** R = Me, R^1 = H
7b R = Et, R^1 = H	**8b** R = Me, R^1 = Me
7c R = allyl, R^1 = H	
7d R = Me, R^1 = Me	
7e R = Et, R^1 = Me	
7f R = allyl, R^1 = Me	

In order to elucidate the effect of the bulkiness of R^2 in the chiral auxiliary we synthesized the new chiral nitroenamines **2-4**,[6] because the coordination of the oxygen of the chiral nitroenamine to zinc enolate was postulated under the reaction conditions.[1c] The new chiral nitroenamines were crystalline, while the previous nitroenamines **1** were oily. Therefore optically pure **2-4** were obtained by recrystallization.

The results of asymmetric nitroolefination of α-alkyl-γ-butyrolactones were summarized in Table 1. The enantioselectivity with **2a**, **3a**, and **4a** were much improved (entries 3-6), compared with **1a** (entries 1 and 2).[1c] Among them, the best result was obtained using nitroenamine **4a** having (*S*)-2-*t*-butyldimethylsiloxymethyl-pyrrolidine as an auxiliary. The alkyl substituents of γ-lactone had little effect on enantiomeric excess (entries 5-7 and 8-10). Introduction of methyl substituent at R^1 in nitroenamine increased enantiomeric excess in 5 - 13 % (entries 8-10), compared with none alkyl substituent (entries 5-7). In the case of entry 9, the enantiomeric excess of the product ran up to 98 % in a quantitative yield.

Table 1. Asymmetric Nitroolefination of α-Alkyl-γ-butyrolactones

	Nitroenamines			Zinc Enolates			Products[7]			
Entry		R^1	R^2		R	Solv.		Yield (%)	ee (%)	$[\alpha]_D$ ($CHCl_3$)
1	**1a**	H	Me	**5a**	Me	DME	**7a**	82	56 [a]	- 21.3 °
2	**1a**	H	Me	**5b**	Et	DME	**7b**	72	63 [a]	- 22.6 °
3	**2a**	H	H	**5a**	Me	THF	**7a**	77	83 [b]	- 31.9 °
4	**3a**	H	Tr	**5a**	Me	THF	**7a**	75	83 [b]	- 30.7 °
5	**4a**	H	TBS	**5a**	Me	DME	**7a**	92	88 [b]	- 34.9 °
6	**4a**	H	TBS	**5b**	Et	DME	**7b**	99	85 [c]	- 30.2 °
7	**4a**	H	TBS	**5c**	Allyl	DME	**7c**	96	86 [c]	- 36.7 °
8	**4b**	Me	TBS	**5a**	Me	THF	**7d**	87	93 [b]	- 55.7 °
9	**4b**	Me	TBS	**5b**	Et	THF	**7e**	99	98 [b]	- 32.8 °
10	**4b**	Me	TBS	**5c**	Allyl	THF	**7f**	92	95 [d]	- 50.6 °

Entries 1 and 2 were cited from ref. 1c. a) Chiral shift analysis [400MHz ^{1}H NMR, $CDCl_3$, Eu(hfc)$_3$]
b) HPLC (DAICEL CHIRALPAK AS, *i*-PrOH) analysis c) HPLC (DAICEL CHIRALCEL OJ, *i*-PrOH) analysis
d) HPLC (DAICEL CHIRALPAK AD, EtOH) analysis

Results of asymmetric nitroolefination of α-methyl-δ-valerolactone with new chiral nitroenamines are compiled in Table 2. Among the chiral nitroenamines, **4a** and **4b** yielded the highest enantiomeric excess. Although it was reported that three equivalents of lactone enolate were essential for giving high chemical yield at -78 °C,[1c] we have found that two equivalents were sufficient to obtain the comparable results when the reaction temperature was raised to -40 °C (entries 2 and 9). A possible model involving a complex through zinc is shown in Figure 1. The zinc enolate coordinated to the oxygen in the auxiliary can be released on the elevated reaction temperature at -40 °C so that the reaction completes with two equivalents of enolate.

The enantioselectivity depended on the bulkiness of OR^2 in the chiral auxiliary; namely the order was OH < OMe < OTr < OTBS. Among the four possible transition states involving the chelated six-membered chair form shown in Figure 2, transition states C and D were excluded because of the strong 1,3-diaxial interaction. The transition state A (formed from path A in Figure 1) should be more stable than the transition state B (from path B), because the zinc chelation involving 5,6-ring system is too strained to form a new carbon-carbon bond. The contribution of transition state B might be reduced with increasing steric interaction between the substituent R^2 and the ligand L. A consideration of above transition states is explicable of the high enantioselectivity in the nitroolefination with the nitroenamine **4** having a bulky substituent TBS.

Table 2. Asymmetric Nitroolefination of α-Methyl-δ-valerolactone

Entry	Nitroenamines	R^1	R^2	6 eq.	Solv.	Products[a]	Yield (%)[b]	ee (%)[c]
1	**1b**	Me	Me	4.0	THF	**8b**	90	95
2[d]	**1b**	Me	Me	2.0	THF	**8b**	87	93
3	**2a**	H	H	4.0	THF	**8a**	24	79
4	**2b**	Me	H	4.0	THF	**8b**	35	90
5	**3a**	H	Tr	4.0	THF	**8a**	66	89
6	**3b**	Me	Tr	4.0	THF	**8b**	76	97
7	**4a**	H	TBS	4.0	DME	**8a**	82	93[e]
8	**4b**	Me	TBS	4.0	THF	**8b**	95	99
9[d]	**4b**	Me	TBS	2.0	THF	**8b**	99	95

a) The configuration of the products **8a,b** was *S* (see ref. 1c).
b) Isolated yield c) Chiral shift analysis [270 MHz ^{1}H NMR, $CDCl_3$, $Eu(hfc)_3$]
d) The reaction temperature was warmed up from -78 °C to -40 °C.
e) HPLC (DAICEL CHIRALPAK AS, *i*-PrOH) analysis

Figure 1

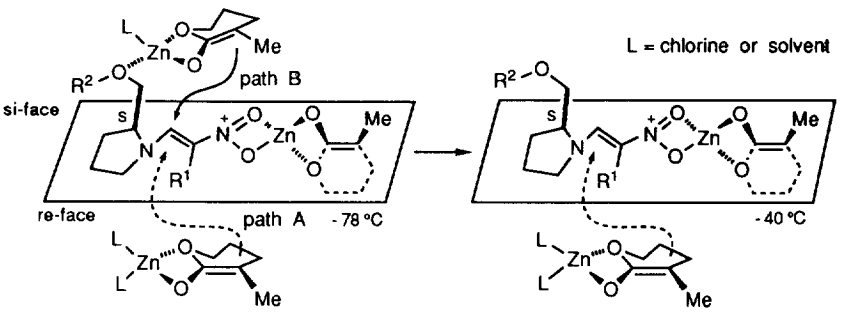
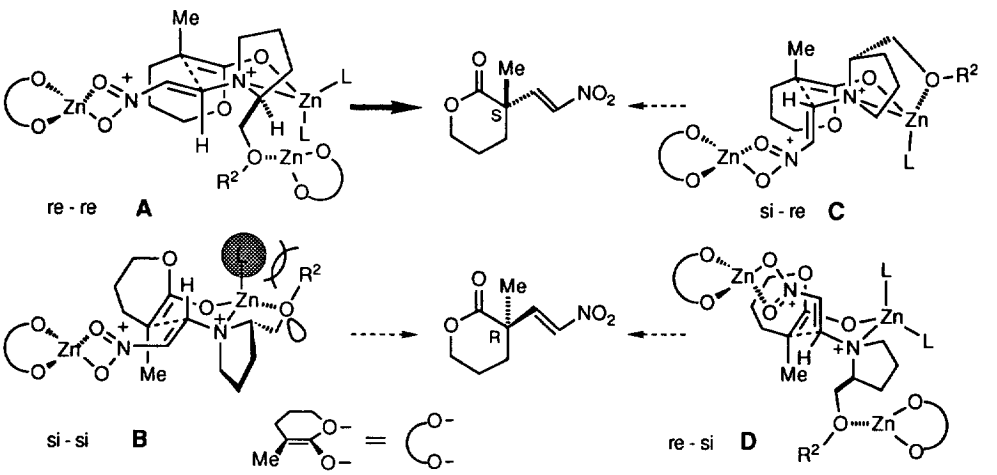


Figure 2



This asymmetric nitroolefination using new nitroenamine **4** could be useful for the total synthesis of the natural products having an asymmetric quaternary carbon. Further studies are on the way to this goal.

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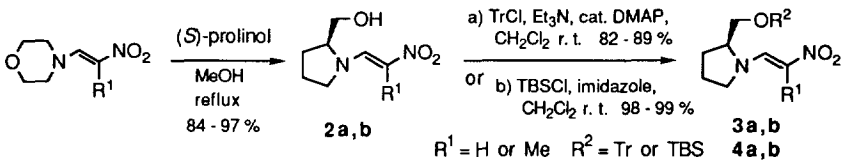
6. The new chiral nitroenamines **2-4** were easily prepared in high yields as follows.



7. The CD spectrum of the products showed the same Cotton effects as those of the products from δ-lactones, which have *S* configuration. It can therefore be presumed that the absolute configuration of the products from γ-lactones was *S*.

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