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Enantioselective aldol reaction of silyl ketene acetals promoted by a Lewis base-activated Lewis acid catalyst

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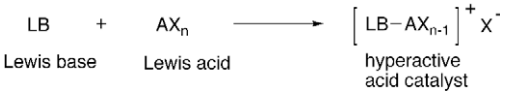
ABSTRACT

The enantioselective aldol reaction of a silyl ketene acetal was promoted by chiral phosphine oxide-activated tetrachlorosilane to afford the corresponding adduct in high yield with moderate enantioselectivity.

1. Introduction

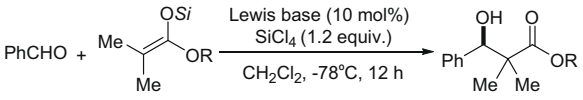
The Lewis acid-catalyzed aldol reaction of silyl enol ethers, the so-called Mukaiyama-type aldol reaction, is an important method for constructing a C–C bond.[1,2] Although various chiral metal complexes have been used in enantioselective aldol reactions to afford aldol adducts in high stereoselectivities, the emergence of Lewis base-activated Lewis acid catalysis pioneered by Denmark is a recent topic in this area.[3] Upon coordination to a Lewis base, the central atom in the Lewis acid (tetrachlorosilane) becomes more electrophilic and generates a cationic species, which significantly increases the Lewis acidity (Eq. 1). In this concept, Denmark realized high stereoselectivities in the enantioselective aldol reactions of silyl enol ethers and silyl ketene acetals by using catalytic amounts of chiral phosphoramides as activators for stoichiometric amounts of tetrachlorosilane.[4] This catalytic system has been applied to a wide range of asymmetric reactions, including allylation,[5z] addition of isocyanides[5b] or silyl ketene imines[5c] and vinylogous aldol reactions.[5d] However, the Lewis bases used in these reactions have been restricted to chiral phosphoramides. In our pursuit to develop new organocatalyses promoted by *N*-oxides or phosphine oxides,[6,7] we herein report enantioselective aldol reactions promoted by *N*-oxides or phosphine oxide-activated tetrachlorosilane.



(1)

2. Results and discussion

We initially examined the aldol reaction of benzaldehyde with the trimethylsilyl ketene acetal derived from methyl isobutyrate in the presence of a stoichiometric amount of tetrachlorosilane (Eq. 2) and a catalytic amount of chiral *N*-oxide. The reaction proceeded, but both the chemical yield and enantioselectivity were



(2)

Table 1
Aldol reaction of silyl ketene acetals derived from methyl isobutyrate with benzaldehyde

Entry	Lewis base[c]	R	*Si*	Yield[a] (%)	ee%[b]
1	BQNO	Me	TMS	48	0
2	BINO	Me	TMS	67	17
3	BINAPO	Me	TMS	96	52
4	DIOPO	Me	TMS	98	7
5	SEGPHOSO	Me	TMS	79	46
6	BINAPO	Me	TBDMS	98	30
7	BINAPO	Et	TMS	93	48
8	BINAPO	^{i}Pr	TMS	49	28

[a] Isolated yields.
[b] ee's were determined by HPLC analysis using chiral column (Daicel chiralcel OJ).
[c] BQNO: (*S*)-3,3-dimethyl-2,2′-biquinoline *N*,*N*′-dioxide; BINO: (*R*)-1,1′-biisoquinoline *N*,*N*′-dioxide; DIOPO: 2,3-*O*-isopropylidene2,3-dihydroxy-1,4-bis(diphenylphosphino)butane dioxide; SEGPHOSO: (*S*)-5,5′-bis(diphenylphosphino)-4,4′-bibenzodioxole dioxide; BINAPO: (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene dioxide.

unsatisfactory (Table 1, entries 1 and 2). Next we employed chiral phosphine oxide BINAP dioxide (BINAPO), and found that the reaction proceeded smoothly to afford the aldol adduct with moderate enantioselectivity (entry 3). Other phosphine oxides, such as SEGPHOS dioxide or DIOP dioxide, were tested (entries 4 and 5), but BINAPO gave the best results.

Using BINPO as the Lewis base catalyst, we then investigated the aldol reactions of various silyl ketene acetal derivatives of isobutyrate. tert-Butyldimethylsilyl enol ether gave the adduct in high yield, but with lower enantioselectivity (entry 6). Increasing

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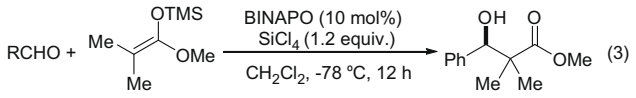
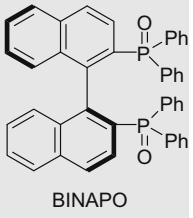
Table 2
Aldol reaction of benzaldehydes with TMS ketene acetal derived from methyl isobutyrate



Entry	R	Yield[a] (%)	ee, % (conf)[b]
1	Ph	96	52 (*R*)
2	4-BrC_6H_4	92	49
3	4-$MeOC_6H_4$	98	62 (*R*)
4	1-Naphthyl	79	67 (*R*)
5	2-Naphthyl	83	35 (*R*)
6	PhCH=CH	12[c]	0
7	$PhCH_2CH_2$	0	—



BINAPO

[a] Isolated yields.
[b] ee's were determined by HPLC analysis using chiral column (Daicel chiralcel OB, OD or OJ). Absolute configurations were assigned by comparing to the literature values of $[\alpha]_D$ or retention time in HPLC.
[c] 1,4-Adduct was obtained in 88% yield.

the bulkiness of the ester substituent decreased both the chemical yields and enantiomeric excesses (entries 7 and 8).[8]

Table 2 summarizes the results obtained with various aldehydes and the trimethylsilyl ketene acetal of methyl isobutyrate.[9] In every case, the benzaldehyde derivatives smoothly reacted to produce adducts in high yield. While bromobenzaldehyde and 2-naphthaldehyde gave lower selectivities, aldehydes with electron-donating or sterically congested groups gave better enantioselectivities. The highest enantioselectivity was obtained in the reaction of 1-naphthaldehyde. Although dihydrocinnamaldehyde did not proceed under these conditions, cinnamaldehyde gave the 1,4-adduct as the major product, exhibiting an interesting feature of a phosphine oxide catalyst compared to that of a phosphoramide.[10]

3. Conclusion

In conclusion, we have demonstrated the effectiveness of BINAPO as a catalyst for the aldol reaction of trimethylsilyl ketene acetals. This is the first example using a phosphine oxide as a Lewis base to activate a Lewis acid in enantioselective aldol reactions. Further studies to enhance the enantioselectivity are currently in progress.

Acknowledgement

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9. Typical experimental procedure: tetrachlorosilane (0.060 mL, 1.2 equiv) in dichloromethane (1 mL) was added to a solution of BINAPO (16.4 mg, 5 mol %), benzaldehyde (53 mg) and silyl ketene acetal (0.23 mL, 2.0 equiv) in dichloromethane over 1 h at −78 °C, and the mixture was stirred for 12 h at the same temperature. The reaction was quenched with methanol, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and evaporated. Purification by silica gel column chromatography afforded the adduct (100 mg, 96%). The ee was determined by chiral HPLC (Daicel chiralcel OJ).
10. Denmark has reported that the phosphoramide-catalyzed reaction of silyl ketene acetal with cinnamaldehyde gives the aldol adduct in high yield (Ref. [3]). This is the first example of a conjugate addition of silyl ketene acetal promoted by Lewis base-activated Lewis acid catalyst.