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Catalytic, Enantioselective Aldol Additions to Ketones

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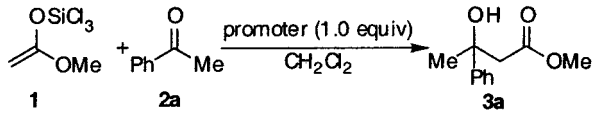
The number of methods for catalytic, diastereo-, and enantioselective aldol additions of ketones, esters, and their derivatives to aldehyde acceptors is legion.[1] In contrast, the available methods for any type of stereocontrolled aldol additions to ketones are nearly nonexistent.[2,3] The singular examples on record are the copper-bisoxazoline-catalyzed additions of enolsilanes to α-diketones and pyruvate esters masterfully developed by Evans.[4] In these cases, the chelating ability of the α-dicarbonyl unit is essential for both activation and stereoselection. This requirement serves to highlight the two major challenges facing the development of a general and selective method, namely: (1) the attenuated reactivity of ketones and (2) the lesser steric dissimilarity of the two entities flanking the carbonyl group compared to aldehydes. The first feature mandates a solution that overcomes the intrinsic endothermicity of aldol additions to ketones,[5] for example, chelation or silylation of the aldolate. The second feature, which makes enantiofacial discrimination difficult, has been addressed with various levels of success in the context of metal-catalyzed nucleophilic additions to ketones.[6] We describe herein our initial studies toward a solution to these problems in the application of chiral Lewis base catalysis.

To overcome the unfavorable kinetics (and thermodynamics) of additions to ketones, we made recourse to the highly reactive trichlorosilyl enolate of methyl acetate (**1**). This reagent was featured in our first disclosure on the chemistry of enoxytrichlorosilanes,[7] and although susceptible to chiral Lewis base catalysis,[8] its hyperreactivity toward aldehydes led to only modest enantioselectivities. Moreover, the strong chelation of the trichlorosilyl fragment promised to render the additions essentially irreversible. Indeed, orienting experiments showed that uncatalyzed addition of **1** to acetophenone (**2a**) took place, albeit sluggishly even at 0 °C.

Because it is likely that ketones would respond differently than aldehydes, it was deemed profitable to survey a broad range of Lewis basic promoters for the aldol addition. In keeping with our mechanistic hypothesis that the Lewis base functions by coordination and ionization of a chloride ion, we examined those compound classes known to effectively create silyl cations.[9] Thus, among the many bases tested,[10] HMPA and trimethylamine-*N*-oxide were the most effective. Intrigued by the superior characteristics of the *N*-oxide,[11] we next investigated those structural features that would impart activity at subambient temperatures. The results compiled in Table 1 revealed that pyridine *N*-oxide possessed the greatest capability to promote the aldol addition; however, for the catalysis of this process, higher temperatures were necessary.

The successful addition of trichlorosilyl ketene acetal **1** to acetophenone was particularly satisfying because this substrate bears three enolizable protons of significant acidity. We were concerned, given the lower reactivity of the ketone carbonyl group, that the enolization of the substrate might interfere. Thus, before embarking on an extensive optimization of the reaction conditions in anticipation of developing a catalytic enantioselective variant, we first chose to survey the scope of the reaction with regard to ketone substrate. A wide variation in structure was chosen with representatives in all basic structural classes (aromatic, heteroaromatic, olefinic, acetylenic, aliphatic, branched, and linear) as shown in Chart 1.

Table 1. Survey of *N*-Oxide Promoters for Addition of **1** to **2a**



1 **2a** **3a**

entry	promoter	temp, °C	time, min	conv., %[a]
1	none	−50	240	0
2	Me_3NO	−78	240	10
3		−20	50	76[b]
4	NMO	−78	70	25[c]
5	quinuclidine *N*-oxide	−78	70	35[c]
6	pyridine *N*-oxide (**4**)	−78	70	37
7		−50	50	97
8[d]		rt	120	100

[a] Reaction monitored by ^{1}H NMR analysis. [b] Reaction completed upon warming. [c] No further conversion upon warming. [d] 10 mol % of pyridine *N*-oxide used.

The results of catalyzed addition of **1** to these ketones are compiled in Table 2. This survey was performed under a standard set of conditions with pyridine *N*-oxide as the catalyst (10 mol %). All reactions proceeded cleanly and provided uniformly high yields (of analytically pure materials) for hindered and enolizable ketones as well as those with multiple reactive sites. Only two cases were aberrant: pinacolone (**2p**), which required 8 h at room temperature for completion (nevertheless in 93% yield), and 2-tetralone (**2q**) which afforded only a 45% yield of the addition product **3q** and returned 45% of unreacted starting material, most likely from competitive enolization.

Confident in the broad substrate generality of the transformation, we next initiated the search for a suitable chiral catalyst. Initial studies with camphor-derived pyridine *N*-oxides[12] were disappointing both in terms of reactivity and selectivity. Ongoing mechanistic[13] and preparative studies on chiral phosphoramide-catalyzed aldolization[14a] and allylation[14b,c] have clearly demonstrated that two catalyst molecules are involved in the stereochemistry-determining transition structure as well as the selectivity enhancement that accrues from chelating, chiral bis-phosphoramides. We therefore reasoned that chiral *bis-N-oxides* might offer similar advantages to the bis-phosphoramides employed previously.

Accordingly, we prepared and tested the bis-quinoline-based bis-*N*-oxides **5**[11a] and **6**,[15] Chart 2. These compounds could effectively catalyze the addition of **1** to **2a** albeit with only modest enantioselectivity as shown in Table 3. The next class of bis *N*-oxides was inspired by the work of Bolm who prepared the chiral 2,2′-

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Chart 1

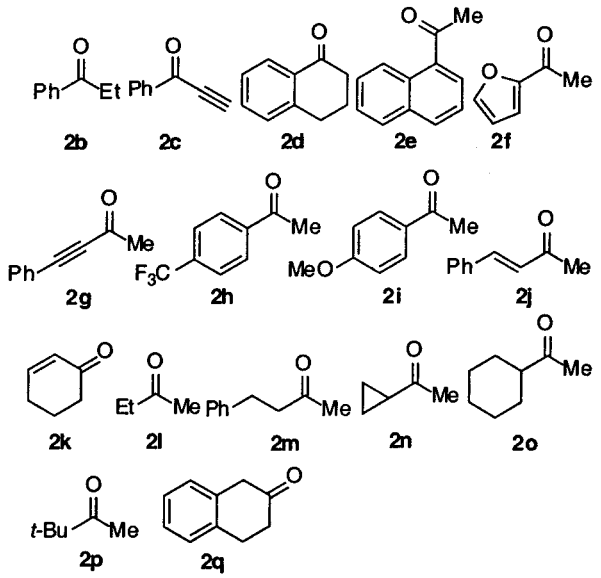
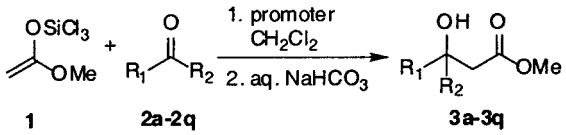


Table 2. Catalyzed Additions of **1** to Ketones



			promoter/catalyst		
			4[a]	*P*-(*R*,*R*)-**8a**[b]	
entry	substrate	product	yield, %[c]	yield, %[c]	er[d]
1	**2a**	**3a**	94	96	91.2/8.7[e]
2	**2b**	**3b**	92	90	90.3/9.7
3	**2c**	**3c**	72	89	93.1/6.9[e]
4	**2d**	**3d**	87	90	90.1/9.9
5	**2e**	**3e**	91[f]	89[g]	77.9/22.1
6	**2f**	**3f**	91	87	74.3/25.7
7	**2g**	**3g**	92	94	67.6/32.4
8	**2h**	**3h**	90[h]	91[g]	88.0/12.0
9	**2i**	**3i**	94	94	83.9/16.1
10	**2j**	**3j**	92	87	55.4/44.6
11	**2k**	**3k**	71	86	53.9/46.1
12	**2l**	**3l**	83[i]	84	66.1/33.9
13	**2m**	**3m**	94	97	67.5/32.5
14	**2n**	**3n**	87	84	60.1/39.9
15	**2o**	**3o**	94	91	66.0/34.0
16	**2p**	**3p**	93[i]	87[j]	71.5/28.5
17	**2q**	**3q**	45	–	–

[a] All reactions performed on a 2.0 mmol scale (0.2 M) for 2 h at room temperature unless otherwise noted. [b] All reactions performed on a 2.0 mmol scale (0.2 M) for 12 h at −20 °C unless otherwise noted. [c] Yields of analytically pure materials. [d] Determined by CSP-GC or CSP-SFC. [e] Absolute configuration *S* by correlation. [f] Reaction time 16 h. [g] Reaction time 20 h. [h] Reaction time 4 h. [i] Reaction time 8 h. [j] Reaction time 32 h.

bipyridyl precursor for **7** bearing stereocenters in the 6,6′-positions.[16] After successfully repeating the Bolm procedures, we secured the target bis-*N*-oxides by MCPBA oxidation. Gratifyingly, both of these compounds gave improved enantioselectivities, with the butyl ether **7b** affording a 64% ee of **3a** in nearly quantitative yield. Inspection of molecular models clearly reveals a nonplanar conformation of **7** when complexed to enolate **1**, but unlike **5** or **6** the atropisomerism is not controlled. We therefore prepared the analogous ligands **8** in which the 3,3′-methyl groups serve to fix the configuration of the chiral axis. Because the synthesis is modular, it was relatively straightforward to modify the group R^1

Chart 2

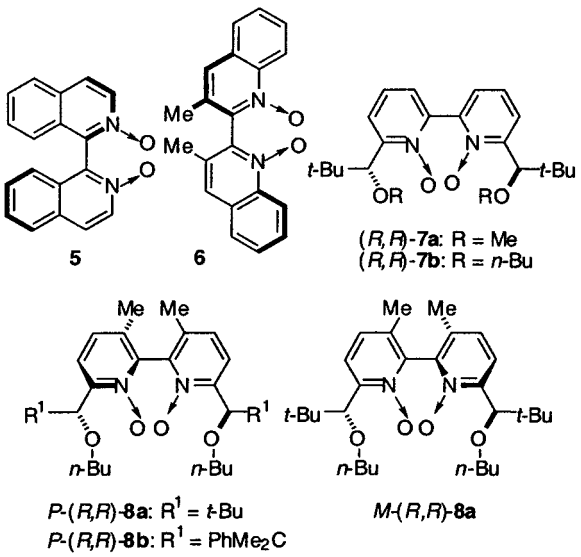


Table 3. Survey of Chiral *N*-Oxide Catalysts for Addition of **1** to **2a**

entry	catalyst	yield, %	er	config.
1	**5**		72.5/27.5	
2	**6**		63.0/37.0	
3	**7a**	92	77.5/22.5	*S*
4	**7b**	94	82.0/18.0	*S*
5	*P*-**8a**	90	87.0/13.0	*S*
6	*P*-**8a**	94	92.0/8.0	*S*
7	*M*-**8a**	89	71.5/28.5	*R*
8	*P*-**8b**	90	90.0/10.0	*S*

on the 6,6′-substituent and also to access both diastereomeric atropisomers.[17] We were pleased to find that the *P*-isomer[18] of **8a** gave improved enantioselectivity which could be further enhanced by simply carrying out the reaction at −20 °C for 12 h (compare entries 5 and 6, Table 3). Interestingly, the *M*-isomer catalyzed the aldol addition in high yield but afforded the opposite enantiomer of **3a** with modest selectivity. Thus, it is clear that the sense of asymmetric induction is dominated by the configuration of the chiral axis and that the 6,6′-stereocenters play a secondary role. This conclusion was supported by the negligible influence of the larger phenyldimethyl substituent in catalyst **8b** (entry 8).

With a suitable catalyst in hand we next examined the asymmetric induction with the assortment of ketones detailed above. In general, aromatic ketones gave the highest enantioselectivities (80−86% ee) wherein the two flanking groups are reasonably different in size (entries 1−4). In this regard, the modest selectivity seen with 1-acenaphthone (entry 5) was surprising. A noticeable electronic effect was manifest in the lower selectivities for both electron-poor and electron-rich ketones (cf. entries 1, 8, and 9). Furyl methyl ketone was also modest and may hint at association of the furan oxygen with the silicon center. The olefinic ketones were clearly the poorest performers, inferior still to the aliphatic ketones. Although the latter class did not give results that could be considered synthetically useful (20−41% ee), it is nonetheless remarkable in our view that such sterically balanced substrates were able to deliver the products with any selectivity at all (entries 12−16). Indeed, the similar selectivities observed for such sterically disparate substrates as **2m** and **2p** indicate that such a simplistic analysis is insufficient and that a deeper understanding of the coordination geometry and substrate−catalyst interactions will be needed to design the next generation of catalysts.

In conclusion we have taken the first steps toward the realization of catalytic enantioselective aldol additions to ketones in the use of ester trichlorosilyl enolates and have demonstrated the potential of chiral bis *N*-oxide catalysts. Mechanistic and preparative investigations of this newly designed class of Lewis basic catalysts are in progress.

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Supporting Information Available: Procedures for the preparation and full characterization of catalysts **7** and **8**; aldolization products along with representative procedures for the addition reactions and correlation of absolute configuration of **3a** and **3c** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) These ligands were prepared in a relatively short sequence; see Supporting Information for full details and characterization.

(18) The configuration of these ligands was assured by X-ray crystallographic analysis of a complex with silicon tetrachloride. The details of this structure will be described in a full account.

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