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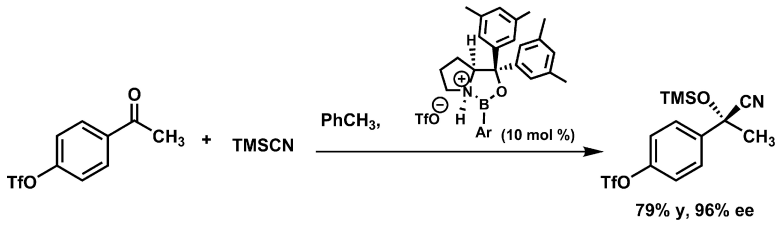

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Enantioselective Cyanosilylation of Ketones Catalyzed by a Chiral Oxazaborolidinium Ion

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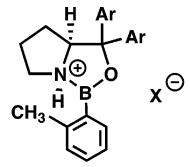
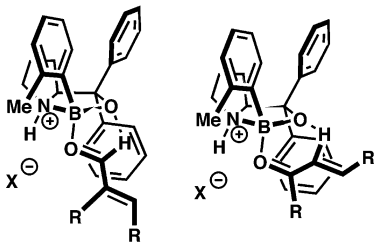
Abstract: The chiral oxazaborolidinium salt **1** (X = TfO) is an excellent catalyst for the cyanosilylation of methyl ketones promoted by trimethylsilyl cyanide and diphenylmethyl phosphine oxide as co-reactants (to generate $Ph_2MePOTMS(N{=}C{:})$ as a reactive intermediate). The face selectivity of this reaction parallels that previously observed for the corresponding reaction of aldehydes. A unifying and rational mechanistic explanation is provided for these enantioselective reactions. Evidence is presented to support the importance of α-C−H···O hydrogen bonding, π,π-interaction of the complexed ketonic carbonyl with the mexyl group of **1**, and an early transition state for high enantioselectivity. The cyanosilylation reaction described herein provides access to many useful chiral compounds.

Chiral oxazaborolidinium salts such as **1** and **2** have been shown to be remarkably effective catalysts for a broad range of enantioselective Diels−Alder reactions.[1] The absolute stereochemical course of each of these reactions can be predicted by a logical and clear mechanistic rationale.[1,2] The face selectivity of the enantioselective Diels−Alder reaction depends on the structural type of the dienophile component. For 2-substituted α,β-enals, formyl C−H···O hydrogen bonding[2] leads to a preferred pathway via **3**,[1a,b,2] whereas for α,β-unsaturated carbonyl compounds having an α-C−H substituent (e.g. esters, ketones, quinones) α-C−H···O hydrogen bonding favors reaction via complex **4**.[1b,c] Two aspects of these catalytic pathways are critical to the success of this new and powerful methodology: (1) the oxazaborolidinium ions **1** and **2** are strong Lewis acids that are capable of promoting Diels−Alder reactions between components of only modest reactivity, and (2) the complexed dienophilic carbonyl group retains its positive charge even in the Diels−Alder transition state, which preserves the strong attractive interaction between the coordinated carbonyl group of the dienophile and the proximal π-electron-rich Ar group of **1** or **2**.[3] We recently investigated the question of whether catalysts such as **1** and **2** could function effectively in Lewis acid-catalyzed enantioselective 1,2-additions to the formyl group of aldehydes. In principle, the same factors that operate to ensure face-selectivity in Diels−Alder reactions of α,β-enals



1, Ar = 3,5-dimethylphenyl (mexyl)
2, Ar = phenyl



3 **4**
X = TfO or Tf_2N

with dienes could serve to promote highly selective 1,2-addition to aldehydes, e.g. cyanosilylation to form chiral cyanohydrin derivatives.[4] We were able, in fact, to find conditions for effecting highly enantioselective cyanosilylation of a variety of aldehydes.[4] For instance, the reaction of benzaldehyde with trimethylsilyl cyanide (TMSCN) using 10 mol % of the oxazaborolidinium salt **1** and 20 mol % of triphenylphosphine oxide in toluene at 0 °C proceeded in 94% isolated yield to form the TMS derivative of mandelonitrile of 95% ee.[4] In this reaction a reactive cyanide donor, $Ph_3P(OTMS)(N{=}C{:})$, is generated from TMSCN and Ph_3PO which then adds to the complex **5** (from coordination of **1** to benzaldehyde) to form

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(1) (a) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808−3809. (b) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992−9993. (c) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388−6390. (d) Zhou, G.; Hu, Q.-Y.; Corey, E. J. *Org. Lett.* **2003**, *5*, 3979−3982. (e) Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800−4802. (f) Hu, Q.-Y.; Rege, P. D.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 5984−5986. (g) Hu, Q.-Y.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 13708−13713.
(2) Corey, E. J.; Lee, T. W. *J. Chem. Soc., Chem. Commun.* **2001**, 1321−1329.
(3) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650−1667.
(4) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8106−8107.

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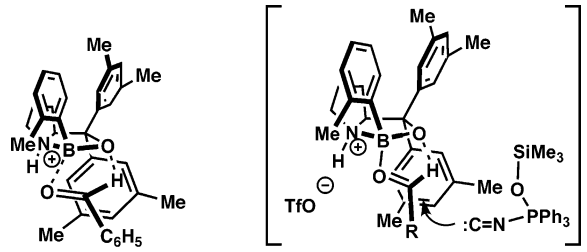
the *R* cyanosilylation product by attack at the *si* face; see transition-state assembly **6**.

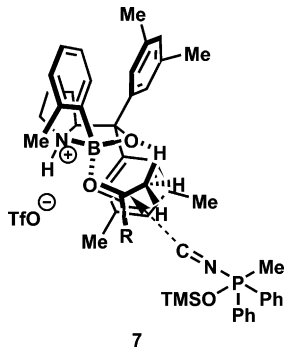


5 **6**

The meta xylyl (mexyl) catalyst **1** effected cyanosilylation with greater enantioselectivity than the phenyl analogue **2**, indicating clearly the importance of π-electron basicity in the neighboring aromatic group of the catalyst.[3,4] Enantioselectivities were superior with Ph_3P(OTMS) (N═C:) as cyanide donor than with TMSCN alone, probably due to the greater reactivity of the former and the advantage of an earlier transition state.[4,5]

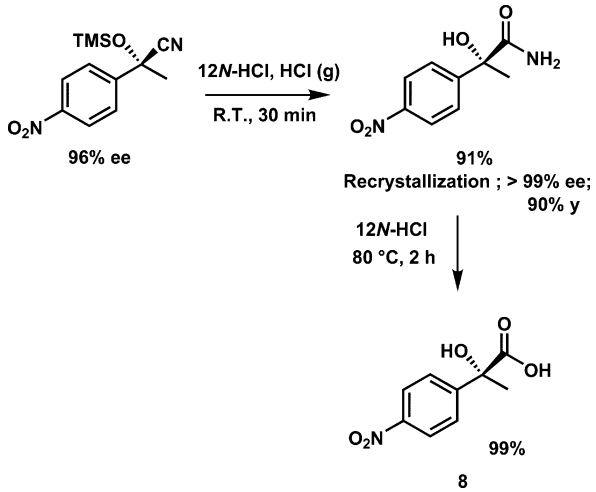
In this study we investigated the possibility of extending the catalytic enantioselective cyanosilylation using TMSCN to methyl ketones. **CAUTION!** *TMSCN is volatile and toxic and must be used in a well-ventilated hood.* Until recently, the cyanosilylation of ketones had not been achieved. At present only the titanium[6] and lanthanide[7] systems of Shibasaki and co-workers, the aluminum−peptide complexes of Hoveyda,[8] and basic cinchona alkaloid catalysts[9] have been used for this purpose. We describe herein the development of a successful enantioselective cyanosilylation of methyl ketones, the critical conditions for optimal enantioselectivity, the dependence of the process on the structure of the ketonic substrate, and the mechanistic implications of this study.

Cyclohexyl methyl ketone was selected as the substrate for screening experiments to optimize the following parameters: (1) substituent on boron of the oxazaborolidine ring, (2) the *gem*-diaryl substituent on that ring, (3) the counterion (i.e., the acid for oxazaborolidine activation), (4) phosphine co-reactant, (5) solvent, and (6) temperature. As a result of this evaluation it emerged that the *o*-tolyl group was the optimal boron appendage, as had been found previously in studies of Diels−Alder reactions catalyzed by **1**, **2**, and analogues.[1,10] The mexyl group was superior to phenyl as *gem*-diaryl substituents on the oxazaborolidine ring. The triflate counterion afforded somewhat better results than Tf_2N^-, as phosphine oxide co-reactant Ph_2-MePO appeared superior to Ph_3PO, $PhMe_2PO$, *p*-tol_3PO, or (*p*-$MeOC_6H_4)_3PO$.[11] Toluene was definitely better in terms of yield and ee of product than CH_2Cl_2 or CH_3CN. Optimal temperatures were in the range 25−45 °C, depending on substrate. Table 1 summarizes the most significant experiments of this study with a variety of substrates. Using optimized conditions, good yields and enantioselectivities were obtained with the (*S*)-catalyst **1** (X = TfO) and a range of different methyl ketones. The reactions were generally faster with aliphatic methyl ketones than with aryl methyl ketones. As shown in entries 1−6 of Table 1, the predominating enantiomer from the (*S*)-catalyst **1** is the (*R*)-cyanosilylation product which is formed by addition of CN to the *si* face of the coordinated methyl ketone.[12] This is the same face selectivity that has been observed for the cyanosilylation of aldehydes[4] and can be rationalized by the transition-state assembly (TSA) **7**. This is analogous to the TSA (**6**) for



7

the cyanosilylation of aldehydes but involves α-C−H···O hydrogen bonding as an organizing element instead of formyl C−H···O hydrogen bonding. Table 1 also reveals a very significant and surprising effect of para substituents in the acetophenone series on enantioselectivity of cyanosilylation. First of all, it is clear that the enantioselectivity is greater with 4-nitro- and 4-triflyloxyacetophenone (95−96% ee) than with acetophenone itself (Table 1, entries 3, 5, and 6). Because of their very high enantioselectivities the reactions of entries 5 and 6 are especially valuable synthetically. As shown below,



8

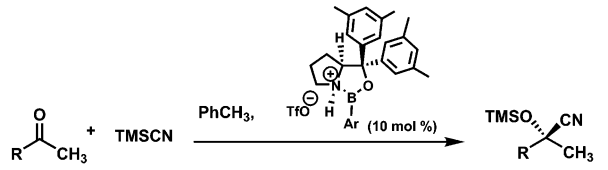
the product of entry 5 can be converted easily and efficiently into (*R*)-4-nitroatrolactic acid (**8**) of 100% ee. This process represents the best route to this useful chiral acid. Since the 4-triflyloxy group in the product of entry 6 is easily replaced by a large variety of other substituents using Pd(0) catalysis, the enantioselective silylation of entry 6 in Table 1 represents

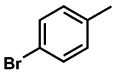
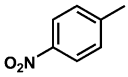
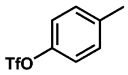
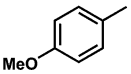
(5) The earlier the transition state in the 1,2-addition to the complexed carbonyl, the greater the attractive interaction between carbonyl and neighboring mexyl groups and the greater the degree of organization of the reactants as shown in Table 1, entry 6.

(6) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412−7413.
(7) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908−9909.
(8) Tian, S.-K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900−9901.
(9) Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1009−1012.

(10) Higher enantioselectivities were observed with an *o*-tolyl substituent on boron relative to phenyl, methyl, or *n*-alkyl.
(11) In the absence of phosphine oxide as co-reactant the enantioselectivities were considerably lower.
(12) Data on the determination of enantioselectivities and absolute configurations of the cyanosilylation products are provided in the Supporting Information.

Table 1. Oxazaborolidinium-Catalyzed Cyanosilylation of Methyl Ketones

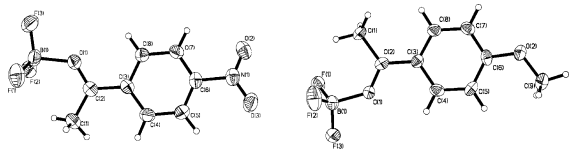


Entry	Substrate R	Ar	Reaction Condition Co-reactant (eq.)	Temp. (°C)	Time (day)	% yield, % ee
1		Ph	Ph_3PO (0.2)	25	4	97, 80
		Ph	$MePh_2PO$ (0.11)	25	3	62, 88
		o-Tolyl	$MePh_2PO$ (0.11)	25	3	95, 85
2		Ph	Ph_3PO (0.11)	25	2	92, 96[a]
3		Ph	Ph_3PO (0.1)	25	4	49, 65
		o-Tolyl	$MePh_2PO$ (0.11)	25	14	77, 83
4		*o*-Tolyl	$MePh_2PO$ (0.11)	45	10	73, 81
5		*o*-Tolyl	$MePh_2PO$ (0.11)	45	10	83, 96
6		*o*-Tolyl	$MePh_2PO$ (0.11)	45	10	79, 95
7		*o*-Tolyl	$MePh_2PO$ (0.11)	25	7	45, 32[b]

[a] Absolute configuration of the product is *S*. [b] The absolute configuration of the major product is *S*, i.e. in contrast to the results of entries 3−6.

a practical link to a large number of other interesting 4-substituted atrolactic acids.

The beneficial effect of electron-withdrawing para substituents on the enantioselectivity of the cyanosilylation of acetophenones with catalysis by **1** can be rationalized in a logical way. Although an electron-withdrawing para substituent can be expected to diminish the basicity of the acetophenone carbonyl group and thus the degree of complexation to catalyst **1**, the transition state for the cyanosilylation would occur at an earlier stage along the reaction coordinate than would be the case for more basic acetophenones. Consequently, the interaction of the partially positive complexed carbonyl carbon and the neighboring mexyl group would be greater for the less basic substrates, and the enantioselectivity should be higher, as it in fact is. As documented in entry 7 in Table 1, the strongly electron-supplying para methoxy group of 4-methoxyacetophenone causes a drastic reduction in enantioselectivity as compared to the other acetophenones of Table 1 (entries 3−6). Remarkably, the predominating absolute stereochemical course of the catalytic cyanosilylation of 4-methoxyacetophenone is *opposite* to that of the other acetophenones. We think that this large difference is a consequence of the transition-state argument that is summarized above. The complex between catalyst **1** and 4-methoxyacetophenone is especially stable with substantial



9 **10**

Figure 1. X-ray structures of BF_3·4-nitroacetophenone (**9**) and BF_3·4-methoxyacetophenone (**10**).

positive charge on the para methoxy substituent and diminished charge on the carbonyl carbon. This fact and the displacement of the transition state to a later point along the reaction coordinate serve to severely negate the interaction between the not-so-positive carbonyl carbon and the π-electron-rich mexyl substituent leading to a disorganization of the transition state (i.e., $B-O_{CO}$ rotomers) and low enantioselection.

Although it might be argued that the large difference in the cyanosilylation reactions of 4-nitroacetophenone and 4-methoxyacetophenone could be due to a different geometry of coordination of ketone to catalyst **1**, for instance very different $B-O-C_{CO}$ angles, we have obtained strong evidence against this possibility. Crystalline complexes of 4-nitroacetophenone and 4-methoxyacetophenone with boron trifluoride were prepared and structurally examined by single-crystal X-ray diffraction analysis. The structures of these complexes, **9** and **10** respectively, are shown in Figure 1.

The structures found for these complexes, **9** and **10**, each involve coordination of BF_3 to the lone pair on the carbonyl group syn to the methyl group, as shown in the proposed TSA **7**. In addition, the shortest distances between the methyl hydrogen and the nearest fluorine are 2.38 and 2.41 Å. These distances are appreciably shorter than the sum of the van der Waals radii for H and F, 2.67 Å, which points to the attractive H−F interaction. A similar H−O interaction may help organize the TSA **7**. There are small, but interesting, differences in the X-ray-determined structures of the boron trifluoride complexes **9** and **10**. The bond between boron and the coordinated carbonyl oxygen is longer in the *p*-nitro complex **9** (1.588(3) Å), than in the *p*-methoxy complex **10** (1.531(12) Å), as expected from the greater basicity of 4-methoxyacetophenone relative to that of 4-nitroacetophenone. There is a small difference, in the expected direction, between the formyl C=O bond distance in **9** (1.251 Å) and that in **10** (1.266 Å). Differences in the $B-O-C_{CO}$ angles are clearly insufficient to account for the divergent enantioselectivities observed in the cyanosilylation of 4-nitro- and 4-methoxyacetophenones, those angles being 126.3° for **9** and 129.3° for **10**. The detailed X-ray crystallographic data for **9** and **10** are provided in the Supporting Information.

Conclusions

This research has shown that the chiral catalyst **1** is highly effective for the enantioselective cyanosilylation of a range of methyl ketones. The absolute stereochemical course of these carbonyl additions can be rationalized in a logical way using mechanistic considerations that have proved highly successful in predicting many Diels−Alder reactions in previous work.[1] The reactive intermediate $Ph_2MePOTMS(N{=}C)$, generated from Ph_2MePO and TMSCN, leads to considerably higher enantioselectivity in cyanosilylation than does TMSCN. As demonstrated from comparative experiments with 4-substituted acetophenones, higher enantioselectivities result with the more

electron-withdrawing substituents because these favor early transition states and a stronger attractive interaction between the coordinated methyl ketone carbonyl and the neighboring π-electron-rich mexyl group of **1**. Electron-supplying groups have the opposite effect, leading to stereochemically variable pathways possibly involving $B-O_{CO}$ rotamers, and low, in fact opposite, enantioselectivity. The face selectivity in the cyanosilylation of methyl ketones under catalysis by **1** (*si* face) parallels that established for aldehydes. It is proposed that the former process involves α-C$-$H$\cdots$O hydrogen bonding as an organizing element, whereas the latter involves formyl C$-$H$\cdots$O hydrogen bonding. The highly enantioselective cyanosilylations described herein are synthetically valuable since they open pathways for the synthesis of many useful chiral compounds, for example, chiral atrolactic acids.

Supporting Information Available: General procedure for the enantioselective cyanosilylation of methyl ketones using catalyst **1** and characterization data for each product. This material is available free of charge via the Internet at http://pubs.acs.org.

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