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Catalytic Asymmetric Cyanosilylation of Ketones with Chiral Lewis Base

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Catalytic asymmetric cyanation of prochiral ketones provides an attractive enantioselective approach toward chiral building blocks containing a quaternary center via optically active tertiary cyanohydrins.[1,2] Enantioselective cyanosilylation and cyanocarbonation of ketones with chiral metal-based Lewis acids[3−6] and organic bases,[7] respectively, have been reported. These reactions provide useful methods for the enantioselective creation of quaternary stereocenters bearing two electronically or sterically different substituents (R^1 and R^2).[8] However, a broadly applicable catalytic approach for the construction of quaternary stereocenters, especially those bearing two electronically and sterically analogous substituents, remains a desirable yet challenging goal. Herein, we describe an advance toward this goal via the realization of the first highly enantioselective cyanosilylation of ketones with an organic chiral Lewis base.

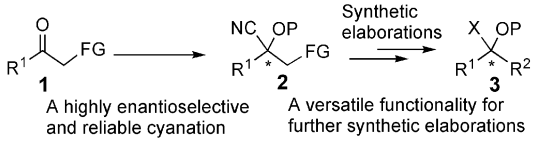
Our strategy involves a catalytic enantioselective cyanation of ketones bearing a versatile functional group, followed by transformations of the versatile functional groups into a wide range of other structures (Scheme 1). For such an approach to become broadly useful, ketones **1** should be readily accessible and the catalytic cyanation must be highly enantioselective and extremely general with respect to the R^1 group of ketone **1**. These desirable properties should be, ideally, attained with readily available catalysts.

Of particular interest to us was to explore this approach via the development of a metal-free catalytic enantioselective cyanation of ketones **1** with the readily accessible modified cinchona alkaloids,[9] in light of the ability of modified cinchona alkaloids to function as broadly effective organic chiral Lewis base and nucleophilic catalysts.[7,10−15] The implementation of the strategy illustrated in Scheme 1 with catalysts based on a cinchona alkaloid skeleton requires an amine-catalyzed cyanation that is effective for both conjugated and unconjugated ketones. Unfortunately, the recently reported modified cinchona alkaloid-catalyzed cyanocarbonation of ketones is ineffective with conjugated ketones.[7] Although only sporadic examples of amine-catalyzed cyanosilylations have been reported for cyclohexanone,[16] 1,1,1-trifluoro-4-ethoxybut-3-en-2-one,[17] and acetophenone,[18] they nevertheless indicate that an amine may be able to efficiently catalyze the cyanosilylation of both conjugated and unconjugated ketones.

Indeed, our initial catalyst screening studies revealed that DABCO is an effective catalyst for both conjugated and unconjugated ketones (Scheme 2). High-yielding cyanosilylation can be achieved even with the sterically hindered pinacolone (**4b**). Moreover, cyanosilylation of chalcone (**4d**) afforded exclusively the corresponding 1,2-addition product.

We next focused on the cyanosilylation of ketones with modified cinchona alkaloids. We were especially interested in the asymmetric cyanosilylation of the readily accessible α,α-dialkoxy ketones (acetal ketones).[19] We reasoned that, in addition to serving as a versatile handle for synthetic elaborations of the product, ketone cyanohydrin, the acetal group should also enhance the activity of the ketone toward the nucleophilic enantioselective cyanosilylation.

Scheme 1. A General Approach for Catalytic Enantioselective Construction of Quaternary Stereocenters



Scheme 2. DABCO-Catalyzed Cyanosilylation of Ketones

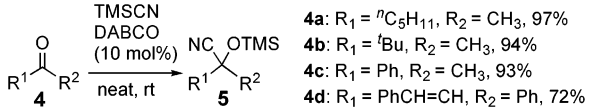
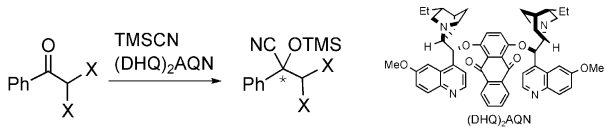


Table 1. $(DHQ)_2AQN$-Catalyzed Asymmetric Cyanosilylation of $PhCOCHX_2$ [a]



entry	ketone	X	cat./mol%	*T*/°C	time/h	conv/%[c]	ee/%[d]
1	**4c**	H	10	−24	16	91	31
2	**6a**	O*c*-C_6H_{11}	10	−24	7	100	57
3	**6b**	$OCH_2CH{=}CH_2$	10	−24	7	100	63
4	**6c**	O*n*-C_8H_{17}	10	−24	7	100	73
5	**7a**	OEt	10	−24	7	100	74
6[b]	**7a**	OEt	2	−50	19	100	90

[a] Unless specified, the reaction was run with 4.0 equiv of TMSCN and the catalyst in chloroform. [b] Three equivalents of TMSCN was used. [c] Determined by GC analysis. [d] Determined by HPLC analysis.

Cyanosilylations of acetal ketones **6a−c**, **7a** with various cinchona alkaloid derivatives were performed, and at −24 °C in the presence of $(DHQ)_2AQN$ they were found to proceed with increased rate and enantioselectivity relative to the cyanosilylation of acetophenone **4c** (entries 2−5 vs entry 1, Table 1). Importantly, the cyanosilylation of acetal ketone **7a** at −50 °C was found to proceed in complete conversion and 90% ee with 2 mol % of $(DHQ)_2AQN$ (entry 6, Table 1).

As summarized in Table 2, excellent enantioselectivity and yield is obtained with acetal ketones **7** bearing a broad range of aryl, alkenyl, alkynyl, and alkyl substituents.[20] Even acetal ketone **7m**, in which both the α- and the α′-carbon are disubstituted, is converted to the corresponding ketone cyanohydrin in 94% ee (entry 17, Table 2). Interestingly, $(DHQ)_2AQN$ in chloroform and $(DHQD)_2PHAL$ in ethyl acetate afford the highest ee for the formation of the two enantiomers of the product (**8**), respectively (entries 3−4, 6−7, 10−11, 13−14, Table 2). The cyanosilylation of acetal ketone **7j** was performed on a 0.10 mol scale (Scheme 3). Both the isolation of product **8j** (92% ee) and the recovery of the $(DHQ)_2AQN$ were achieved in quantitative yield using a simple extractive procedure.[21] These results were duplicated with the recovered $(DHQ)_2AQN$.

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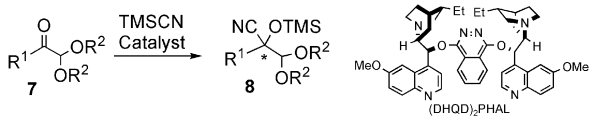
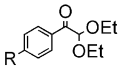
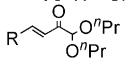
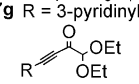
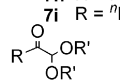
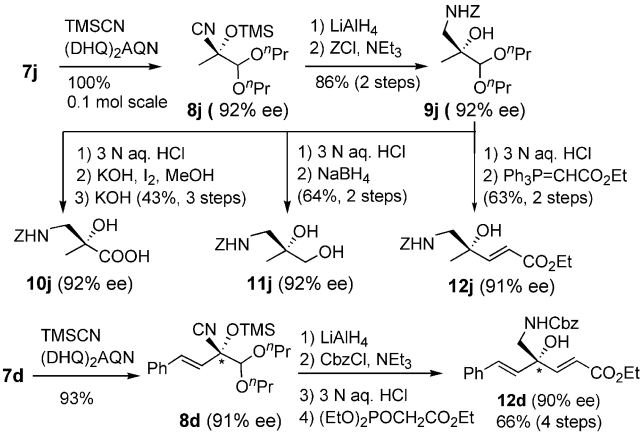
Table 2. Modified Cinchona Alkaloid-Catalyzed Asymmetric Cyanosilylation of Acetal Ketones[a]



Entry	Ketone	Catalyst (mol%)	T (°C)	time (h)	Yield[c] (%)	ee[d] (%)
1		**7a** (DHQ)$_2$AQN (2)	-50	19	98	90
2		**7b** (DHQ)$_2$AQN (2)	-50	18	94	97
3	**7a** R = H	**7c** (DHQ)$_2$AQN (2)	-50	18	96	98
4[b]	**7b** R = OMe **7c** R = Cl	**7c** (DHQD)$_2$PHAL (10)	-50	40	99	94
5		**7d** (DHQ)$_2$AQN (2)	-50	16	93	91
6		**7e** (DHQ)$_2$AQN (2)	-50	18	92	90
7[b]	**7d** R = Ph	**7e** (DHQD)$_2$PHAL (10)	-30	21	96	92
8	**7e** R = *p*-MeOC$_6$H$_4$ **7f** R = *p*-ClC$_6$H$_4$	**7f** (DHQ)$_2$AQN (2)	-50	18	95	92
9	**7g** R = 3-pyridinyl	**7g** (DHQ)$_2$AQN (2)	-50	18	97	93
10		**7h** (DHQ)$_2$AQN (2)	-50	19	93	96
11[b]		**7h** (DHQD)$_2$PHAL (10)	-30	21	96	93
12	**7h** R = Ph **7i** R = ^{n}Bu	**7i** (DHQ)$_2$AQN (2)	-50	18	94	95
13		**7j** (DHQ)$_2$AQN (2)	-50	46	97	92[e]
14[b]		**7j** (DHQD)$_2$PHAL (5)	-50	88	95	96
15	**7j** R = Me, R' = ^{n}Pr	**7k** (DHQ)$_2$AQN (20)	-50	24	96	97
16	**7k** R = BnCH$_2$, R' = ^{n}Pr **7l** R = ^{n}Bu, R' = Et	**7l** (DHQ)$_2$AQN (5)	-50	18	92	90
17	**7m** R = ^{i}Pr, R' = Et	**7m** (DHQ)$_2$AQN (20)	-40	94	81	94

[a] Unless specified, the reaction was performed by treatment of the ketone (0.20 mmol) with TMSCN (3.0 equiv) and the catalyst in chloroform (0.20 mL). [b] The reaction was run with 2.0 equiv of TMSCN in ethyl acetate. [c] Isolated yield. [d] Determined by HPLC or GC analysis as described in the Supporting Information. [e] The absolute configuration is determined to be *R* as described in the Supporting Information.

Scheme 3. Catalytic Enantioselective Synthesis of Amino Alcohols Bearing Quaternary Stereocenters



* The absolute configurations of **8d** and **12d** are assigned by analogy.

We have applied this cyanosilylation to the synthesis of several optically active multifunctional chiral building blocks bearing a quaternary stereocenter (**10**−**12j**, **12d**, Scheme 3). Especially noteworthy is the synthesis of **12d**, which contains a quaternary stereocenter bearing two substituents that are highly analogous to each other in terms of both steric and electronic properties.

In summary, we have developed the first highly enantioselective cyanosilylation of ketones catalyzed by a chiral Lewis base. The reaction employs commercially available and fully recyclable catalysts, involves a simple experimental procedure, and is exceedingly general for acetal ketone **7**. Coupled with the synthetic versatility of the acetal functionality, this reaction provides a new, practical, and broadly applicable approach toward chiral building blocks bearing quaternary stereocenters. Although, to our knowledge, previously unexplored in asymmetric synthesis, acetal ketones **7** demonstrate unusual reactivity and selectivity toward the enantioselective cyanosilylation, thereby suggesting that they may be interesting substrates for other catalytic enantioselective reactions.

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Supporting Information Available: Experimental procedures and characterization of the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Choi, M. C. K.; Chan, S.-S.; Chan, M.-K.; Kim, J.-C.; Matsumoto, K. *Heterocycles* **2002**, *58*, 645.
(19) As described in the Supporting Information, a wide variety of α,α-dialkoxy ketones (**6a**−**c**, **7a**−**m**) can be prepared from commercially available reagents such as α,α-dialkoxyacetonitrile, arylglyoxal monohydrate, and 1,3-dihydroxyacetone dimer in one or two steps.
(20) Simple ketones afford generally modest enantioselectivity (10−76% ee).
(21) For experimental details, see the Supporting Information.

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