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Asymmetric Strecker Reaction of Aldimines Using Aqueous Potassium Cyanide by Phase-Transfer Catalysis of Chiral Quaternary Ammonium Salts with a Tetranaphthyl Backbone

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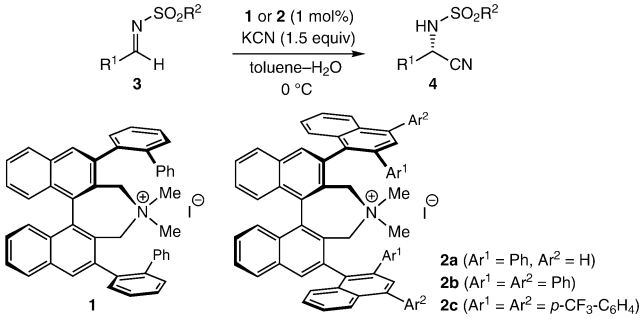
The catalytic asymmetric cyanation of imines, Strecker reaction, represents one of the most direct and viable methods for the asymmetric synthesis of α-amino acids and their derivatives. Numerous recent efforts in this field have resulted in the establishment of highly efficient and general protocols, which provide reliable access to a wide range of optically active α-amino nitriles, including those with α-quaternary stereocenters.[1−3] However, all the previously elaborated catalytic asymmetric Strecker methodologies rely on the use of either alkylmetal cyanide or anhydrous hydrogen cyanide generally at low temperature, which poses an important problem to be addressed, particularly, when large-scale industrial applications are considered. In this regard, we have been interested in the possibility of employing potassium cyanide (KCN) as a cyanide source within the context of our research program for the development of new and practical synthetic strategies by asymmetric phase-transfer catalysis.[4,5] Herein, we disclose the first example of phase-transfer-catalyzed, highly enantioselective Strecker reaction of aldimines using aqueous KCN based on the molecular design of chiral quaternary ammonium salts **2** bearing the tetranaphthyl backbone as a remarkably efficient catalyst (Scheme 1).

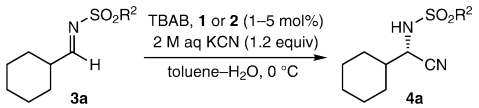
Scheme 1



We initiated our search for an appropriate reaction system with an imine of cyclohexanecarboxaldehyde as a model substrate in order to realize its cyanation under biphasic conditions (aq KCN, organic solvent). For this purpose, the imine nitrogen substituent, solvent, and concentration of KCN were screened using TBAB (5 mol %) as catalyst, which revealed that a *N*-arylsulfonyl imine, such as **3a** (R^2 = *p*-Tol), was uniquely reactive for cyanation with 2 M aqueous KCN in toluene−H_2O at 0 °C (entry 1, Table 1). The marked rate retardation observed without TBAB demonstrates the essential role of the catalyst in extracting the cyanide anion from the aqueous phase as an ammonium cyanide with enhanced nucleophilicity (entry 2).

With this information in hand, we set out to study the phase-transfer-catalyzed asymmetric Strecker reaction. Since initial attempts with our *N*-spiro-type catalysts were ineffective,[6] we designed new chiral quaternary ammonium salts that would exert sufficient reactivity and stereoselectivity. Our chief concern was to endow the ammonium cation with the ability to achieve a facile anion extraction and a precise enantiofacial discrimination of the prochiral imine. To this end, we first assembled chiral ammonium iodide **1** possessing the hydrophilic dimethylammonium cation moiety linked to the lipophilic binaphthyl-derived subunit. A key feature of this catalyst design is the introduction of *ortho*-aryl-substituted aromatic groups at the 3,3′-positions of the chiral binaphthyl unit. Our expectation was that the *ortho*-phenyl groups caused rotational restriction around the naphthyl−phenyl biaryl axes, which would provide a configurational bias to create a stereochemically defined molecular cavity over the nitrogen.

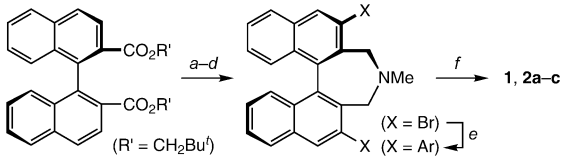
Table 1. Optimization of the Asymmetric Strecker Reaction of Aldimine **3a** under Phase-Transfer Conditions Using Aqueous KCN[a]



entry	catalyst	R^2	reaction time (h)	% yield[b]	% ee[c] (config)[d]
1	TBAB	*p*-tolyl	0.5	76	
2[e]		*p*-tolyl	0.5	15	
3	**1**	*p*-tolyl	2	84	24 (*S*)
4	**1**	mesityl	8	81	57 (*S*)
5	**2a**		4	83	89 (*S*)
6	**2b**		4	90	90 (*S*)
7	**2c**		4	89	94 (*S*)
8[f]	**2c**		2	89	95 (*S*)

[a] Unless otherwise noted, the reaction was carried out with 1.2 equiv of 2 M aq KCN and TBAB (5 mol %), **1** or **2** (1 mol %) in toluene−H_2O (v/v 1:3) at 0 °C. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Absolute configuration was assigned after facile derivatization to the corresponding amino nitrile hydrochloride. See the Supporting Information. [e] Without catalyst. [f] With 1.5 equiv of 2 M aq KCN.

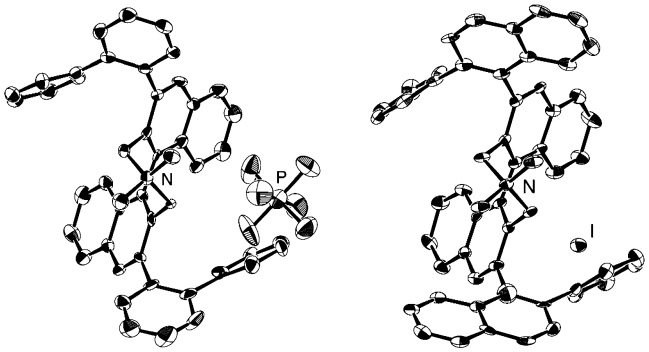
Scheme 2 [a]



[a] Reagents and conditions: (a) $Mg(TMP)_2$, THF, 0 °C to rt; Br_2, −78 °C to rt, 71%; (b) DIBAL-H, CH_2Cl_2, 0 °C to rt; (c) PBr_3, CH_2Cl_2, 0 °C to rt; (d) $MeNH_2/H_2O$, THF, 0 °C, 64% (three steps); (e) $ArB(OH)_2$, $Pd(OAc)_2$, PPh_3, Cs_2CO_3, DMF, 90 °C; (f) MeI, rt, 63−70% (two steps).

The synthesis of **1** was implemented in a six-step sequence, as illustrated in Scheme 2. Although three diastereomers could be formed after installation of the 3,3′-*ortho*-phenylphenyl groups, two stereoisomers (symmetric and asymmetric) were obtained in a ratio of 4:1 (^{1}H NMR).[7] The major isomer was converted to **1** by alkylation with methyl iodide. The three-dimensional molecular structure of **1** was unequivocally determined by the single-crystal

10.1021/ja058066n CCC: $33.50



(a) (b)

Figure 1. ORTEP diagrams of **1**−PF_6 (a) and **2a** (b). Hydrogen atoms and solvent molecules are omitted for clarity.

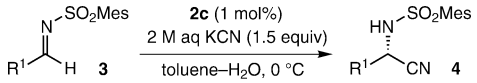
X-ray diffraction analysis of **1**−PF_6, revealing its *R*,*R*,*R* configuration (Figure 1a). As expected, each phenyl substituent at the 3,3′-positions of the binaphthyl unit is nearly perpendicular to the attached naphthalene ring, extending over the central cationic nitrogen. Further, the two pendant *ortho*-phenyl groups are parallel to each other, which extends the aromatic surface in the reaction cavity. This could position the imine functionality in an ideal proximity to the cyanide ion in the chiral environment, enabling an efficient and stereoselective bond formation.

To examine this hypothesis, we evaluated the potential of **1** as a catalyst for the asymmetric cyanation of **3a** (R^2 = *p*-Tol) under the biphasic conditions. Thus, a mixture of **3a** (R^2 = *p*-Tol) and **1** (1 mol %) in toluene−aqueous KCN (1.2 equiv) was vigorously stirred at 0 °C. TLC monitoring indicated the complete consumption of the substrate after 2 h, and the desired **4a** (R^2 = *p*-Tol) was isolated in 84% yield with 24% ee (entry 3, Table 1). The *N*-mesitylenesulfonyl imine **3a** (R^2 = Mes) enhanced the enantioselectivity to 57% ee, though longer reaction time was required (entry 4). These promising results support the molecular design concept used for catalyst optimization, which was further improved by replacing the 3,3′-substituents with the 2-phenyl-1-naphthyl group. The chiral quaternary ammonium iodide **2a** with the stereochemically homogeneous tetranaphthyl backbone was prepared in a manner similar to that of **1** (Scheme 2). Subsequent crystallographic analysis confirmed the enlarged chiral cavity, which suggested the possibility of enhanced enantiofacial selectivity (Figure 1b). Indeed, catalyst **2a** exhibited high chiral efficiency in the reaction of **3a** (R^2 = Mes) under similar conditions to afford **4a** (R^2 = Mes) with 89% ee (entry 5). Moreover, the additional phenyl substituents at the 4-position of the outer naphthyl units (**2b**) gave even better enantiocontrol (entry 6). Finally, the introduction of an electron-withdrawing trifluoromethyl group to all the appended phenyl groups (**2c**) improved the enantioselectivity further (entry 7). The phase-transfer cyanation of **3a** (R^2 = Mes) with 1.5 equiv of KCN and **2c** was completed in 2 h to produce **4a** (R^2 = Mes) in 89% yield with 95% ee (entry 8).

Other selected examples in Table 2 demonstrate the effectiveness of this new asymmetric Strecker protocol for a variety of aliphatic aldimines.[8] Generally, 1 mol % of **2c** with 1.5 equiv of KCN was sufficient for efficient reactions, and the corresponding protected amino nitriles **4** were obtained in high yield with excellent enantioselectivity. This system accommodates substrates having α-*tert*-alkyl substituents, such as pivalaldimine (entries 5−7). This enables a facile synthesis of enantiomerically enriched *tert*-leucine and its various analogues, which are important chiral building blocks not accessible by the asymmetric alkylation of glycine derivatives.[4]

In conclusion, we have accomplished the phase-transfer-catalyzed, highly enantioselective cyanation of aldimines using aqueous KCN as a cyanide source through the development of new chiral quaternary ammonium iodide **2c** bearing a stereochemically defined tetranaphthyl backbone. This study represents a new approach to asymmetric Strecker-type reactions, which holds distinctive practical advantages and should fulfill the continuing demand for the availability of a broad range of α-amino acids in diverse scientific disciplines.

Table 2. Phase-Transfer-Catalyzed Asymmetric Strecker Reaction of Aldimines **3**[a]



entry	**3** (R^1)	reaction time (h)	% yield[b]	% ee[c]	product
1	*c*-Oct	2	88	97	**4b**
2	*i*-Pr	3	85	93	**4c**
3	$Ph(CH_2)_2$	2	81	90	**4d**
4	$(CH_3)_2CHCH_2$	3	82	88	**4e**
5	*t*-Bu	3	94	94	**4f**
6	$Ph(CH_3)_2C$	8	95	98	**4g**
7	Ad	8	98	97	**4h**

[a] The reaction was conducted with 1.5 equiv of 2 M aq KCN and **2c** (1 mol %) in toluene−H_2O (v/v 1:3) at 0 °C. [b] Isolated yield. [c] Determined by HPLC analysis. Absolute configuration was deduced from that of **4a**.

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Supporting Information Available: Representative experimental procedures and spectroscopic characterization of new compounds (PDF); the crystallographic data for **1**−PF_6 and **2a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) For representative results, see the Supporting Information.

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