Asymmetric Hydrocyanation of *N*-Phosphinoyl Aldimines with Acetone Cyanohydrin by Cooperative Lewis Acid/Onium Salt/Brønsted Base Catalysis

Thorsten Junge,[a] Marvin Titze,[a] Wolfgang Frey,[a] and René Peters*[a]

α-Amino acids are of fundamental importance for life. Both natural and artificial α-amino acids also play a crucial role for pharmaceutical purposes. The catalytic asymmetric Strecker reaction still provides one of the most attractive strategies to prepare scalemic α-amino acids. Here we disclose a new concept for Strecker reactions, in which an achiral Brønsted base cooperates with a Lewis acid and an aprotic ammonium salt, which are both arranged in the same chiral catalyst entity. The described method could successfully address various long-standing practical issues of this reaction type. The major practical advantages are that (1) the *N*-protecting group is readily removable, (2) acetone cyanohydrin is attractive as cyanation reagent in terms of atom economy and cost efficiency, (3) an excess of the cyanation reagent is not necessary, (4) the new method does not require additives and (5) is performed at ambient temperature.

The synthesis of α-amino acids by 1,2-addition of HCN to imines followed by hydrolysis of the formed α-amino nitriles – well-known as Strecker reaction – has a very long history initiated by the original report in 1850.[1] A number of enantioselective catalytic methods giving access to highly enantioenriched amino acids were described since the first report by Lipton et al. in 1996.[2,3] Since gaseous, highly toxic HCN is laborious and costly to handle in a safe manner, liquid synthetic equivalents of it have been utilized in the majority of applications.[3] As such, trimethylsilyl cyanide and alkyl cyanoformates are the most commonly employed cyanide transfer reagents. Whereas silyl protecting groups are undesired in production processes for technical reasons,[4] with cyanoformates, for which usually a significant excess is required for useful results, carbonate side products are formed that need to be removed.[3] From a practical point of view, a stoichiometric amount of acetone cyanohydrin, acting as both cyanide and proton source, is considered as more attractive cyanation agent in this reaction type, because in the optimal case the only side product that is formed is one equivalent of acetone. In addition, acetone cyanohydrin is relatively inexpensive, because it is technically widely used, for instance for the synthesis of methacrylic acid and thus acrylic glass.[5] Nevertheless, to our knowledge, acetone cyanohydrin has to date not been reported in highly enantioselective hydrocyanations of aldimines.[6–8]

Another practical issue is the circumstance that a number of asymmetric Strecker reactions are limited to the use of imines equipped with *N*-protective groups that require relatively harsh reaction conditions to be removed from follow-up products.[3] In this regard, phosphinoyl protecting groups are attractive, because they are removable under mild conditions. Compared to *N*-Boc protected imines, *N*-phosphinoyl aldimines have a higher storage stability, whereas the former usually need to be stored in the form of α-aminosulfones.[9] Still, there is only one method reported by Yamamoto et al. for the highly enantioselective cyanation of *N*-phosphinoyl aldimines, which favored ethyl cyanoformate (1.5 equiv.) as cyanation agent.[10,11]

Here, we report the first asymmetric hydrocyanation of *N*-phosphinoyl aldimines with acetone cyanohydrin. This method provides a rapid and practical access towards enantioenriched α-amino acids. It does neither require additives nor an access of cyanation reagent. The presented method is enabled by the combination of a catalytic achiral Brønsted base and our concept of cooperative asymmetric bifunctional Lewis acid/onium salt catalysis.[12–15]

The Lewis acidic metal center is supposed to activate the imine electrophile, whereas the onium moiety should stabilize the cyanide anion – in situ released by the catalytic base – and spatially control its trajectory for an imine attack to attain effective enantioface differentiation (Figure 1).

The investigation started with complex **C1-I** (Table 1, entry 1, 5 mol%) carrying a diethylmethyl ammonium iodide

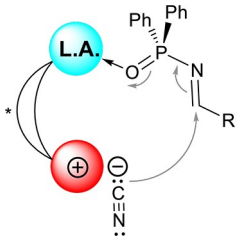

Figure 1. Cooperative intramolecular Lewis acid/onium salt catalysis concept.

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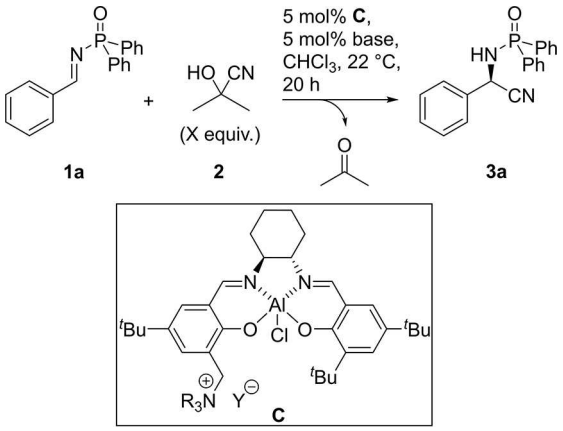
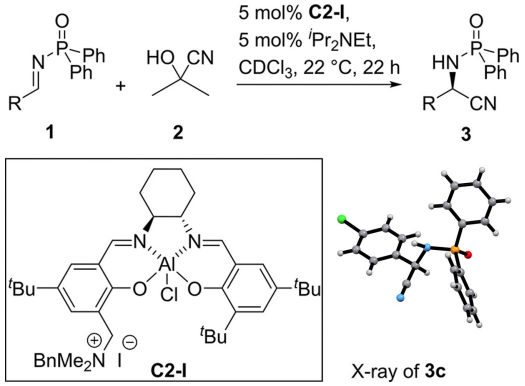
Table 1. Development of the asymmetric hydrocyanation of *N*-phosphinoyl aldimine **1a** with acetone cyanohydrin **2** by Lewis acid/onium salt catalysis.



Entry	C	NR_3	Y^-	Base	X	Yield [%][a]	er[b]
1	**C1-I**	NEt_2Me	I^-	NEt_3	2.0	68	79:21
2	**C1-I**	NEt_2Me	I^-	$^iPr_2NEt$	2.0	90	89:11
3	**C1-I**	NEt_2Me	I^-	DMAP	2.0	81	90:10
4	**C1-Br**	NEt_2Me	Br^-	$^iPr_2NEt$	2.0	99	88:12
5	**C1-Cl**	NEt_2Me	Cl^-	$^iPr_2NEt$	2.0	99	88.5:11.5
6	**C2-I**	NMe_2Bn	I^-	$^iPr_2NEt$	2.0	94	93.5:6.5
7	**C3-I**	pyridine	I^-	$^iPr_2NEt$	2.0	95	90:10
8	**C4-I**	quinuclidine	I^-	$^iPr_2NEt$	2.0	91	87.5:12.5
9	**C2-I**	NMe_2Bn	I^-	$^iPr_2NEt$	1.1	90	94:6

[a] Yield of isolated product **3a**. [b] Enantiomeric ratio (er) determined by HPLC. DMAP = 4-dimethylaminopyridine.

Table 2. Investigation of the reaction scope.



Entry	1/3	R	Yield 3 [%][a]	er 3[b]
1	**a**	Ph-	95	94:6
2	**b**	2-Cl–C_6H_4-	90	85:15
3	**c**	4-Cl–C_6H_4-	97	95:5
4	**d**	4-F–C_6H_4-	74	89:11
5	**e**	4-Br–C_6H_4-	83	91:9
6	**f**	4-I–C_6H_4-	66	95:5
7	**g**	4-Me–C_6H_4-	92	95:5
8	**h**	4-MeO–C_6H_4-	97	87:13
9	**i**	1-naphthyl-	71	92:8
10	**j**	2-naphthyl-	63	90:10
11	**k**	2-furyl-	95	93:7
12	**l**	2-pyrrolyl-	39	88:12
13	**m**	(*E*)-Me–CH=CH-	81	83:17
14	**n**	(*E*)-Ph–CH=CH-	83	85:15

[a] Yield of isolated product **3**. [b] Enantiomeric ratio (er) determined by HPLC.

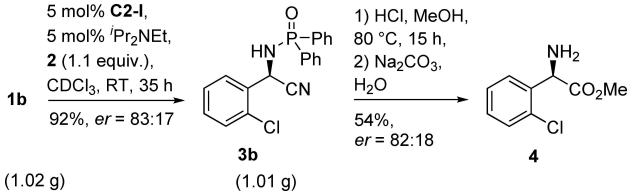
moiety. Triethylamine was used as catalytic base to release a cyanide anion from acetone cyanohydrin. In chloroform at room temperature the product was formed with moderate yield, but promising enantioselectivity. Different bases were then screened and improvements were achieved with ethyldiisopropylamine (entry 2) and 4-dimethylaminopyridine (DMAP, entry 3). Weaker bases like pyridine did not allow for product formation. Investigation of different ammonium counterions revealed only small differences between the different halide ions (entries 4 & 5). Various ammonium moieties were also examined and an improvement was achieved by a benzyldimethylammonium group (entry 6). Most other onium salt moieties resulted in lower enantioselectivity (see e.g. entries 7 & 8). Finally, for the sake of practicality the quantity of acetone cyanohydrin was decreased to a nearly equimolar amount (entry 9).[16] This change had almost no effect on the yield of **3a** (90%), which was formed with an enantiomeric ratio of 94:6 (*i.e.* 88% ee).[17]

The optimized conditions of Table 1, entry 9 were then employed for the investigation of the substrate scope (Table 2).[18] On preparative scale the model reaction gave a similar yield with unchanged enantioselectivity (entry 1) compared to the initial screening. Notably, catalyst **C2-I** could also be readily recycled and reused by an extraction protocol taking advantage of its polar ionic nature (for details see the Supporting Information).

Aromatic imines with both electron withdrawing and donating substituents (entries 2–6 & 7–8) were also well tolerated. The absolute configuration was determined to be (*R*) for **3c**.

Experiments on gram scale were performed with **1b** (Scheme 1) and provided similar results as on smaller scale (see Table 2/entry 2). It was also shown that *N*-deprotection and nitrile hydrolysis of **3b** is possible under mild conditions with nearly no racemization.[19] Product **4** is a precursor towards Clopidogrel, a drug that prevents platelet activation and aggregation and is commonly used for secondary prevention of ischemic events like stroke and myocardial infarction.[20]

Also polycyclic aromatic residues were well accommodated (Table 2, entries 9–10), as well as heteroaromatic rings (entries 11–12). Moderate enantioselectivities yet good yields were



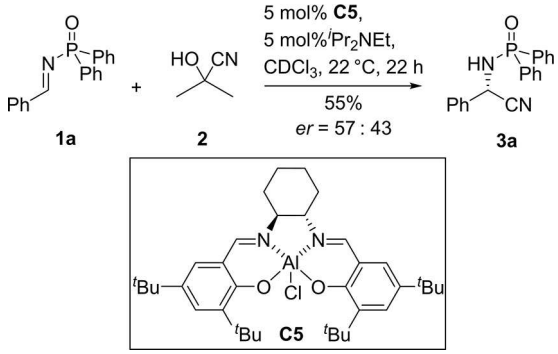
Scheme 1. Gram scale synthesis of **3b** and further transformation to (2-chlorophenyl)glycine methyl ester (**4**), a precursor towards Clopidogrel.

attained from α,β-unsaturated imines (entries 13–14). In contrast, aldimines that are aliphatic, those bearing additional π-acceptors and ketimines[21] did not provide useful data so far.

Several investigations were performed to learn more about the reaction mechanism. Continuous reaction monitoring by ^{1}H-NMR spectroscopy showed no induction period. The enantiomeric ratios were found to be stable during the course of the reaction showing that partial racemization is not an issue.

Moreover, NMR studies revealed a cyanide release by deprotonation of acetone cyanohydrin by Hünig's base (see Supporting Information). The cyanide ion is expected to be picked up by the ammonium moiety of the catalyst in a reversible anion exchange. Using catalytic NaH (5 mol%) instead of Hünig's base resulted in significantly lower conversion (44%), yield (41%) and enantioselectivity (*er* = 67:33). If the role of the non-nucleophilic base was just to generate a catalytic amount of cyanide, similar reaction outcomes would be expected for both bases. It thus appears likely that the generated conjugated acid of Hünig's base – and not **2** – is acting as the main proton source to release the product. It was also found that the rate of imine and acetone cyanohydrin conversion is nearly identical.

A non-linear effect (NLE)[22] was not found (see ESI) supporting a scenario in which only one catalyst molecule is involved. An intramolecular cooperation between the Lewis acidic Al center and the aprotic ammonium residue within this catalyst molecule was confirmed by a control experiment in which catalyst **C5**[3g] lacking an ammonium moiety was employed (Scheme 2). In this case the enantioselectivity was significantly diminished and the opposite (*R*) configured enantiomer was formed in slight excess.



Scheme 2. Control experiment with catalyst **C5** lacking an ammonium moiety.

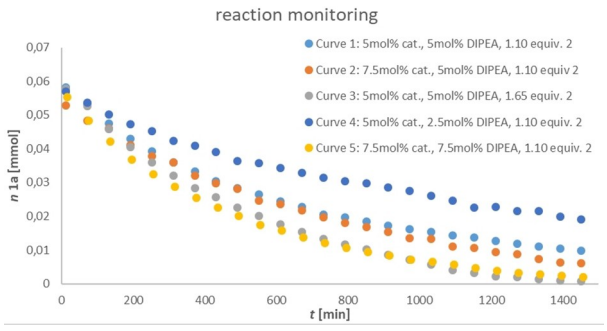


Figure 2. Reaction monitoring showing the amount of imine **1a** during the course of reaction for different amounts of catalyst, base and acetone cyanohydrin (DIPEA = ^{i}Pr$_2$NEt).

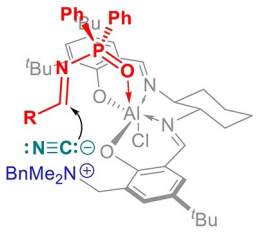


Figure 3. Working model.

In addition, kinetic studies were performed (Figure 2). It was found that the reaction rate got higher by a larger amount of the cyanation reagent **2** (compare curves 1 & 3). These experiments also showed that the reaction rate is not increased by a higher catalyst amount without simultaneously increasing the amount of base (compare curves 1, 2 & 4). In contrast, simultaneously increasing the amount of base and catalyst considerably accelerated the reaction (curve 5). Unfortunately, an excess of base relative to catalyst slowed the reaction (maybe due to blocking the Lewis acid by coordination) and catalyst decomposition was found. The results of Figure 2 suggest that the release of cyanide by deprotonation of **2** is the rate limiting factor and the catalyst in not involved in that step.

To explain the enantioselectivity, Figure 3 depicts our working hypothesis, which is in agreement with the absolute configuration of products **3**. According to this model, the imine coordinates by its electron rich phosphinoyl oxygen atom to the hard Al center. The imino moiety points away from the cyclohexane backbone thus allowing for a cyanide direction by the ammonium moiety to facilitate the 1,2-addition step.

In conclusion, we developed the first asymmetric hydrocyanation of storable *N*-phosphinoyl aldimines with acetone cyanohydrin. This method provides a rapid access towards enantioenriched α-amino acids. The major practical advantages are that (1) the *N*-protecting group is readily removable, (2) acetone cyanohydrin is attractive in terms of atom economy and cost efficiency, (3) an excess of the cyanation reagent is not necessary, (4) the new method does not require additives and (5) is performed at ambient temperature. These features were enabled by the combination of a catalytic achiral Brønsted base and our concept of cooperative asymmetric bifunctional Lewis acid/onium salt catalysis.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: 1,2-addition · aluminum · amino acid · amino nitrile · cooperative catalysis

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Cooperative catalysis strikes again: α-Amino acids are crucial for drug development. The asymmetric Strecker reaction offers one of the most attractive ways to prepare scalemic α-amino acids. Here a new concept for Strecker reactions is disclosed, in which an achiral Brønsted base cooperates with a Lewis acid and an aprotic ammonium salt both arranged in the same chiral catalyst entity. The described method successfully addresses long-standing practical issues of this reaction type.