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Catalytic, Enantioselective α-Additions of Isocyanides: Lewis Base Catalyzed Passerini-Type Reactions

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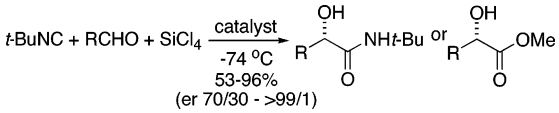

The generality of catalytic, enantioselective α-additions of isocyanides to aldehydes has been demonstrated (Passerini-type reactions). The catalytic system of silicon tetrachloride and a chiral bisphosphoramide (*R,R*)-**1b** provided high yields and good to excellent enantioselectivities for the addition of *tert*-butyl isocyanide to a wide range of aldehydes (aromatic, heteroaromatic, olefinic, acetylenic, aliphatic). Aqueous workup afforded the α-hydroxy *tert*-butyl amides whereas a low-temperature methanol quench followed by basic workup afforded the α-hydroxy methyl esters. The reaction is also successful for other isocyanides, albeit with reduced enantioselectivity. Reaction conditions, particularly the rate of addition of the isocyanide was found to be crucial for good yields and high selectivities.

Introduction

As a rare class of stable divalent carbon nucleophiles, isocyanides have the interesting ability of forming multiple bonds on the terminal carbon atom in a single reaction. Passerini, Ugi, and others have long recognized the unique synthetic utility of isocyanides when combined with various reagents and serving as a latent amide function.[1] In the classical Passerini reaction, the combination of an isocyanide with a ketone or an aldehyde and a carboxylic acid produces an α-acyloxy carboxamide. The reaction is believed to proceed via a nitrilium ion adduct which is intercepted by the carboxylate to form an acyl imidate. Subsequent Mumm rearrangement affords the α-acyloxy carboxamide product.[2] In the Ugi reaction, an α-amido carboxamide is formed from the reaction of an isocyanide with an imine (usually generated in situ) and a carboxylic acid.[3] Both of these reactions have been featured in numerous applications such as generating molecular diversity for drug discovery and in heterocycle synthesis[4,5]

Because these synthetically useful reactions generate stereogenic centers, they have been the subject of many studies on methods of stereocontrol. Apart from the diastereoselectivity that attends the use of chiral aldehydes,[6] the use of chiral auxiliaries have been most

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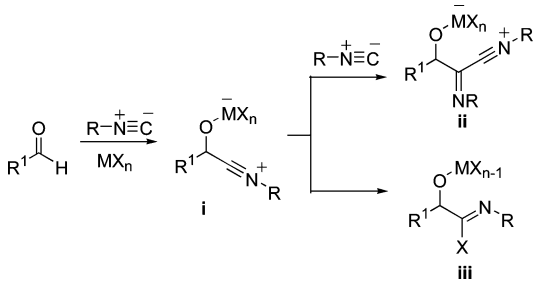
extensively developed.[7−9] In the early studies by Ugi and co-workers, excellent diastereoselectivities have been accomplished in the addition of isocyanides to chiral imines with ferrocenyl auxiliaries. More recently, Kunz and co-workers have demonstrated that chiral scaffolds derived from carbohydrates induce high selectivities in the Lewis acid mediated Ugi reaction.[8] On the other hand, the use of α-methylbenzylamine auxiliary proved to be ineffective for asymmetric induction.[9] With regard to the use of chiral isocyanide, only one successful example has been reported by Ugi and co-workers for the addition reaction with aldehydes.[10] Despite the fact that high diastereoselectivities can be achieved by the use of certain chiral auxiliaries, all of these methods suffer from the fact that chiral auxiliaries have to be stoichiometrically incorporated and then removed from the product. In view of the similarity of these reactions to cyanohydrin additions and Strecker reactions[11] it is surprising that prior to our initial communication, there were no examples of catalytic enantioselective process. Subsequently, two reports have appeared; one that employs chiral Bronsted catalysis with modest enantioselectivity and a second that employs a copper bisoxazoline complex and gives generally higher selectivities with a broader range of substrates.[12]

Background

The formal divalency of the isocyanide nucleophile provides a challenge to the successful development of chiral Lewis acid catalysis in the α-addition reactions. The primary adduct of the α-addition is a zwitterionic nitrilium ion **i**, Scheme 1. In the classical Passerini and Ugi reactions, a carboxylate combines with **i** and leads to productive reaction pathways. However, for the Lewis-acid-mediated α-addition, without a facile transfer of the counterion X, this intermediate is subject to further

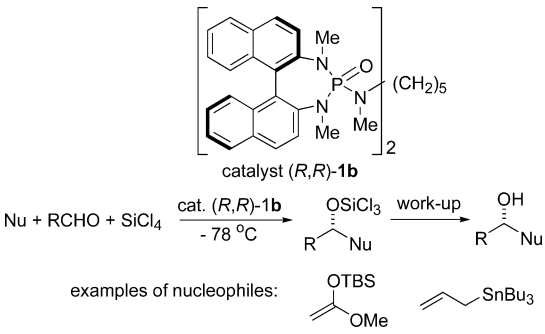
SCHEME 1



addition of isocyanide and often generates multiple addition product **ii**.[13c,14c] Furthermore, even if the adduct **iii** could be generated, the dissociation of the MX_n1 unit from this intermediate would be required for the turnover of Lewis acid catalyst, which has rarely seen success.[14]

We recognized that these problems could be addressed by application of the newly introduced concept of Lewis base activation of Lewis acids.[15] This concept has been successfully demonstrated in the context of various enantioselective carbon−carbon bond-forming reactions.[16] Chiral binaphthyldiamine-derived bisphosphoramide (*R*,*R*)-**1b** effectively activates a weak Lewis acid, $SiCl_4$, and generates a highly reactive and selective silyl cation for the asymmetric additions of allylstannanes, trialkylsilyl ketene acetals and silyl enol ethers to aldehydes (Scheme 2).[15] An important feature of these reactions is

SCHEME 2



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(13) For early examples of Lewis acid promoted α-addition reaction of isocyanides, see: (a) Muller, E.; Zeeh, B. *Liebigs Ann. Chem*. **1966**, *696*, 72−80. (b) Muller, E.; Zeeh, B. *Liebigs Ann. Chem*. **1968**, *715*, 47−51. (c) Saegusa, T.; Taka-Ishi, N.; Fujii, H. *Tetrahedron* **1968**, *24*, 3795−3798. (d) Seebach, D.; Schiess, M. *Helv. Chim. Acta* **1983**, *66*, 1618−1623. (e) Seebach, D.; Adam, G.; Gees, T.; Schiess, M.; Weigand, W. *Chem. Ber*. **1988**, *121*, 507−517. (f) Carofiglio, T.; Cozzi, P. G.; Floriani, C.; Chiesa-Villa, A.; Rizzoli, C. *Organometallics* **1993**, *12*, 2726−2736.

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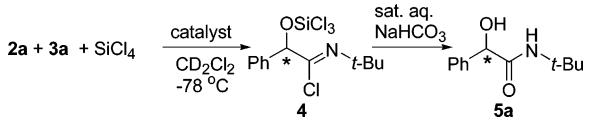
that the weak Lewis acid, $SiCl_4$, can be used in stoichiometric quantities without the fear of achiral pathways promoted by $SiCl_4$ because the kinetically competent species are formed only upon binding of $SiCl_4$ to the chiral catalyst. Furthermore, in these reactions, catalyst turnover is the transfer of the phosphoramide from a trichlorosilyl species to the bulk of the achiral Lewis acid $SiCl_4$ instead of the cleavage of the bond between the $SiCl_3$ unit and the product of the addition reaction.

The use of a stoichiometric amount of a weak Lewis acid and the fundamental change in the catalyst turnover step are ideally suited for the development of catalytic, asymmetric α-addition reactions. This report details our full investigation on the scope and limitation of the Lewis base catalyzed, $SiCl_4$-mediated, Passerini-type reactions.[17]

Results

1. α-Additions of *tert*-Butyl Isocyanide to Benzaldehyde. 1.1. Survey of Lewis Base Catalyst. In the orienting experiments, the ability of various Lewis bases to accelerate the $SiCl_4$-mediated α-additions of isocyanides to aldehydes was examined. Because of their proven promoting ability in the $SiCl_4$-mediated addition reactions, HMPA, pyridine *N*-oxide, and the chiral bisphosphoramide (*R,R*)-**1b** were tested in this reaction between *tert*-butyl isocyanide **2a** to benzaldehyde (**3a**). The initial survey was conducted in a series of VT ^{1}H NMR experiments, and the results are summarized in Table 1.

TABLE 1. $SiCl_4$-Mediated Addition of *t*-BuNC to Benzaldehyde



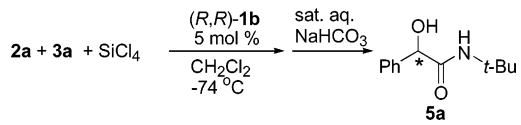
entry	catalyst	loading, mol %	conv, %	yield,[a] %	er[b]
1	none		83	79	
2[c]	(*R,R*)-**1b**	100	0		
3	HMPA	10	100	90	
4	pyridine *N*-oxide	10	100	94	
5	(*R,R*)-**1b**	5	100	83	90.2/9.8

[a] Yields of chromatographically homogeneous material. [b] Determined by CSP-SFC. [c] No $SiCl_4$ was used, and the reaction temperature was 25 °C for 24 h.

Low-temperature ^{1}H NMR analysis indicated that $SiCl_4$ alone could effectively promote the addition of *t*-BuNC to benzaldehyde. In the presence of a stoichiometric amount of $SiCl_4$, the addition proceeded to 83% conversion within 4 h at −78 °C, and the imidoyl chloride intermediate **4** was formed cleanly. After aqueous workup, the hydroxy amide product **5a** was obtained in 79% yield (Table 1, entry 1). On the other hand, bisphosphoramide (*R,R*)-**1b** alone did not promote the addition (Table 1, entry 2). Gratifyingly, the combination of a small amount of a Lewis base and a stoichiometric amount of $SiCl_4$ was most effective in promoting the addition. In the presence of 10 mol % of HMPA or pyridine *N*-oxide, the $SiCl_4$-mediated addition proceeded to completion within 4 h at −78 °C (Table 1, entries 3 and 4). Furthermore, the use of 5 mol % chiral bisphosphoramide (*R,R*)-**1b** delivered the product **5a** (from a mild quench with aqueous base) in good enantioselectivity which provided conclusive evidence that the $SiCl_4$-mediated addition was highly responsive to Lewis base catalysis (Table 1, entry 5).

1.2. Optimization of Reaction Conditions for Enantioselective Addition. To improve the enantioselectivity, the ratio between the catalyzed, asymmetric pathway and the achiral pathway has to be increased. The presence of an achiral background reaction has not been seen in other reactions with $SiCl_4$, but in this case it is not surprising because the isocyanide nucleophile is itself a Lewis base. Because the bisphosphoramide is used in trace amounts, a simple solution to suppressing the background reaction is to decrease the instantaneous concentration of the isocyanide by slow addition to a mixture of all the other reaction components.[18] Another source of background reaction could be Bronsted acid catalysis[2] from traces of HCl in the $SiCl_4$.[15d] Experiments to examine the effect of addition rate were performed by adding a solution of *t*-BuNC in CH_2Cl_2 (1.0 M) to a solution of the mixture of $SiCl_4$, benzaldehyde, phosphoramide catalyst (*R,R*)-**1b**, and Hünig's base in CH_2Cl_2 (1.0 M) over the period of time as indicated in Table 2.

TABLE 2. Optimization for (*R,R*)-1b-Catalyzed Addition of *t*-BuNC to Benzaldehyde



entry	addition time, h	*i*-Pr_2NEt, mol %	yield,[a] %	*S*/*R*[b,c]
1[d]			83	90.2/9.8
2[e]	2		94	94.3/5.7
3[e]	3	30	89	98.1/1.9
4[e]	4	10	96	> 99.0/1.0

[a] Yields of chromatographically homogeneous material. [b] Determined by CSP-SFC. [c] Absolute configuration is *S* by correlation.[19] [d] Isocyanide was added in one portion. [e] Reaction mixture was kept at −74 °C for 4 h after the addition of the isocyanide.

The results show clearly that the enantioselectivity was dependent on the rate of the addition of *t*-BuNC. When a 2 h addition period was used rather than one portion addition, the enantiomeric ratio increased from 90.2/9.8 to 94.3/5.7 (Table 2, entries 1 and 2). Further increases in the enantioselectivity were observed when the isocyanide was added over 3 h in the presence of 30 mol % of Hünig's base (Table 2, entry 3). The enantioselectivity reached the maximum when a 4 h addition protocol was used in the presence of 10 mol % of Hünig's base (Table 2, entry 4). Thus, the key factors for sup-

(16) For full accounts of the development of this concept, see: (a) Denmark, S. E.; Fujimori, S. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 2, Chapter 7. (b) Denmark, S. E.; Beutner, G. L.; Wynn, T. Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774−3789.

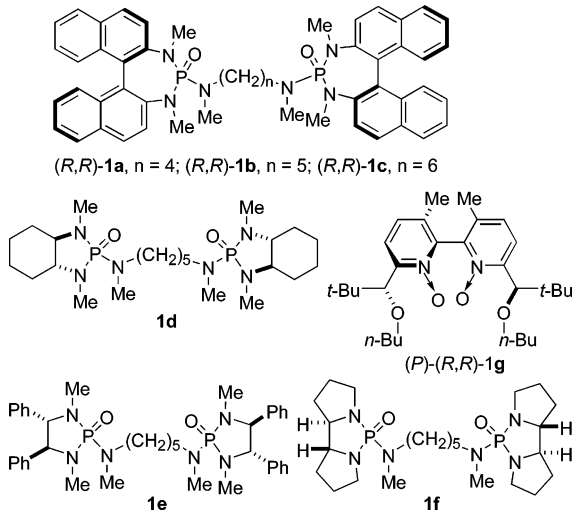
(17) Part of this work has been communicated: Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7824−7827.

(18) Lowering the concentration of the isocyanide may also disfavor the background reaction if the order in isocyanide is higher in this process than in the catalyzed addition. By analogy to other reactions, we expect that the isocyanide is first order in the catalyzed process: (a) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2000**, *122*, 12021−12022. (b) Denmark, S. E.; Pham, S. *Helv.* Chem. Acta **2000**, *83*, 1846−1853. (c) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488−9489.

pressing achiral background reaction were identified: minimizing the concentration of the isocyanide nucleophile and the suppression of Brønsted acid catalysis. Under the optimized conditions, the single enantiomer of the hydroxy amide **5a** was obtained in near quantitative yield. From the sign of optical rotation ($[\alpha]_D^{24}$ +28.8, MeOH), the absolute configuration of the product obtained with catalyst (*R*,*R*)-**1b** was determined to be *S* by correlation to the literature value.[19] This configuration indicated a *Re*-face attack on the aldehyde by the isocyanide, which is in agreement with the sense of asymmetric induction observed in the addition of allyltributylstannane and trialkylsilyl ketene acetals to benzaldehyde.[15]

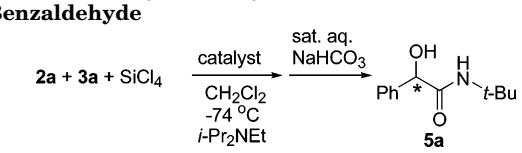
1.3. Catalyst Survey. Clearly, chiral binaphthyldiamine-derived catalyst (*R*,*R*)-**1b** is highly effective in discriminating the enantiotopic faces of benzaldehyde in the α-addition reaction. To identify other potentially useful catalysts for a broader range of aldehyde classes, a survey of catalyst structures was deemed profitable. A wide variety of dimeric Lewis bases have been synthesized in this laboratory, and hence several were investigated in the addition of *t*-BuNC to benzaldehyde (Chart 1).[20] Bisphosphoramides (*R*,*R*)-**1a** and (*R*,*R*)-**1c**, prepared

CHART 1



by linking two axially chiral 1,1′-binaphthyl-2,2′-diamine molecules with aliphatic diamine chains, were chosen to examine the effect of the linker length on enantioselectivity. The influence of varying the structure of the chiral backbones on the enantioselectivity was investigated using bisphosphoramides **1d**, **1e**, and **1f**. To access the reactivity and selectivity of the class of bis-*N*-oxides, catalyst (*P*)-(*R*,*R*)-**1g**, possessing both central and axial chiral elements, was employed.[20] The optimized reaction protocol was used for this catalyst survey: a solution of *t*-BuNC in CH_2Cl_2 (1.0 M) was added over 4 h to a solution of the mixture of $SiCl_4$, benzaldehyde, catalyst, and 10 mol % of Hünig's base in CH_2Cl_2 (1.0 M). The results are summarized in Table 3.

TABLE 3. Catalyst Survey for the Addition of *t*-BuNC to Benzaldehyde



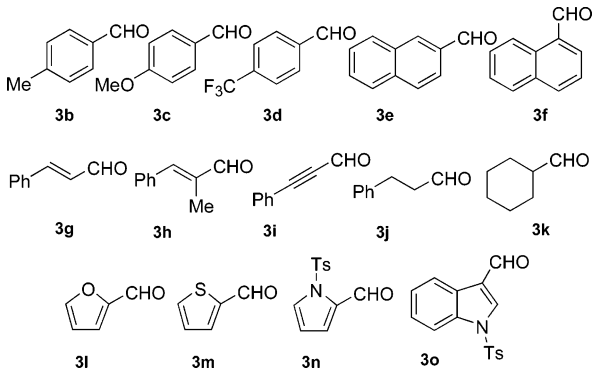
entry	catalyst	loading, mol %	yield,[a] %	*S*/*R*[b]
1	(*R*,*R*)-**1a**	5	93	96.4/3.6
2	(*R*,*R*)-**1c**	5	86	95.6/4.4
3	**1d**	10	82	34.7/65.3
4	**1e**	10	92	51.4/48.6
5	**1f**	10	87	66.3/33.7
6	*P*-(*R*,*R*)-**1g**	10	87	51.5/48.5

[a] Yields of chromatographically homogeneous material. [b] Determined by CSP-SFC.

Not surprisingly, the selectivity was highly sensitive to the structure of the diamine backbone, linker length and identity of the Lewis-base catalyst. Within the class of dimeric phosphoramides, chiral 1,1′-binaphthyl-2,2′-diamine-derived bisphosphoramides **1a**−**c** proved to be the most selective (Table 3, entries 1 and 2). Although all three linker lengths provided excellent enantioselectivity, the optimal linker length between two binaphthdiamine was found to be five methylene units (Table 3, entry 4).[21] On the other hand, none of the bisphosphoramides **1d**−**f**, derived from cyclohexane-1,2-diamine, stilbene-1,2-diamine, and 2,2′-bispyrrolidine, delivered useful selectivity (Table 3, entries 3−5). Bis-*N*-oxide (*P*)-(*R*,*R*)-**1g** was not selective at all; nearly racemic product was obtained (Table 3, entry 6).

2. Aldehyde Substrate Survey. A broad survey of the structure of the aldehyde acceptor was conducted to explore the scope of the enantioselective addition reaction with *t*-BuNC. Aldehydes from all basic structural classes, including aromatic (**3b**−**f**), olefinic (**3g**,**h**), acetylenic (**3i**), linear (**3j**), and branched aliphatic (**3k**) (Chart 2), were investigated in the addition of *t*-BuNC. Also, aldehydes containing common heterocycles are also included in this survey (**3l**−**o**).

CHART 2



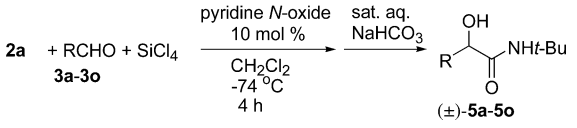
2.1. Additions Catalyzed by Pyridine *N*-Oxide. To test the scope of the aldehyde substrate and generate racemic sample to aid enantiomeric analysis, these aldehydes were first studied in the pyridine *N*-oxide catalyzed reaction. Reactions were performed by adding

(19) *S*-**5a**, $[\alpha]_D^{24}$ +28.3 (MeOH), mp 82.5−84 °C: Kelly, S. E.; LaCour, T. *Synth. Commun.* **1992**, *22*, 859−869.

(20) For the preparation bisphosphoramides **1a**−**c**, see ref 15a; **1d**, see ref 18a; **1f**, see 18c. For the preparation of bis-*N*-oxide (*P*)-(*R*,*R*)-**1g**, see: Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233−4235.

(21) For a discussion of the origin of the tether length effect, see: Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2003**, *125*, 2208−2216.

TABLE 4. Additions of *t*-BuNC to Aldehydes Catalyzed by Pyridine *N*-Oxide



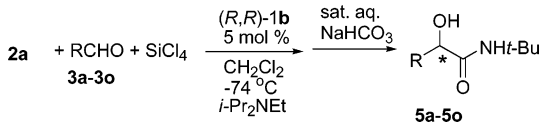
entry	aldehyde	product	yield,[a] %
1	**3b**	(±)-**5b**	87
2	**3c**	(±)-**5c**	92
3	**3d**	(±)-**5d**	89
4	**3e**	(±)-**5e**	90
5	**3f**	(±)-**5f**	87
6	**3g**	(±)-**5g**	73
7	**3h**	(±)-**5h**	86
8	**3i**	(±)-**5i**	85
9[b]	**3j**	(±)-**5j**	44
10[b]	**3k**	(±)-**5k**	37
11	**3l**	(±)-**5l**	76
12	**3m**	(±)-**5m**	89
13	**3n**	(±)-**5n**	95
14	**3o**	(±)-**5o**	99
15[b,c]	**3j**	(±)-**5j**	35
16[bd]	**3j**	(±)-**5j**	59
17[e]	**3j**	(±)-**5j**	89
18[b,d]	**3k**	(±)-**5k**	37
19[e]	**3k**	(±)-**5k**	62
20[f]	**3k**	(±)-**5k**	72

[a] Yields of chromatographically homogeneous material. [b] Unreacted aldehyde was recovered. [c] The reaction temperature was −24 °C. [d] The isocyanide was added over 4 h. [e] The isocyanide was added over 8 h. [f] The isocyanide was added over 12 h.

a solution of *t*-BuNC in CH_2Cl_2 (1.0 M) to a solution of the mixture of $SiCl_4$, aldehyde, and 10 mol % of pyridine *N*-oxide in CH_2Cl_2 (1.0 M) at −74 °C over 30 min.

Under this set of reaction conditions, all the aldehydes reacted and the corresponding hydroxy amides products were obtained after workup (Table 4, entries 1−14). A trend in the reactivity is readily apparent: the addition of *t*-BuNC to all conjugated aldehydes proceeded to completion within 4 h at −74 °C, and the hydroxy amide products were obtained in excellent yields (Table 4, entries 1−8 and 11−14); on the other hand, only low yields of the products were obtained with both aliphatic aldehydes (Table 4, entries 9 and 10). In these low-yielding reactions, the aldehyde starting material was recovered after aqueous workup. To improve the yield with aliphatic aldehydes the effect of increasing the reaction temperature was investigated. However, for both linear and α-branched structures the increase in the temperature did not improve the conversions, and both aldehyde starting materials were recovered (Table 4, entries 15 and 18). In many other addition reactions studied in these laboratories, aliphatic aldehydes have been notoriously slow substrates. Their sluggish reaction rates have been rationalized by in situ formation of unreactive α-chloro trichlorosilyl ethers in the presence of $SiCl_4$ and a phosphoramide catalyst.[16b] In the case at hand, there is a competing reaction between $SiCl_4$ and the isocyanide that has analogy in the reactions with $TiCl_4$.[13] Consideration of this unproductive pathway led to the hypothesis that decreasing the concentration of the isocyanide would increase the yield of the α-addition product and thus, the effect of slow addition of the isocyanide was studied. Indeed, a significant improvement in the yield was observed when a 4 h addition protocol was used for the addition of *t*-BuNC to hydrocinnamaldehyde (**3j**) (Table 4, entry 16). The yield was further enhanced when the isocyanide was added over a longer period of time (Table 4, entry 17). The slow addition protocol was also effective with the α-branched aldehyde (**3k**) (Table 4, compare entries 19−20 with entry 10). A respectable yield of the product was obtained albeit a long addition time was necessary (Table 4, entry 20).

TABLE 5. Additions of *tert*-Butyl Isocyanide to Aldehydes Catalyzed by (*R*,*R*)-1b



entry	aldehyde	product	yield,[a] %	er[b]
1	**3b**	**5b**	91	99.9/0.1
2	**3c**	**5c**	89	98.3/1.7
3	**3d**	**5d**	89	96.5/3.5
4	**3e**	**5e**	93	99.7/0.3
5	**3f**	**5f**	92	92.2/7.8[c]
6	**3g**	**5g**	81	97.8/2.2
7	**3h**	**5h**	86	67.4/32.6
8	**3i**	**5i**	76	77.0/23.0
9[e,g]	**3j**	**5j**	92	81.9/18.1
10[f,g]	**3k**	**5k**	53	87.1/12.9[d]
11	**3l**	**5l**	83	95.9/4.1[d]
12	**3m**	**5m**	86	96.2/3.8
13	**3n**	**5n**	89	94.2/5.8
14	**3o**	**13o**	81	94.3/5.7

[a] Yields of chromatographically homogeneous material. [b] Determined by CSP-SFC. [c] Determined by CSP-HPLC. [d] Determined by CSP-GC. [e] Isocyanide was added over 8 h. [f] Isocyanide was added over 12 h. [g] No Hünig's base was used.

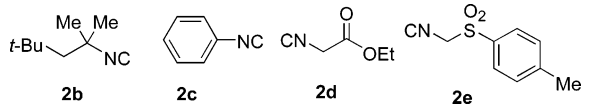
2.2. Additions Catalyzed by (*R*,*R*)-1b. The enantioselectivity in the addition of *t*-BuNC to the same set of aldehydes catalyzed by the chiral bisphosphoramide (*R*,*R*)-**1b** was investigated. The optimized conditions established for the addition to benzaldehyde were employed: *t*-BuNC in CH_2Cl_2 (1.0 M) was added over 4 h to a solution of the mixture of an aldehyde, $SiCl_4$, 5 mol % of (*R*,*R*)-**1b**, and 10 mol % of Hünig's base in CH_2Cl_2 (1.0 M).

The enantioselectivities, compiled in Table 5, were found to be highly dependent on the structure of the aldehyde. Aromatic and heteroaromatic aldehydes were among the best performers and generally gave excellent enantioselectivities. In contrast, results with olefinic and aliphatic aldehydes were highly variable. Subtle electronic influences on the enantioselectivity were observed in the class of 4-substituted benzaldehydes. 4-Tolualdehyde, a moderately electron-rich substrate, gave the same results as benzaldehyde (Table 5, entry 1). On the other hand, noticeable decreases in the enantioselectivity were observed with strongly electron-rich and electron-poor aldehydes (Table 5, entries 2 and 3). Variations of the steric encumbrance of the aldehyde acceptor had significant influence on the enantioselectivity. Whereas 2-naphthaldehyde provided essentially the same result as benzaldehyde, the enantioselectivity with sterically encumbered 1-naphthaldehyde decreased significantly (Table 5, entries 4 and 5). Excellent yields were obtained in the addition to nonaromatic conjugated aldehydes. However, enantioselectivities with this class of aldehydes were highly variable. (*E*)-Cinnamaldehyde provided the best result, but with sterically more congested 2-methylcinnamaldehyde or less encumbered phenylpropargyl alde-

hyde the enantioselectivity decreased dramatically (Table 5, entries 6−8). With aliphatic aldehydes, the presence of Hünig's base proved to be deleterious to the yields of the products. It was necessary to perform the reaction without the use of Hünig's base. Thus, under the conditions employed for the pyridine *N*-oxide catalyzed addition, aliphatic aldehydes (**3j** and **3k**) gave similar yields of the hydroxy amide products in the enantioselective additions (Table 5, entries 9 and 10). Unfortunately, both the linear and α-branched aliphatic aldehydes gave lower enantioselectivities than aromatic aldehydes. It is noticeable that the α-branched aldehyde (**3k**) delivered a slightly higher enantioselectivity than the linear aldehyde (**3j**) (Table 5, compare entries 9 and10). Electron-rich heteroaromatic aldehydes, such as furfural and 2-thiophenecarboxaldehyde, reacted cleanly and provided the product in good yields (Table 5, entries 11 and 12). Nitrogen-containing heteroaromatic aldehydes with strong electron-withdrawing protecting group were also highly reactive and delivered high yields of the products as well (Table 5, entries 13 and 14). Despite the structural difference, very good enantioselectivities were obtained with all these heteroaromatic aldehydes (Table 5, entries 11−14).

3. Survey of Isocyanide Structure. The isocyanide provides a useful dimension of structural diversity in these reactions. Because isocyanides can be easily prepared from primary amines,[22] this is an easily modifiable component. In addition, the structure of the isocyanide may influence the rate and selectivity of the addition. Accordingly, the commercially available isocyanides shown in Chart 3 were investigated. 1,1,3,3-Tetramethylbutyl isocyanide (**2b**) was chosen to study the effect of increasing the size of the isocyanide on the enantioselectivity. Because hydrocinnamaldehyde (**3j**) gave poor enantioselectivity in the addition of *t*-BuNC (**2a**), it was chosen as the acceptor partner for the addition of **2b**. Phenyl isocyanide (**2c**) was chosen as the representative of electronically deactivated isocyanides. Ethyl isocyanoacetate (**2d**) and tosylmethyl isocyanide (**2e**), both of which possess two protons of significant acidity, were employed to investigate the functional group tolerance of the $SiCl_4$−Lewis base system.

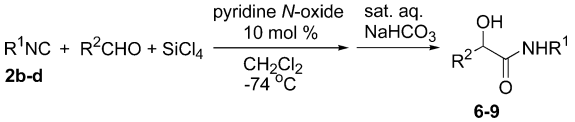
CHART 3



2b **2c** **2d** **2e**

3.1. Additions Catalyzed by Pyridine *N*-Oxide. To provide a direct comparison for the reactions with *t*-BuNC (**2a**), the slow addition protocol (8 h) employed for the addition of to hydrocinnamaldehyde (**3j**) was applied in the reaction with **2b**. Under these conditions, despite the increase in the steric bulk of the isocyanide (**2b**), the hydroxy amide product **6** was produced in good yield (Table 6, entry 1). On the other hand, with benzaldehyde, isocyanides (**2c**−**e**) were added over 30 min (Table 6, entries 2−4). Under this set of conditions, electronically deactivated isocyanide (**2c**) and enolizable isocyanides (**2d** and **2e**) delivered respectable yields of the hydroxy amide products within 4 h at −74 °C.[23]

TABLE 6. Addition of Isocyanides to Aldehydes Catalyzed by Pyridine *N*-Oxide

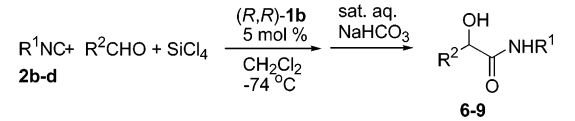


entry	isocyanide	product	yield,[a] %
1[b,c]	**2b**	(±)-**6**	84
2[d,e]	**2c**	(±)-**7**	76
3[d,e]	**2d**	(±)-**8**	72
4[d,e]	**2e**	(±)-**9**	69

[a] Yields of chromatographically homogeneous material. [b] Hydrocinnamaldehyde (**3j**) was used. [c] Isocyanide (**2b**) was added over 8 h. [d] Benzaldehyde (**3a**) was used. [e] Isocyanide **2c** was added over 30 min.

3.2. Additions Catalyzed by (*R*,*R*)-1b. The dependence of enantioselectivity on the structure of the isocyanide in reactions catalyzed by (*R*,*R*)-**1b** was next examined, Table 7. To provide a direct comparison in the enantioselectivity, the same reaction protocol was employed for the additions of *t*-BuNC (**2a**) and **2b** to hydrocinnamaldehyde (**3j**). Under this set of conditions, the bulkier nucleophile **2** provided a good yield of the hydroxy amide product **6** but with diminished enatioselectivity (compare Table 7, entry 1, and Table 5, entry 9). For the additions of **2c**−**e** to benzaldehyde, the yields of the products were high, but the selectivities of the reactions were dependent on the structure of the isocyanide. Whereas the aromatic isocyanide **2c** gave a modest selectivity (Table 7, entry 2), both functionalized aliphatic aldehydes delivered respectable enantioselectivities when the reactions were carried out in the absence of Hünig's base and the isocyanide is added in one portion (Table 7, entries 3 and 4). Additions of **2c**−**e** to other aldehydes or with other catalysts were not attempted.[24]

TABLE 7. Addition of Isocyanides to Aldehydes Catalyzed by (*R*,*R*)-1b



entry	isocyanide	aldehyde	product	yield,[a] %	er[b]
1[c]	**2b**	**3j**	(−)-**6**	87	70.0/30.0
2[d,e]	**2c**	**3a**	(+)−**7**	82	73.2/26.9
3[d]	**2d**	**3a**	(+)-**8**	83	83.3/16.7
4[d]	**2e**	**3a**	(−)-**9**	80	88.5/11.5

[a] Yields of chromatographically homogeneous material. [b] Determined by CSP-SFC. [c] **2b** was added over 8 h. [d] Isocyanides were added in one portion. [e] 10 mol % of *i*-Pr_2NEt was used.

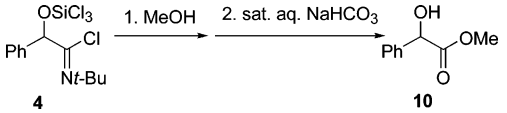
4. Conversion of Imidoyl Chlorides to Carboxylic Esters. The immediate products of the addition reaction are likely α-trichlorosilyloxy imidoyl chlorides (see the

(22) (a) Ugi, I.; Meyr, R.; Lipinski, M.; Bodesheim, F.; Rosendahl, F. *Org. Synth.* **1961**, *41*, 13−15. (b) Gokel, G. W.; Widera, R. P.; Weber, W. P. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 232−235.

(23) In the presence of Hünig's base, reaction of **2d** with benzaldehyde afforded **8** in 43% yield along with a double addition product **13** in 10% yield. Under these conditions, **2e** afforded **9** in 64% yield along with two byproducts, benzoin (**14a**) in 9% yield and tosylmethylformamide (**14b**) in 7% yield; see the Discussion and Supporting Information.

Discussion). Imidoyl chlorides and ethers are versatile intermediates in organic synthesis and can be converted into a variety of useful products.[25] Up to now, the simple hydrolysis of this intermediate has provided α -hydroxy carboxamides in good yield. Direct transformation of the imidoyl chloride into carboxylic esters would have obvious synthetic utility. However, because the alcoholysis of the intermediate also produces four equivalents of HCl, racemization under such acidic conditions was of concern. Initial studies therefore focused on the effects of bases and buffers on the efficiency of methanolysis. These studies were performed by quenching a solution of **4** (generated from the addition of *t*-BuNC to benzaldehyde) under the indicated conditions with 60 equiv of methanol. The reaction mixture from the methanol quench was poured into a saturated aqueous $NaHCO_3$ solution. From the ratio of the ester product **10** to the amide product **5a**, the efficiency of methanolysis was evaluated, Table 8.

TABLE 8. Conversion of Imidoyl Chloride to Methyl Ester



4 **10**

entry	base	equiv	*T*, °C	time, min	yield of **10**,[a] %	yield of **5a**,[a] %
1	none		−74	40	83	0
2	*i*-Pr_2NEt	20.0	−74	120	0	86
3	*i*-Pr_2NEt	20.0	25	120	17	66
4	NaOMe	4.8	25	120	89	0
5[b,c]	none		−74	40	95	0
6[b,d]	NaOMe	4.8	25	120	89	0

[a] Yields of chromatographically homogeneous material. [b] The imidoyl chloride was prepared by the asymmetric addition protocol using bisphosphoramide catalyst (*R*,*R*)-**1b**. [c] *S*/*R* ratio of the ester product was determined by SFC and was greater than 99/1. [d] *S*/*R* ratio was 90.9/9.1.

In the absence of base, methanolysis of **4** proceeded to completion within 40 min at −74 °C to afford (after workup with saturated aqueous $NaHCO_3$ solution) a high yield of the ester **10** (Table 8, entry 1). In contrast, under basic conditions, imidoyl chloride **4** was resistant to methanolysis. When the reaction mixture was buffered with Hünig's base, the imidoyl chloride group was intact after 2 h −74 °C as evidenced by the high yield of the hydroxy amide product **5a** (Table 8, entry 2). Increasing the temperature afforded a small amount of methyl ester **10** but with low efficiency (Table 8, entry 3). Further increase in the temperature (to 40 °C) led to the decomposition of **4** and did not improve the yield of **10**. The stronger base, sodium methoxide, proved to be reactive toward **4** and provided a high yield of **10** after 2 h at 25 °C (Table 8, entry 4). The two methods for the conversion of imidoyl chloride **4** to ester **10** were then tested for the intervention of racemization. Thus, from the addition of *t*-BuNC to benzaldehyde catalyzed by (*R*,*R*)-**1b**, the *S*-enantiomer of imidoyl chloride **4** was generated in situ and was independently subjected to both conditions. Quenching of **4** with methanol alone at low temperature (followed by workup with saturated aqueous $NaHCO_3$ solution) afforded **10** in excellent yield and with no detectable racemization (Table 8, entry 5). On the other hand, the use of sodium methoxide led to significant racemization (Table 8, entry 6).

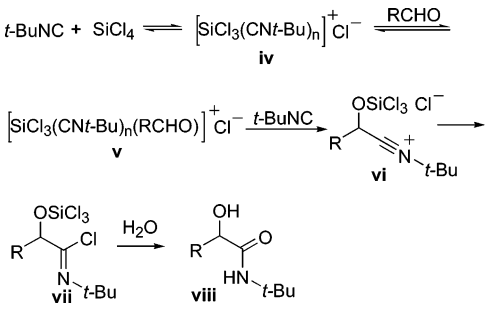
This protocol was then applied as a quench/workup procedure for the reactions of an olefinic (**3g**) and an aliphatic aldehyde (**3j**). In both cases, the corresponding esters, **11** and **12** were obtained in good yields (71% and 88%, respectively) and enantioselectivities comparable to those for the carboxamides (97.9/2.1 and 81.8/18.2, respectively). Finally, the absolute configurations of the ester products was determined to be *S* (see the Experimental Section), confirming the same sense of asymmetric induction for aromatic, conjugated, and aliphatic aldehydes in the isocyanide additions.

Discussion

1. $SiCl_4$-Mediated Additions of Isocyanides to Aldehydes. As a Lewis acid promoter, $SiCl_4$ is unique for the α-additions of isocyanides to aldehydes. In the presence of $SiCl_4$ alone, the addition of *t*-BuNC to benzaldehyde proceeds to 83% conversion within 4 h at −78 °C and produces the imidoyl chloride **4** cleanly (Table 1, entry 1). This reaction is remarkable for a number of reasons including: (1) the mild conditions, (2) the absence of byproducts from multiple addition of the isocyanide and (3) the scarcity of high yielding Lewis acid promoted α-addition reactions. Moreover, isocyanides behave differently compared to other nucleophiles employed in the $SiCl_4$-mediated additions to aldehydes. π-Nucleophiles such as trialkylsilyl ketene acetals, silyl enol ethers and allyltrialkylstannanes do not add to aldehydes in the presence of $SiCl_4$ alone.[15] However, the addition of all these nucleophiles is dramatically accelerated in the presence of both a strong Lewis base promoter and $SiCl_4$. Considering the Lewis basicity of the isocyanide and the highly responsive nature of $SiCl_4$ toward Lewis base activation, it must be concluded that the unique reactivity of isocyanide in the $SiCl_4$-mediated addition reactions stems from activation of $SiCl_4$ by the isocyanide.

Although the mechanism by which isocyanide activates $SiCl_4$ has not been studied, it is reasonable to propose that isocyanide behaves like other activating Lewis bases as well as the nucleophile in this reaction (Scheme 3).

SCHEME 3



Thus, ionization of $SiCl_4$ takes place upon binding one or two molecules of sterically unencumbered isocyanide

(24) A number of experiments were performed with (*S*)-1-phenylethyl isocyanide to determine the influence of a chiral isocyanide alone and in double diastereoselection with catalyst (*R*,*R*)-**1b**. In the addition to benzaldehyde, high yields were obtained, but in no case was the influence of the stereogenic center on the isocyanide manifested.

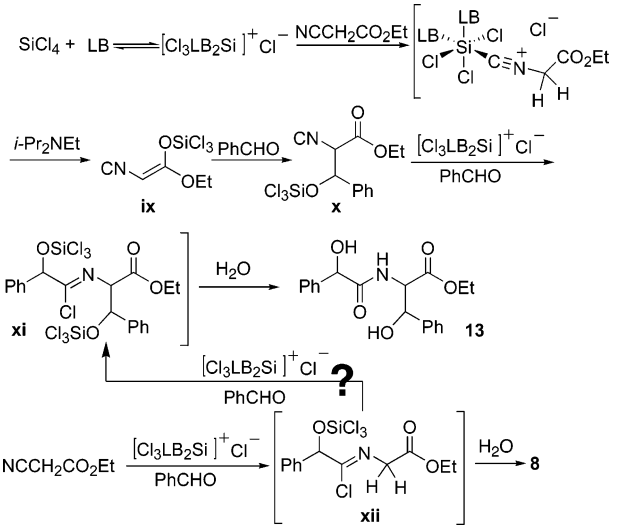
(25) *The Chemistry of Amidines and Imidates*; Patai, S., Rapoport, Z., Eds.; John Wiley: New York, 1991.

and results in the formation of a zwitterionic species **iv**. The addition of t-BuNC to the complexed aldehyde in activated complex **v** leads to the formation of a nitrilium species **vi**. Subsequent capture of **vi** by the nucleophilic fragment results in the formation of imidoyl chloride **vii**, which precludes further attack by the isocyanide. Upon aqueous workup, the hydroxy amide product **viii** is obtained.

2. Scope of the Aldehyde Acceptor. All basic structural types of aldehydes are reactive in the $SiCl_4$-mediated additions of isocyanides, including aromatic, heteroaromatic, olefinic, acetylenic, and aliphatic aldehydes, albeit with variable rates and selectivities. In general, conjugated aldehydes were much more reactive than aliphatic aldehydes in both the pyridine *N*-oxide and the chiral bisphosphoramide catalyzed additions. The same trend was also observed in other Lewis base catalyzed, $SiCl_4$-mediated additions, but the range of reactivity was not as pronounced in the additions of *t*-BuNC. In addition, for aliphatic aldehydes, slow addition of the isocyanide was necessary to achieve good yields of the hydroxy amide products. Although the origin of this improvement is not certain, it clearly relates to the well-known production of α-chloro trichlorosilyl ethers from aliphatic aldehydes. Ordinarily, the formation of these unreactive intermediates leads only to attenuated addition rates, but with *t*-BuNC an unproductive consumption of the nucleophile intervenes, such that extended times or elevated temperatures afford no improvement. Apparently, when the isocyanide is added slowly, reaction with the small amount of activated aldehyde present at equilibrium can compete with decomposition of the nucleophile.

3. Scope of the Isocyanide. Both aromatic and aliphatic isocyanides participate in the $SiCl_4$-mediated additions to aldehydes. However, with aliphatic isocyanides containing acidic protons (**2d** and **2e**), the outcome of the reactions were highly dependent on the protocol. To obtain good yields, it was necessary to perform these reactions in the absence of a Brønsted base and the isocyanides must be added in one portion. The lower yields obtained in the presence of Hünig's base are due to unproductive pathways initiated by enolization of the isocyanides (Scheme 4). It is likely that the acidity of the

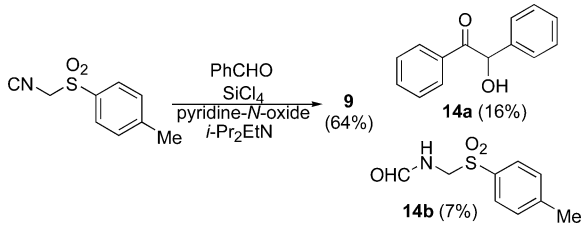
SCHEME 4



enolizable protons would be enhanced by the coordination of these isocyanides to $SiCl_4$ or to a highly electrophilic trichlorosilyl cation. Thus, even a sterically encumbered base can deprotonate the isocyanides and form the trichlorosilyl enolate **ix**. The addition of **ix** to benzaldehyde leads to the formation of intermediate **x** which then can function as an isocyanide in the normal capacity with a second molecule of benzaldehyde to form **xi** which, after hydrolysis affords byproduct **13**. Although we cannot rule out the possibility that **13** is a secondary product of **8**, we believe the acidity of the methylene hydrogens in **xii** is considerably reduced.

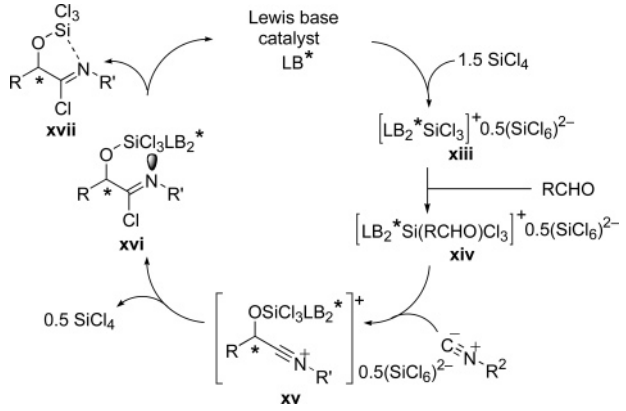
When tosylmethyl isocyanide (TOSMIC) was employed as the nucleophile in the presence of Hünig's base, two byproducts were obtained along with the desired product **9** (Scheme 5). Whereas the formation of the formamide **14b** arises from simple hydrolysis of TOSMIC, the mechanism of formation of benzoin **14a** under these conditions is obscure.

SCHEME 5



4. Mechanism of Chiral Bisphosphoramide Catalyzed Addition. A hypothetical catalytic cycle for the Lewis base catalyzed, $SiCl_4$-mediated, Passerini-type reaction is shown in Scheme 6. The details of this cycle

SCHEME 6



nicely illustrate the unique features of Lewis base catalysis and also serve to distinguish the roles of each component. Binding of a neutral Lewis base (catalyst) to $SiCl_4$ causes ionization to generate an chirally modified-siliconium ion **xiii**. This complex (which exists as a hexachlorosilicate ion pair)[16b] is the catalytically active species, but as it is consumed in each cycle is more accurately described as a "pseudocatalyst".[26] Thus, the addition of the isocyanide to the activated aldehyde in complex **xiv** would produce nitrilium ion intermediate

(26) For the IUPAC definitions of catalyst and pseudocatalyst see http://www.chem.qmul.ac.uk/iupac/gtpoc/.

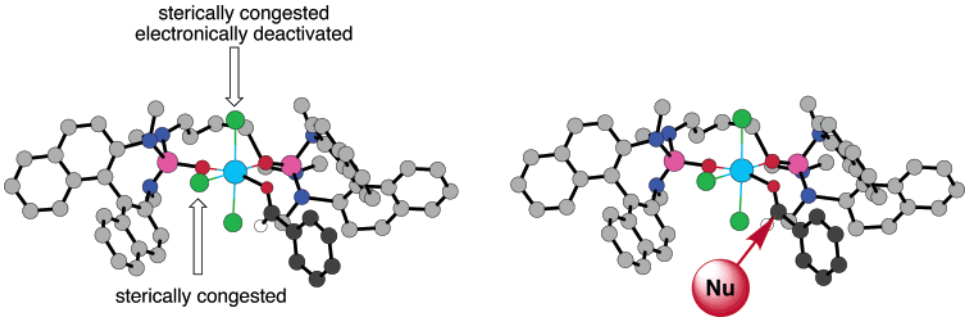


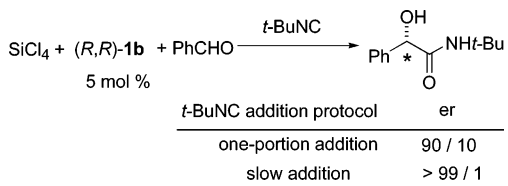
FIGURE 1. Stereochemical model for the α-addition of isocyanides.

xv. Subsequent capture of **xv** by the chloride anion would result in the formation of an imidoyl chloride **xvi**. The newly generated nonbonding pair on the nitrogen has two important consequences: (1) by coordinating the $SiCl_3$ fragment, the bulk product of the reaction **xvii** can be removed from the catalytic cycle and (2) the attenuated Lewis acidity of the silicon center in **xvii** would assist the dissociation of the Lewis base catalyst to repeat the catalytic cycle.

Because the isocyanide itself is a strong Lewis base, several types of silyl cations can be generated in a mixture of isocyanide and phosphoramide: a complex with two isocyanide molecules, a complex with one isocyanide and one Lewis base molecule, and a complex with two Lewis base molecules. Each of these species could activate aldehyde toward nucleophilic attack and the relative contribution from each of these species would depend on their ability to activate the aldehyde as well as the concentration of these species under the reaction conditions.

Without kinetic measurements it is impossible to quantitatively evaluate the contribution from each of these pathways. However, the results from reaction optimization can provide a qualitative ordering of the importance of these pathways in the α-additions. In the presence of 5 mol % of (*R*,*R*)-**1b**, the $SiCl_4$-mediated additions of *t*-BuNC to a wide range of conjugated aldehydes proceed with excellent enantioselection. Such a high level of asymmetric induction supports the notion that this reaction is controlled by chiral catalyst and the influence from the isocyanide promoted pathways are less significant, as long as the concentration of the isocyanide is minimized. However, because a lower enantioselectivity is obtained when the isocyanide is added in one portion (Scheme 7), it must be concluded that the isocyanide-promoted achiral addition can be competitive to the phosphoramide-promoted addition.

SCHEME 7



5. Origin of Enantioselection with Catalyst (*R*,*R*)-1b. Chiral binaphthyldiamine-derived catalyst (*R*,*R*)-**1b** has demonstrated extraordinary ability in discriminating the enantiotopic faces of aromatic aldehydes in the $SiCl_4$-mediated addition reactions.[16] It is believed that an in situ generated cationic silicon complex [(*R*,*R*)-**1b**•$SiCl_3$] + Cl− is responsible for enantioselection. A stereochemical model has been proposed to account for the origin of the enantioselection by the cationic silicon complex (*R*,*R*)-**1b**•$SiCl_3$ (Figure 1).[27] In the active complex, the carbonyl oxygen is coordinated *trans* to the phosphoramide donor in a canonical sp hybridized orbital. The alternative binding sites are both sterically and electronically less favorable (hypervalent orbitals). In this position, the conformation of benzaldehyde may be stabilized by the $\pi-\pi$ interaction between the benzene ring and one of the naphthyl units in an edge-on fashion. The *Re*-face of the aldehyde thus is exposed to nucleophilic attack while the *Si*-face is shielded by one of the *N*-methyl groups on the chiral scaffold. This topicity has been seen for the addition of many classes of nucleophiles to bound aldehydes.

Conclusion

In summary, the first catalytic, enantioselective α-addition reaction of isocyanides has been demonstrated with an $SiCl_4$•bisbinaphthyldiamine phosphoramide catalyst. Good yields have been obtained with aromatic, heteroaromatic, conjugated nonaromatic and nonbranched aliphatic aldehydes. Aromatic, aliphatic and functionalized isocyanides provided high yields of α-addition products. Enantiomeric ratios ranging from 92/8 to 99/1 have been achieved in the addition of *tert*-butyl isocyanide to aromatic aldehydes. The imidoyl chloride intermediates has been directly converted into chiral α-hydroxy amides and carboxylic esters without loss in enantiomeric purity. Studies to improve catalyst design for aliphatic aldehydes and development of new methods for the transformation of the chloro imidate intermediates are ongoing.

Experimental Section

General Experimental Procedures. See the Supporting Information.

***N*-*tert*-Butyl-2-hydroxy-2-(2-naphthyl)acetamide ((±)-5e).** A solution of *tert*-butyl isocyanide (125 μL, $d = 0.735$, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (2.0 mL) was added via a syringe pump over 30 min to a cold (−74 °C, internal temperature) solution of 2-naphthaldehyde **3e** (156 mg, 1.0 mmol), pyridine *N*-oxide (9.5 mg, 0.1 mmol, 0.1 equiv), and $SiCl_4$ (125 μL, $d =$

(27) The calculations on a complex of benzaldehyde and the dimeric phosphoramide (*R*,*R*)-**1b** bound trichlorosilyl cation were performed using the PC version of GAMESS(US) QC Package employing the PM3 basis set.

1.483, 1.1 mmol, 1.1 equiv) in a two-necked, round-bottomed flask fitted with an argon inlet adapter and thermocouple. The reaction solution was stirred for 4 h at −74 °C, warmed to rt, and was transferred dropwise to a vigorously stirred, ice-cold, saturated aqueous solution of $NaHCO_3$ (20 mL). The mixture was further stirred for 2 h at rt. The white precipitate was filtered off through Celite, and the filtrate was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (20 mm column, 60 g SiO_2, R_f 0.17, hexane/EtOAc, 3/1) to afford 230 mg (90%) of (±)-**5e** as a white solid. White crystals of (±)-**5e** (204 mg, 80%) were obtained after recrystallization from a 3/1 mixture of heptane and benzene: mp 118−119°C (heptane/benzene, 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) 7.45−7.87 (m, 7 H, aryl), 5.72 (bs, 1 H, NH), 5.06 (d, J = 3.7, 1 H, HC(2)), 3.88 (d, J = 3.4, 1 H, OH), 1.31 (s, 9 H, 3 × $H_3C(2'')$); ^{13}C NMR (100 MHz, $CDCl_3$) 171.2 (C(1)), 137.2 (C(2′)), 133.4 (C(9′) or C(10′)), 133.2 (C(9′) or C(10′)), 129.0 (C(8′)), 128.0 (C(3′)), 127.8 (C(4′)), 126.5 (C(5′)), 126.4 ((C(1′) or C(6′)), 126.3 (C(6′) or C(1′)), 124.0 (C(7′)), 74.2 (C(2)), 51.6 (C(1′′)), 28.6 (C(2′′)); IR ($CHCl_3$) 3612 (m), 3413 (m), 3010 (m), 2973 (m), 1677 (s), 1602 (s), 1523 (s), 1425 (w), 1394 (w), 1367 (m), 1278 (w), 1267 (m), 1234 (w), 1170 (w), 1124 (w), 1079 (m), 877 (w); TLC R_f 0.17 (hexane/EtOAc, 3/1); SFC (*R*)-**5e**, t_R 3.71 min (50.3%); (*S*)-**5e**, t_R 4.58 min (49.7%) (Chiracel AD, 10.0% MeOH in CO_2, 125 bar, 40 °C, 3.0 mL min^{-1}); MS (FI, 70 eV) 258 (19), 257 (100). Anal. Calcd for $C_{16}H_{19}NO_2$ (257.33): C, 74.68; H, 7.44; N, 5.44. Found: C, 74.65; H, 7.70; N, 5.61.

***N-tert*-Butyl-2-hydroxy-2-(2-naphthyl)acetamide ((+)-5e).** A solution of *tert*-butyl isocyanide (125 μL, d = 0.735, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was added via a syringe pump over 4 h to a cold (−74 °C, internal temperature) solution of 2-naphthaldehyde **3e** (156 mg, 1.0 mmol), catalyst (*R*,*R*)-**1b** (43 mg, 0.05 mmol, 0.05 equiv), $SiCl_4$ (125 μL, d = 1.483, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μL, d = 0.742, 0.1 mmol, 0.1 equiv) in CH_2Cl_2 (1.0 mL) in a two-necked, round-bottomed flask fitted with an argon inlet adapter and thermocouple. The mixture was stirred further for 4 h at −74 °C. The reaction mixture was then transferred dropwise to a vigorously stirred, ice-cold, saturated aqueous solution of $NaHCO_3$ (20 mL). The mixture was stirred for 2 h at rt. The white precipitate was filtered off through Celite, and the filtrate was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (20 mm column, 60 g SiO_2, R_f 0.17, hexane/EtOAc, 3/1) to afford 242 mg (93%) of (+)-**5e** as a white solid. An analytically pure sample was obtained after sublimation (90 °C/0.5 mmHg): mp 94−96 °C (sublimed); SFC (*R*)-**5e**, t_R 3.73 min (0.3%); (*S*)-**5e**, t_R 4.58 min (99.7%) (Chiracel AD, 10% MeOH in CO_2, 125 bar, 40 °C, 3.0 mL min^{-1}); $[\alpha]_D^{24}$ +44.9 (c = 0.96, MeOH). Anal. Calcd for $C_{16}H_{19}NO_2$ (257.33): C, 74.68; H, 7.44; N, 5.44. Found: C, 74.60; H, 7.54; N, 5.66.

(*S*)-(+)-Methyl-2-hydroxy-2-phenylacetate ((*S*)-10). A solution of *tert*-butyl isocyanide (125 μL, d = 0.735, 1.2 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was added via a syringe pump over 4 h to a cold (−74 °C, internal temperature) solution of benzaldehyde (104 μL, d = 1.044, 1.0 mmol), catalyst (*R*,*R*)-**1b** (43 mg, 0.05 mmol, 0.05 equiv), $SiCl_4$ (125 μL, d = 1.483, 1.1 mmol, 1.1 equiv), and diisopropylethylamine (18 μL, d = 0.742, 0.1 mmol, 0.1 equiv) in CH_2Cl_2 (1.0 mL) in a two-necked, round-bottomed flask fitted with an argon inlet adapter and thermocouple. The mixture was stirred for 4 h at −74 °C whereupon dry MeOH (2.5 mL) was added dropwise to the reaction mixture at −74 °C. After being stirred for 40 min at −74 °C, the mixture was transferred dropwise to a vigorously stirred, ice-cold, saturated aqueous solution of $NaHCO_3$ (20 mL) and stirred for 2 h further at rt. The white precipitate was filtered off through Celite, and the filtrate was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to provide the crude product. Purification afforded 160 mg (97%) of (*S*)-**10** after silica gel column chromatography (20 mm column, 60 g SiO_2, R_f 0.31, hexane/EtOAc, 3/1). Bulb-to-bulb distillation provided 158 mg (95%) of (*S*)-**10** as colorless oil, which solidified upon standing. From the sign of optical rotation of the product ($[\alpha]_D^{24}$ +143.2, MeOH), the absolute configuration was deduced to be *S* (lit.[6] (*S*) enantiomer, $[\alpha]^{24}_D$ +144.0, MeOH): mp 56−58 °C; bp 120 °C (0.5 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) 7.33−7.44 (m, 5 H, aryl); 5.18 (d, J = 5.3, 1 H, HC(2)); 3.77 (s, 3 H, OCH_3); 3.42 (d, J = 4.7, 1 H, OH)); TLC R_f 0.31 (hexane/EtOAc, 3/1); SFC (*S*)-**10**, t_R 3.97 min (99.9%); (*R*)-**10**, t_R 4.31 min (0.1%) (Chiracel AS, 1.4% MeOH in CO_2, 125 bar, 40 °C, 2.5 mL min^{-1}); $[\alpha]_D^{24}$ +143.2 (c = 0.57, MeOH).

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Supporting Information Available: Full characterization of all products along with optimization experiments and detailed procedures for the addition reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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