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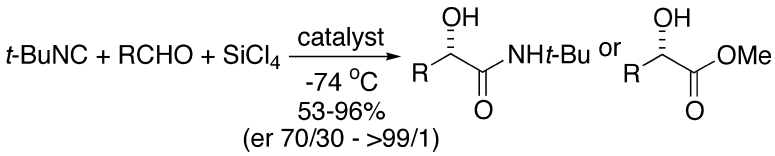
J. Am. Chem. Soc., **2003**, 125 (26), 7825-7827• DOI: 10.1021/ja035410c • Publication Date (Web): 07 June 2003



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Published on Web 06/07/2003

The First Catalytic, Asymmetric α-Additions of Isocyanides. Lewis-Base-Catalyzed, Enantioselective Passerini-Type Reactions

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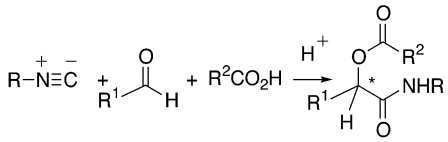
Bearing a formally divalent carbon, isocyanides are capable of engaging in a unique class of carbon−carbon bond forming reactions known as α-additions. Since the early studies by Passerini,[1] and by Ugi and co-workers,[2] the power of the α-addition reaction in constructing polyfunctional molecules has been well appreciated. In the classical Passerini reaction, an α-acyloxy carboxamide is formed in one step from three components, an isocyanide, a ketone or an aldehyde, and a carboxylic acid (Scheme 1). In the Ugi reaction, four components, an isocyanide, an amine, a carbonyl compound, and a carboxylic acid, react to form an α-acylamino amide. Although both reactions have been widely applied, generating molecular diversity for drug discovery and natural product synthesis,[3] the challenge of stereocontrol, wherever a new stereocenter is generated, has not been satisfactorily addressed. Diastereoselective approaches developed by Ugi and others achieved varying degrees of success in controlling the stereochemical outcome of the α-additions of isocyanides.[4−7] However, all of these methods suffer from low efficiency in that chiral auxiliaries have to be removed from the product destructively. A method for the catalytic, asymmetric α-addition of isocyanides is still lacking.

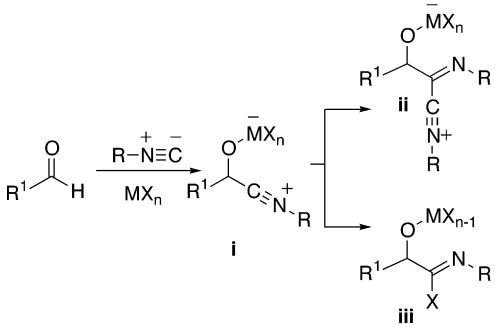
Scheme 1



The absence of a catalytic, enantioselective variant of this class of reactions is striking, particularly in light of the recent development of chiral Lewis acid catalysts for stereoselective carbon−carbon bond formation with both carbonyl and imine substrates.[8] The problems facing the development of Lewis-acid-catalyzed, asymmetric α-addition of isocyanides are intrinsically associated with the formal divalency of the nucleophile. The primary adduct of the α-addition is the zwitterionic intermediate **i**, Scheme 2. In the classical Passerini and Ugi reactions, a carboxylate combines with this adduct, and the subsequent Mumm rearrangement leads to the observed products. However, for the Lewis-acid-mediated α-addition, in the absence of the carboxylate, this adduct is subject to further addition of isocyanide and often leads to undesired pathways (**ii**, Scheme 2).[9] Moreover, catalyst turnover for conventional Lewis acid catalysis requires the cleavage of the bond between the MX_n unit and the product, which has seen only limited success for α-additions.[10,11] Furthermore, asymmetric modification of the Lewis acid leads to diminished reactivity.[11b]

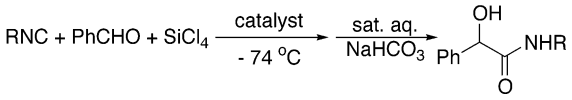
We recognized that the newly introduced concept of Lewis base activation of Lewis acid is ideally suited to address these problems. Recent publications from these laboratories have demonstrated that the weak Lewis acid, $SiCl_4$, can be activated by a Lewis basic phosphoramide through displacement of a chloride ion which results in the formation of a cationic silicon species.[12] The trichlorosilyl adduct is capable of activating aldehydes toward nucleophilic attack. An important advantage of this system is that the weak Lewis acid can be used in stoichiometric quantities without the fear of competing achiral pathways because kinetically competent species are formed only upon binding the chiral ligand. Unlike with conventional chiral Lewis acids, catalyst turnover is the transfer of the chiral ligand from the intermediate product to the Lewis acid, not the cleavage of the bond between the MX_n unit and the product. Furthermore, the nitrilium ion intermediate could capture the chloride ion and be converted into an imidoyl chloride (M = Si, X = Cl, **iii**, Scheme 2), which would preclude further addition of an isocyanide. Finally, the attenuated Lewis acidity of the silicon center in the imidoyl chloride would result in facile transfer of the Lewis base catalyst to $SiCl_4$. Herein, we report the successful combination of these features in a chiral-Lewis-base-catalyzed, enantioselective Passerini-type reaction.[13]

Scheme 2



Initial studies employed the addition of *tert*-butyl isocyanide **1a** to benzaldehyde **2a**. Low-temperature ^{1}H NMR analysis indicated that $SiCl_4$ alone effectively promoted this reaction. The addition proceeded to 83% conversion within 4 h at −78 °C, and the hydroxy amide product **3a** was obtained in 79% yield after aqueous workup under basic conditions (Table 1, entry 1). This result was in sharp contrast to the allylation and the Mukaiyama aldol reaction wherein no background was observed in the absence of the Lewis base promoter.[12] The susceptibility of the reaction to nucleophilic catalysis was next examined. In the presence of 10 mol % of HMPA (**4a**) or pyridine-*N*-oxide (**4b**), quantitative conversion was observed under the same reaction conditions. Conclusive evidence of Lewis base catalysis was forthcoming from the use of 5 mol % of the chiral bisphosphoramide **5a**,[12,17] which gave promising enantioselectivity (entry 4).[14] To further improve the selectivity, we focused on improving the rate ratio between the catalyzed asymmetric and the achiral pathways. Consideration of the mechanistic differences between the two pathways led to the conclusion that decreasing

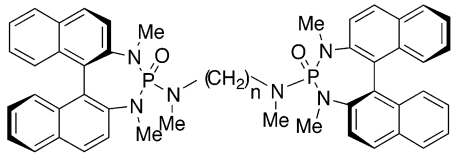
Table 1. Addition of Isocyanides to Benzaldehyde



entry	isocyanide	product	catalyst	yield, %[a]	er[b]
1[c]	**1a**	**3a**		79	
2[d]	**1a**	**3a**	**4a**	90	
3[e]	**1a**	**3a**	**4b**	94	
4[f,g]	**1a**	**3a**	**5a**	83	90.2/9.8
5[f,h]	**1a**	**3a**	**5a**	94	94.3/5.7
6[f,i]	**1a**	**3a**	**5a**	89	98.1/1.9
7[f,j]	**1a**	**3a**	**5a**	96	>99/1[k]
8[e,l]	**1b**	**3n**	**4b**	76	
9[f,j]	**1b**	**3n**	**5a**	82	73.2/26.8
10[e,m]	**1c**	**3o**	**4b**	72	
11[f,m]	**1c**	**3o**	**5a**	83	83.3/16.7
12[e,m]	**1d**	**3p**	**4b**	69	
13[f,m]	**1d**	**3p**	**5a**	80	88.5/11.5

[a] Yields of chromatographically homogeneous material. [b] Determined by CSP-SFC. [c] Without promoter. [d] With 10 mol % of **4a**. [e] With 10 mol % of **4b**. [f] With 5 mol % of **5a**. [g] **1a** added in one portion. [h] **1a** added over 2 h. [i] **1a** added over 3 h and with 30 mol % of *i*-Pr_2NEt. [j] Isocyanide added over 4 h with 10 mol % of *i*-Pr_2NEt. [k] Absolute configuration established as *S*, others assigned by analogy. [l] Isocyanide added over 30 min. [m] Isocyanide added in one portion.

the concentration of isocyanide would favor the catalyzed pathway versus the uncatalyzed pathway and thus increase the enantioselectivity.[15] Indeed, the enantioselectivity was found to depend on the rate of addition of **1a** (entries 5−7) and reached a maximum when a 4 h addition protocol was used (entry 7). Furthermore, the addition of 10 mol % of Hünig base to sequester adventitious HCl had no deleterious effects. Under these optimized reaction conditions, **3a** was obtained in >99/1 er in nearly quantitative yield (entry 7). The absolute configuration of (*S*)-**3a** indicated a *Re* face attack on the aldehyde by the isocyanide, which is in agreement with the sense of asymmetric induction observed in the allylation and the Mukaiyama aldol reactions.[12]

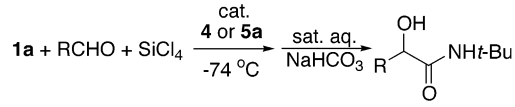


5a, n = 5; **5b**, n = 4; **5c**, n = 6

The scope of isocyanide structures that could be used in the reaction was surveyed next. Results of the addition of three representative isocyanides to **2a** are summarized in Table 1 (entries 8−13). Phenyl isocyanide **1b** provided a similarly high yield of the product in the presence of both pyridine-*N*-oxide and **5a** (entries 8 and 9), albeit with reduced enantioselectivity in the latter. Ethyl isocyanoacetate **1c** and tosylmethyl isocyanide **1d**, both of which possess two protons of significant acidity, were tested for functional group compatibility. In these cases, the hydroxy amide products **3o** and **3p** were obtained in good yields when the isocyanide was added in one portion, albeit after prolonged reaction time. Under these conditions, attenuated but respectable enantioselectivities were obtained for both **1c** and **1d** (entries 11 and 13).

To optimize the enantioselectivity, several bisphosphoramides were briefly surveyed in the addition of **1a** to **2a**. Bisphosphoramides **5a**−**c**,[12a] prepared by linking two chiral binaphthyldiamine units, provided excellent enantioselection with all three tether lengths (**5a** (n = 5), 96% yield, er >99/1; **5b** (n = 4), 93% yield, er 96.4/3/6; **5c** (n = 6), 86% yield, er 95.6/4/4). Other bisphosphoramides derived from 1,2-cyclohexanediamine, stilbene-1,2-diamine, and 2,2′-bispyrrolidine did not provide useful selectivities.[16]

Table 2. Addition of *tert*-Butyl Isocyanide to Aldehydes



			catalyst		
			4b	**5a**	
entry	R	product	yield, %[a,b]	yield, %[a,c]	er[d]
1	4-$CH_3C_6H_5$ (**2b**)	**3b**	87	91	99.9/0.1
2	4-$CH_3OC_6H_4$ (**2c**)	**3c**	92	89	98.3/1.7
3	4-$CF_3C_6H_4$ (**2d**)	**3d**	87	89	96.5/3.5
4	2-naphthyl (**2e**)	**3e**	90	93	99.7/0.3
5	1-naphthyl (**2f**)	**3f**	87	92	92.2/7.8[e]
6	2-furyl (**2g**)	**3g**	76	83	95.9/4.1[f]
7	(*E*)-PhCH=CH (**2h**)	**3h**	73	81	97.8/2.2
8	(*E*)-PhCH=CH(CH_3) (**2i**)	**3i**	86	86	67.4/32.6
9	phenylpropargyl (**2j**)	**3j**	85	76	77.0/23.0
10	$PhCH_2CH_2$ (**2k**)	**3k**	89	92	81.9/18.1
11	cyclohexyl (**2l**)	**3l**	72	53	87.1/12.9[f]
12[g]	$PhCH_2CH_2$ (**2k**)	**3m**	84	87	70.0/30.0

[a] Yields of chromatographically homogeneous material. [b] With 10 mol % of pyridine-*N*-oxide. [c] With 5 mol % of **5a**. [d] Determined by CSP-SFC. [e] Determined by CSP-HPLC. [f] Determined by CSP-GC. [g] 1,1,3,3-Tetramethylbutyl isocyanide (**1e**) served as the nucleophile.

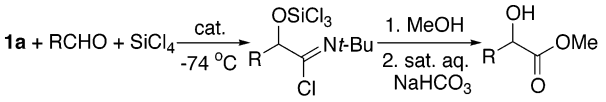
A survey of substrate scope with aromatic, conjugated, and aliphatic aldehydes was next conducted in the addition of **1a**, under the slow-addition protocol. We were delighted to find that all of the aldehydes reacted and provided the desired products in high yield, Table 2. Aromatic and conjugated aldehydes were found to react faster than aliphatic aldehydes in the presence of both pyridine-*N*-oxide (**4b**) and the chiral catalyst **5a** (compare entries 1−9 and entries 10−12). Whereas the reaction with most aromatic and conjugated aldehydes proceeded to completion within 8 h, aliphatic aldehydes required longer reaction times.

The enantioselectivities were also highly dependent on the aldehyde structure. Aromatic aldehydes gave excellent enantioselectivities. Subtle electronic and steric influence on enantioselectivity was observed. Whereas 4-tolualdehyde gave the same results as benzaldehyde, a detectable but minimal erosion in enantioselectivities was observed with both strongly electron-rich and electron-poor aldehydes (entries 1−3). Slight erosion was also observed when the aldehyde moiety became sterically encumbered. Although 2-naphthaldehyde provided essentially the same result as benzaldehyde, the enantioselectivity for 1-naphthaldehyde decreased (entries 4 and 5). Electron-rich heteroaromatic aldehydes, such as furfural, were compatible with the catalyst system and provided the product in high enantioselectivity (entry 6). Nonaromatic conjugated aldehydes reacted cleanly and in good yield, but with variable enantioselectivity. (*E*)-Cinnamaldehyde gave the best results, but with either greater or lesser steric encumbrance near the aldehyde, the enantioselectivities eroded (entries 7−9). On the other hand, for aliphatic aldehydes, the enantioselectivities increased with increasing steric bulk (entries 10 and 11). The influence of increasing the size of isocyanide on the enantioselectivity of the addition to hydrocinnamaldehyde was briefly examined. Although bulkier than **1a**, 1,1,3,3-tetramethylbutyl isocyanide **1e** was found to react with **2k** smoothly and provided good yields in the presence of both pyridine-*N*-oxide and **5a** (entry 12). However, the increased size of the isocyanide decreased the enantioselectivity, suggesting that the dependence of the enantioselectivity on the size of isocyanides is different for aromatic aldehydes and aliphatic aldehydes. The absolute configurations of **3a**, **3h**, and **3k** were

assigned as *S* by comparison of optical rotations of the derived methyl esters (vide infra). All others were assumed to be *S* by analogy.

To circumvent the reactivity and selectivity dependence on the isocyanide, we next explored the possibility of employing the most selective isocyanide **1a** and directly converting the imidoyl chloride intermediate into a carboxylic ester (Table 3). Gratifyingly, the corresponding methyl ester could be obtained by a simple two-step workup procedure. After complete consumption of the aldehyde, the intermediate imidoyl chloride was first converted to a methyl imino ether upon addition of methanol. Subsequent hydrolysis of the imino ether under basic conditions provided carboxylic ester in high yield. This procedure was successfully applied to all three classes of aldehydes. In each case, the stereochemical integrity was preserved; the enantiomeric composition of the ester product matched that of the corresponding hydroxy amide. The absolute configuration of all ester products was determined to be *S*, which revealed the same sense of asymmetric induction for all classes of aldehydes.

Table 3. Conversion of Imidoyl Chlorides to Methyl Esters



		catalyst			
		4b	**5a**		
aldehyde	product	yield, %[a,b]	yield, %[a,c]	config	er[d]
2a	**6**	83	97	*S*	>99/1
2h	**7**	74	71	*S*	97.9/2.1[e]
2k	**8**	83	88	*S*	81.8/18.2

[a] Yields of chromatographically homogeneous material. [b] With 10 mol % of pyridine-*N*-oxide. [c] With 5 mol % of **5a**. [d] Determined by CSP-SFC. [e] Determined by CSP-GC.

In summary, the first catalytic, enantioselective, α-additions of isocyanides have been documented. The chiral bisphosphoramide·$SiCl_4$ system catalyzes a Passerini-type reaction for a wide range of aldehydes and isocyanides in high yields with good to excellent enantioselectivities. Application of this catalyst system to the Ugi reaction and development of new Lewis base activated Lewis acid systems for catalytic, asymmetric α-addition reactions are in progress.

Acknowledgment. We are grateful to the National Science Foundation for generous financial support (NSF CHE 0105205). Y.F. thanks the Boehringer Ingelheim Pharmaceutical Co. for a graduate fellowship.

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

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(14) A control experiment with **1a**, benzaldehdye, and **5a** (10 mol %) in $CDCl_3$ showed no reaction after 4 h at room temperature.
(15) We speculate that the catalyzed reaction is first order in isocyanide by analogy to the allylation and aldol processes (ref 16), whereas the "uncatalyzed reaction" is promoted by the isocyanide and is likely higher order.
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(17) Catalyst **5a** is commercially available from Obiter Research, LLC. Contact waboulanger@obiterresearch.com.

JA035410C