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New Entries in Lewis Acid−Lewis Base Bifunctional Asymmetric Catalyst: Catalytic Enantioselective Reissert Reaction of Pyridine Derivatives

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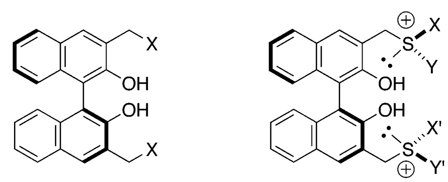
Chiral piperidines are among the most important building blocks for biologically active molecules and natural products. Many synthetic methodologies have been developed to access these useful heterocyclic compounds.[1] Among them, nucleophilic asymmetric addition to activated pyridine derivatives such as *N*-acyl pyridinium salts is a direct and attractive method. There are potential difficulties in this strategy, however, with regard to regio- and enantiocontrol. Typically, three reaction sites (2-, 4-, and 6-positions) on *N*-acyl pyridinium contain close electrophilicities, which generally results in nonregioselective additions. Moreover, rotation of the acyl carbon−nitrogen bond of the *N*-acyl pyridinium intermediate should be fixed in the transition state to achieve high enantioselectivity. Previous pioneering work in this field overcame these difficulties using various methods.[2] Although some of these reactions are practical and useful, stoichiometric amounts of chiral controllers were required, and the nucleophiles were restricted to reactive organometallics such as Grignard or organocopper reagents. We describe herein the first catalytic enantioselective Reissert reaction of pyridine derivatives, which significantly expands the utility of this strategy in chiral piperidine synthesis.

We developed a catalytic enantioselective Reissert reaction of quinolines and isoquinolines using an asymmetric bifunctional catalyst prepared from Et_2AlCl and **1** in a 1:1 ratio (**1**−Al).[3] The basic concept of this catalysis is that both the electrophile (*N*-acyl (iso)quinolinium) and nucleophile (TMSCN) are activated at defined positions by the Lewis acid (aluminum) and the Lewis base (phosphine oxide) moieties of the asymmetric catalyst, respectively, which controls the access of the nucleophile to the substrate.[4] We planned to extend this concept to a catalytic enantioselective Reissert reaction of pyridine derivatives. A survey of the literature, however, revealed that this type of reaction is very challenging; none of the achiral catalysts promote the reaction at a synthetically useful level,[5] probably due to both an attenuated nucleophilicity of cyanide compared to more reactive organometallic reagents and the lesser polarizability of pyridines compared to isoquinolines and quinolines. Thus, we began by identifying an appropriate substrate for achiral catalyst-promoted reactions. We found that nicotinic amide **7** gave the products in 91% yield using 10 mol % Et_2AlCl, 2 equiv of TMSCN, and 1.4 equiv of EtOCOCl at −78 °C in CH_2Cl_2, although the regioselectivity (the ratio of 1,6- (**8a**) and 1,2-adduct (**9a**)) was 1:1.[6,7]

On the basis of this finding, the catalytic enantioselective reaction was investigated. Use of **1**−Al (10 mol %) as the catalyst allowed the reaction of **7** to proceed at −60 °C; however, the products were obtained with low regio- (**8a**:**9a** = 2.3:1) and enantioselectivity (<9% ee: 91% total yield). To improve the results, we examined the effect of a Lewis base in the catalyst.[8] Specifically, we used a sulfoxide as a Lewis base (**4**−**6**),[9] because such bifunctional catalysts contain additional chiralities on the sulfur atoms, which might enhance the enantioselectivity if it is matched with the axial chirality of the BINOL core. The metal/ligand ratio was also screened to generate a new chiral polymetallic complex of high regio- and enantioselectivity, stabilized by Lewis base coordination to the metal.[10]



1: X = P(O)Ph_2
2: X = P(S)Ph_2
3: X = P(S)$(C_6H_4$–*o*–Et$)_2$

4: X, X' = O^-; Y, Y' = Ph
5: X, X' = Ph; Y, Y' = O^-
6: X, Y' = Ph; X', Y = O^-

Studies based on the above ideas led to the finding that a catalyst prepared from Et_2AlCl and ligand **6**, which is not C_2 symmetric, in a 1:2 ratio (**6**−Al: 5 mol %) gave the product **8a** with significantly higher regio- (11:1) and enantioselectvity (75% ee: 98% total yield) than catalysts prepared from other ligands.[7,11] With this promising catalyst, the chloroformate and the amide part of the substrate were optimized in the presence of **6**−Al. Excellent regioselectivity (12:1∼50:1) and enantioselectivity (up to 96% ee) were obtained using several chloroformates (Table 1; entries 1−4). Bulkier amide **10** gave slightly higher enantioselectivity than **7**. An ester analogue **12** can be also used as a substrate, although the enantioselectivity was moderate (entry 5). Enantiomerically pure product **13** was obtained, however, in a synthetically useful yield through a single recrystallization, taking advantage of the highly crystalline Fmoc-protected amidonitrile.

Next, the optimized conditions were applied to other substrates (**14** and **16**), which might be useful for further derivatization. These substrates, however, produced only moderate regio- (5:1) and enantioselectivity (61 and 52% ee, respectively) using **6**−Al as the catalyst. Thus, we resurveyed the reaction conditions, including the catalyst structure. The catalyst prepared from Et_2AlCl and **3** in a 1:1 ratio (**3**−Al: 10 mol %), containing a tuned phosphine sulfide as a Lewis base, afforded optimum results using neopentyl chloroformate as an acylating reagent:[7,12] products **15** and **17** were obtained in 92 and 89% yields with 91 and 86% ee from **14** and **16**, respectively (entries 6 and 7, regioselectivity = 12:1 and 8:1). Thus, combined with the **6**−Al-catalyzed reaction, these are the first examples of a catalytic enantioselective Reissert reaction of pyridine derivatives. Specifically, these enantioselective catalysts facilitate one specific reaction pathway (1,6-addition from the *Re*-face) out of six possible pathways, thus giving the products with high regio- and enantioselectivity.

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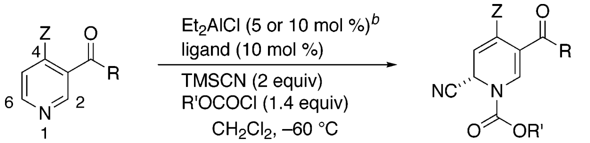
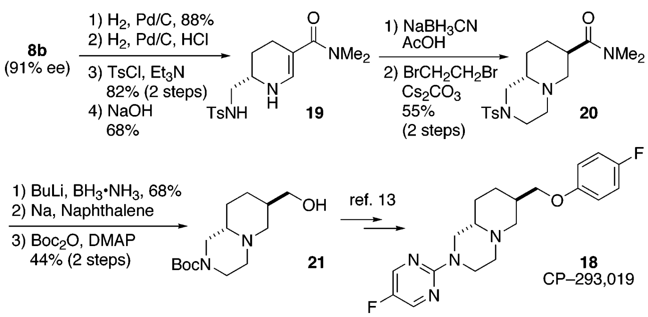
Table 1. Catalytic Enantioselective Reissert Reaction of Pyridine Derivatives[a]



entry	substrate	ligand	R′ (R′OCOCl)	product	yield (%)	ee (%)
1[f]	**7**:R = NMe_2, Z = H	**6**	Me	**8b**	98	91[d]
2[f]	**7**:R = NMe_2, Z = H	**6**	Fm[c]	**8c**	89	93
3[f]	**10**:R = N^iPr_2, Z = H	**6**	Fm[c]	**11a**	98	96
4[f]	**10**:R = N^iPr_2, Z = H	**6**	neopentyl	**11b**	98	93
5[f]	**12**:R = OMe, Z = H	**6**	Fm[c]	**13**	85 (42)[e]	57 (>99)[e]
6[g]	**14**:R = N^iPr_2, Z = Cl	**3**	neopentyl	**15**	92	91
7[h]	**16**:R = N^iPr_2, Z = Br	**3**	neopentyl	**17**	89	86

[a] Yield is isolated yield of the 1,6-adduct. Ee was determined by chiral HPLC. [b] Catalyst was prepared from 5 mol % Et_2AlCl + 10 mol % **6** or 10 mol % Et_2AlCl + 10 mol % **3**. [c] Fm = fluorenylmethyl. [d] Absolute configuration was determined to be (*S*). [e] Value observed after recrystallization. [f] Reaction time = 5 h. [g] Reaction time = 27 h. [h] Reaction time = 36 h.

Scheme 1. Catalytic Enantioselective Synthesis of Intermediate for CP-293,019



The synthetic utility of these reactions was demonstrated by application to a formal catalytic enantioselective synthesis of the dopamine D_4 receptor-selective antagonist, CP-293,019 (**18**)[13] (Scheme 1). Two-step hydrogenation of **8b** (91% ee) followed by a protection−deprotection protocol gave tetrahydropyridine **19**. Reduction of **19** with $NaBH_3CN$ via an iminium cation proceeded in a 4:1 ratio, and the isolated major isomer was annulated to give *trans*-**20**. The known intermediate **21** was synthesized from **20** in three steps. Furthermore, the multifunctionality of the Reissert products allowed for a short-step, stereoselective synthesis of other various useful chiral building blocks.[7]

Although the detailed reaction mechanism is under investigation, the following preliminary information suggests key factors for the success of the present catalysis. First, on the basis of a reaction rate comparison of cyanosilylation of hydrocinnamaldehyde in the presence or absence of the Lewis base, both sulfoxides and phosphine sulfides can activate TMSCN as a Lewis base.[7,14,15] Combined with the previous mechanistic studies of Al−**1**-catalyzed reactions,[3] the high regio- and enantioselectivity are likely due, at least partly, to the dual activation of *N*-acyl pyridinium and TMSCN at the positions defined by the bifunctional asymmetric catalyst. Second, ESI-MS studies suggested a relation between the enantioselectivity and the amount of a bimetallic 2:3 complex composed of aluminum and the ligand in the reactions promoted by sulfoxide-containing catalysts (catalysts derived from **4**−**6**).[7] Thus, a bimetallic complex might be a highly enantioselective catalyst for substrate **7**.[16] These results suggest that sulfoxides of Al−**6** might have dual roles: one is activation of TMSCN, and the other is stabilization of a highly enantioselective bimetallic complex through internal coordination to aluminum.

In conclusion, we achieved the first catalytic enantioselective Reissert reaction of pyridine derivatives through the development of new Lewis acid−Lewis base asymmetric bifunctional catalysts. Detailed mechanistic studies to elucidate the origin of the high regio- and enantioselectivity are currently in progress.

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

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(6) 1,4-Adduct was obtained in less than trace amounts in all cases.
(7) See Supporting Information for details.
(8) We speculated that there is a Lewis base-catalyzed monoactivation pathway of low enantioselectivity for reactive *N*-acyl pyridinium, due to the higher Lewis basicity of a phosphine oxide than a sulfoxide or a phosphine sulfide.
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(11) C_2-symmetric sulfoxide-containing catalysts **4**−Al and **5**−Al gave products in 78% yield with 1.3:1 regioselectivity (15 and 7% ee) and in 56% yield with 1:1 regioselectivity (14 and 4% ee), respectively.
(12) **3**−Al did not give satisfactory results for **7** using neopentyl chloroformate: 1,6-adduct **8d** and 1,2-adduct **9d** were obtained in 56% yield with 80% ee and 15% yield with 0% ee, respectively.
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