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Enantioselective Strecker-type reaction promoted by polymer-supported bifunctional catalyst

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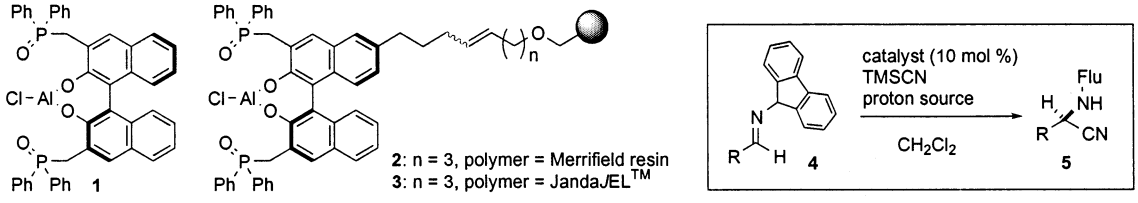
Abstract—The Janda*J*EL™-supported bifunctional catalyst **3** (10 mol%) promoted the Strecker-type reaction of aromatic and α,β-unsaturated imines in excellent yields with 83–87% ee in the presence of ^{t}BuOH (110 mol%). The reactivity of **3** was comparable to the homogeneous analogue **1**, and **3** could be recycled at least four times.

The importance of immobilized asymmetric catalysts is rapidly growing in view of easy separation of the product and reusability of the catalyst.[1] Solid-supported catalysts show considerable advantages over homogeneous ones, especially in large-scale syntheses and high throughput organic chemistry. We have recently reported an enantioselective Strecker-type reaction promoted by the homogeneous bifunctional catalyst **1**.[2,3] The products were obtained with generally high ee (70–95% ee) from a relatively wide range of substrates, such as aromatic and aliphatic imines including α,β-unsaturated imines. The origin of the high enantioselectivity and substrate generality is considered to stem from the dual activation of the imine and TMSCN at the defined positions by the Lewis acid (Al) and the Lewis base (phosphine oxide) of the catalyst.[4] Considering the importance of catalytic enantioselective Strecker-type reaction for providing various chiral amino acid precursors in both laboratory and industrial scales, it is highly desirable that the catalyst could be immobilized on a solid phase and recycled many times.[5] In this paper, we disclose our initial success in this direction.

Since the high enantio-differentiation by the bifunctional catalyst depends on the simultaneous activation of substrate and reagent, it seemed important that the polymer support should not affect the balance of the activation ability of the Lewis acid and the Lewis base. On the basis of preceding reports concerning polymer-supported binaphthyl ligands,[6] we designed the polymer-supported catalysts **2** and **3** possessing a sufficiently long spacer at the 6-position to avoid an adverse effect of the spacer on the asymmetric environment. Since the catalyst contains a Lewis acid metal, a non-coordinating alkenyl linker was selected. The syntheses of **2** and **3** are shown in Scheme 1. After regioselective Friedel–Crafts acylation,[6a] the attachment of the chiral ligand to the polymer was achieved by Wittig reaction.[7] The purity of the final polymer-supported ligand was checked by ^{31}P swollen-resin magic angle spinning (SR-MAS) NMR.[8] The loading of the ligand on polymers was determined based on mass balance (1.02 mmol/g for **2** and 0.52 mmol/g for **3**).



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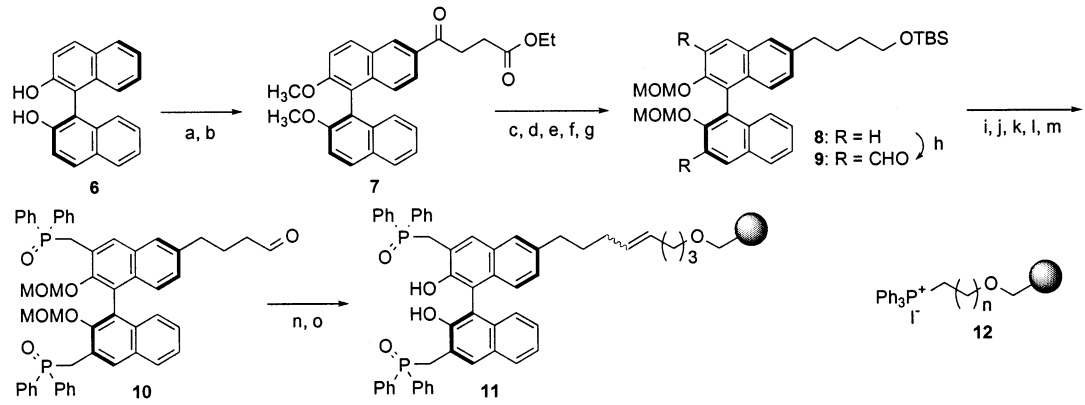

Scheme 1. Reagents and conditions: (a) MeI, K_2CO_3, acetone, 92%; (b) ethyl 4-chloro-4-oxobutyrate, $AlCl_3$, CH_2Cl_2, 80%; (c) Pd/C, H_2, CH_3SO_3H, AcOH/AcOEt/EtOH, 68%; (d) BBr_3, CH_2Cl_2, 64%; (e) MOMCl, $^iPr_2NEt$, CH_2Cl_2; (f) LAH, THF, 76% (two steps); (g) TBSCl, imidazole, DMF, 91%; (h) 1) BuLi (5 equiv.), Et_2O, 2) DMF (6 equiv.), 61%; (i) $NaBH_4$, MeOH, 98%; (j) 1) MsCl, Et_3N, CH_2Cl_2, 2) LiCl, DMF, 86%; (k) $Ph_2P(O)H$ (3 equiv.), NaO^tBu (3.3 equiv.), THF, 100%; (l) TBAF, THF, 89%; (m) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 94%; (n) 1) **12** (1 equiv.), KHMDS (5 equiv.), THF–toluene, rt, 4 h, 2) wash with THF, 3) **11** (1.5 equiv.), THF, −78°C to rt, 15 h, 4) acetaldehyde (capping); (o) $TsOH\cdot H_2O$, CH_2Cl_2–MeOH, 40°C.

Using the homogeneous catalyst **1**, we have found that addition of a proton source was necessary to enhance the reaction rate.[2] The best proton source was PhOH, although other alcohols gave only slightly lower enantioselectivity. Our rationale for the additive effect is that it should protonate the anionic nitrogen generated by the addition of the cyanide to the imine, thus facilitating the ligand exchange on the catalyst. Since PhOH should be partially regenerated from TMSOPh and the product amine, only a catalytic amount (20 mol%) of PhOH was sufficient to give the products with the same ee as with 110 mol% of PhOH. So, we first investigated the effect of the protic additives, using the Merrifield resin-supported catalyst **2**. As shown in Table 1, applying the best reaction conditions to benzaldehyde imine **4a**, using **2** (10 mol%), the product **5a** was obtained in 83% yield with 65% ee (entry 2). However, when a stoichiometric amount of PhOH (110 mol%) was used, the ee became significantly lower (43%, entry 3). Another different tendency from the homogeneous catalyst **1** was observed when an aliphatic alcohol was used (entries 4–6). The ee was improved up to 78% using 110 mol% of ^{t}BuOH as a proton source (entry 6).[9] These different tendencies between the homogeneous catalyst **1** and polymer-supported **2** might be explained as follows. The protic additive should partly react with TMSCN to generate HCN.[10] In the case of the reaction promoted by the homogeneous catalyst **1**, the reactivity of HCN toward the imines was considerably lower than that of TMSCN, since only TMSCN could be activated by the Lewis basic phosphine oxide of **1**.[2] However, in the case of the polymer-supported catalyst **2**, the reactivity difference between HCN and TMSCN is not so significant any more, possibly due to the hindered accessibility of TMSCN to the phosphine oxide by the bulky polymer core. We have confirmed that the reaction using HCN proceeded with the similar rate as TMSCN in the presence of **2**. Compound **5a** was obtained in 41% yield in 30 h with 0% ee by HCN (versus 50% yield with TMSCN-ROH, entries 4, 5). Therefore, the difference of the ee of the product, depending on the proton source, could possibly stem from the amount of HCN in the reaction mixture. The more acidic PhOH should generate a higher amount of HCN than ^{t}BuOH. As a result, the competitive racemic pathway by HCN should become more problematic, especially in the case when a stoichiometric amount of PhOH was used. From these results, we expected that, if the phosphine oxide of the catalyst becomes more accessible to TMSCN, the

Table 1. Optimization of the reaction conditions using benzaldehyde imine **4a**

Entry	Catalyst	Catalyst synthesis	Proton source (mol%)	Reaction	Temp. (°C)	Time (h)	Yield (%)	Ee (%)
1	**1**	–	PhOH (20)	–	−40	44	92	95
2	**2**	Stir	PhOH (20)	Stir	−40	43	83	65
3	**2**	Stir	PhOH (110)	Stir	−40	43	91	43
4	**2**	Stir	MeOH (110)	Stir	−40	30	50	71
5	**2**	Stir	^{i}PrOH (110)	Stir	−40	30	50	71
6	**2**	Stir	^{t}BuOH (110)	Stir	−40	64	86	78
7	**2**	Stir	^{t}BuOH (110)	Shake	−40	16	16	55
8	**2**	Shake	^{t}BuOH (110)	Stir	−40	18	18	16
9	**2**	Shake	^{t}BuOH (110)	Shake	−40	86	86	15
10	**3**	Stir	^{t}BuOH (110)	Stir	−50	60	98	87

Table 2. Catalytic enantioselective Strecker-type reaction of various imines[a]

			3			**2**			**1**[b]		
Entry	Imine (R)	Product	Time (h)	Yield (%)	Ee (%)	Time (h)	Yield (%)	Ee (%)	Time (h)	Yield (%)	Ee (%)
1	**4a** (Ph)	**5a**	60	98	87	64	86	78	44	92	95
2	**4b** (*p*-MePh)	**5b**	64	100	83	–	–	–	–	–	–
3	**4c** (*p*-ClPh)	**5c**	59	98	85	85	74	80	44	92	95
4	**4d** (*p*-MeOPh)	**5d**	41	98	83	85	85	62	44	93	93
5	**4e** (3-Furyl)	**5e**	66	97	86	64	81	76	44	92	90
6	**4f** ((*E*)-PhCH=CH)	**5f**	66	96	83	86	55	53	41	80	96

[a] The reaction was performed at −50°C using **3**, and −40°C using **2** or **1**.
[b] See Ref. 2 for details.

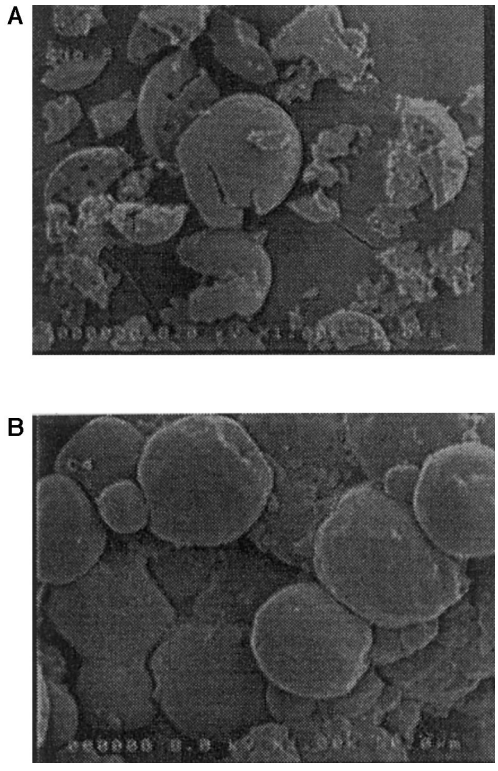

Figure 1. SEM pictures of the resin. A. Resin prepared by stirring. B. Resin prepared by shaking.

highly enantioselective dual activation pathway by TMSCN should be facilitated, thus giving the improved enantioselectivity.

Next, we investigated the effect of the macroscopic structure of the polymer beads. The macroscopic polymer structure could affect the accessibility of the substrate to the catalytic center. Since we synthesized the catalyst with stirring, the polymer beads were physically broken (Fig. 1, A). Therefore, we synthesized the catalyst by just gently shaking the beads. Thereby, we could obtain the catalyst containing the spherical polymer structure (Fig. 1, B). However, this spherical polymer-supported catalyst turned out to be less active as well as less enantioselective (Table 1, entries 8, 9). These results again indicated that the more porous, thus more accessible polymer-supported catalyst (A), should contain the higher activity as well as enantioselectivity.[11]

Therefore, we tried Janda*J*EL™ as polymer support (catalyst **3**).[12] Recently, Janda developed a polystyrene resin containing flexible tetrahydrofuran derived cross-linkers.[13] This resin is reported to swell better than Merrifield resin, and thus the reagents should be more accessible to the catalytic center. As expected, the product **5a** was obtained in 98% yield with 87% ee, using **3** as catalyst (Table 1, entry 10). These results clearly showed that well-swollen Janda*J*EL™ should make the catalyst more accessible, thus making the highly enantioselective dual activation pathway with TMSCN as the nucleophile more predominant.[14] The results of the enantioselective Strecker-type reaction promoted by the Janda*J*EL™-supported bifunctional catalyst **3** are summarized in Table 2.[15] In all cases, **3** was more reactive and gave higher enantioselectivities than **2**. Although **3** was slightly less enantioselective than homogeneous **1**, the reactivity was almost comparable. The sense of enantioselection was the same as for the homogeneous catalyst **1**, indicating that the dual activation of the imine and TMSCN by the Lewis acid metal (Al) and the phosphine oxide should take place, also in the case of the polymer-supported catalyst **3**. However, using aliphatic pivaladehyde imine, the ee of the product was significantly lower (20% ee) compared to **1** (78% ee), which should be the target of the future investigation.

Table 3. Recycle of **3**[a]

Cycle	Time (h)	Yield (%)	Ee (%)
1	60	98	87
2	44	95	81
3	44	78	83
4	110	97	80
5	204	83	77

[a] **4a** was used as substrate.

Finally, we found that **3** could be recovered and recycled at least four times (Table 3), even though the macroscopic structure of the polymer was broken.[16,17]

In conclusion, we have succeeded in immobilizing the Lewis acid–Lewis base bifunctional catalyst **1** on polymer support. Both of the macroscopic and molecular structures of the polymer had a profound effect on the reactivity and enantioselectivity. Using Janda*J*EL™ and a catalyst preparation method under stirred conditions, the catalyst center became more accessible and the highly enantioselective dual activation pathway in which TMSCN acted as the nucleophile became predominant. Moreover, the catalyst was recyclable. Further studies to extend this methodology to a practical large-scale synthesis are underway.

Acknowledgements

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9. Using 20 mol% of ^{t}BuOH did not improve the ee.
10. Mai, K.; Patil, G. *J. Org. Chem.* **1986**, *51*, 3545–3548.
11. The enantioselectivity was not improved using catalysts containing longer linkers. Merrifield resin-supported catalysts synthesized under shaking with $n = 5$ and 7 gave **5a** with 16 and 0% ee, respectively (versus 16% ee by **2** synthesized by shaking).
12. Catalyst **3** was synthesized by stirring.
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14. The difference of loading density of the catalyst on resins may also affect the activity and enantioselectivity.
15. Representative procedure: To the swollen polymer-supported ligand (19.1 mg, loading level = 0.52 mmol/g, 10 μmol) in CH_2Cl_2 (0.4 mL), Et_2AlCl (0.95 M in hexane, 10 μL, 9.5 μmol) was added at ambient temperature and the whole was stirred for 1 h. Cooling down to −50°C, imine **4a** (27 mg, 0.1 mmol) in CH_2Cl_2 (0.25 mL), TMSCN (54 μL, 0.4 mmol) and ^{t}BuOH (0.11 mmol) in CH_2Cl_2 (0.25 mL) were added successively with 10 min interval. After 60 h, satd $NaHCO_3$ (1 mL) was added. Usual workup and purification by silica gel column chromatography afforded pure **5a** in 98% yield. Ee of the product was determined by chiral HPLC (see Ref. 2 for details).
16. The procedure for recycling the catalyst **3** is as follows. After the reaction was completed, dry Et_2O (five times volume to CH_2Cl_2) was added and the reaction mixture was stayed for 3 h. The supernatant containing the product was then taken by a syringe and the catalyst was washed with dry Et_2O five times under an inert atmosphere. Drying the catalyst under reduced pressure for 30 min, CH_2Cl_2 solvent, the imine, TMSCN, and ^{t}BuOH were added at −50°C to start the new cycle.
17. The slightly lower yield in cycle 3 might be due to inevitable loss of the catalyst when the supernatant was taken by a syringe. The longer reaction time in cycles 4 and 5 might be caused by the above-mentioned effect and/or by the partial decomposition of the catalyst.