# Catalytic, Asymmetric Baylis–Hillman Reaction of Imines with Methyl Vinyl Ketone and Methyl Acrylate**

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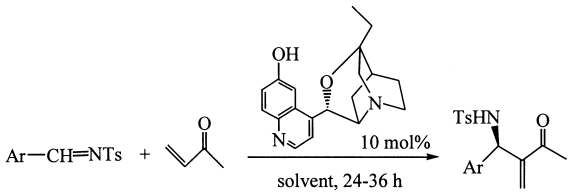
The Baylis–Hillman reaction has made great progress,[1] including development of a catalytic, asymmetric version,[2] since Baylis and Hillman first reported the reaction of acetaldehyde with ethyl acrylate or acrylonitrile in the presence of catalytic amounts of a strong Lewis base such as 1,4-diazabicyclo[2.2.2]octane (DABCO) in 1972.[3] However, the catalytic, asymmetric Baylis–Hillman reaction is still not fruitful, because it is limited to the specialized α,β-unsaturated ketones or acrylates such as ethyl vinyl ketone (71% *ee*) or 1,1,1,3,3,3-hexafluoroisopropyl acrylate (99% *ee*).[2] High enantioselectivity has so far not been reported in Baylis–Hillman reactions involving simple acceptors such as methyl vinyl ketone (MVK) or methyl acrylate. Here we report unprecedented catalytic, asymmetric Baylis–Hillman reactions of imines with MVK or methyl acrylate, in which high enantioselectivities (up to 99% *ee*) were achieved with MVK, the simplest Baylis–Hillman acceptor.

During our investigations on the Baylis–Hillman reaction,[4] we found that the reactions of aryl aldehydes bearing electron-donating groups such as Et or MeO on the phenyl ring with MVK or methyl acrylate were sluggish or did not occur at all under the traditional Baylis–Hillman reaction conditions. Hence, we used *N*-arylidene-4-methylbenzenesulfonamides ArCH=NTs instead of aryl aldehydes in the traditional Baylis–Hillman reaction with MVK, because we expected the tosylated imino group to have high reactivity toward nucleophilic attack, even when the phenyl ring bears electron-donating groups. Indeed, such reactions, promoted by a catalytic amount of a Lewis base such as DABCO or 4-(dimethylamino)pyridine (DMAP), exclusively give the normal Baylis–Hillman adducts in good yields for many *N*-arylidene-4-methylbenzenesulfonamides.[4g,5] We then sought a suitable chiral Lewis base for a catalytic, asymmetric version of this reaction. We chose 4-(3-ethyl-4-oxa-1-azatricyclo[4,4,0,0$^{3,8}$]dec-5-yl)quinolin-6-ol[2d] (TQO, 10 mol%), because it is easily prepared from (+)-quinidine[2a,d] and high enantioselectivities were achieved in the reactions of 1,1,1,3,3,3-hexafluoroisopropyl acrylate with aryl aldehydes.[2] We first used *N*-(4-ethylbenzylidene)-4-methylbenzenesulfonamide and *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide as substrates for the Baylis–Hillman reaction with MVK (Table 1). At 0–20 °C, moderate enantioselectivity (42–78% *ee*) for adducts **1c** and **1e** were achieved in THF or MeCN (Table 1, entries 1, 3, and 7). Moreover, at lower temperatures (−20 to −30 °C), the *ee* values of **1c** and **1e** can reach 81 and 86%, with 64 and 80% yield, respectively (entries 4 and 9). The highest *ee* values (96 and 95%) for **1c** and **1e** were achieved in DMF at −30 to −40 °C with 50 and 51% yield (entries 6 and 10). Thus, the highest *ee* value is attained at −30 °C in DMF, but the best chemical yield at −30 °C in MeCN. To obtain the Baylis–Hillman adducts **1** with high *ee* values and yields, we next investigated the reaction of *N*-(4-ethylbenzylidene)-4-methylbenzenesulfonamide with MVK in MeCN/DMF at −30 °C (Table 2). The best conditions were MeCN/DMF (1:1) at −30 °C, which gave **1e** in 68% yield with 93% *ee* (entry 3). The absolute configuration of **1e** was determined by X-ray crystallography to be *R* (Figure 1).[6]

Table 1. Baylis–Hillman reactions of *N*-(benzylidene)-4-methylbenzenesulfonamide or *N*-(benzylidene)-4-chlorobenzenesulfonamide (1.0 equiv) with MVK in the presence of a chiral Lewis base (10 mol%).




**1**

| Entry | Ar | **1** | Solvent | *t* [h] | *T* [°C] | Yield of **1** [%][a] | *ee* value [%] |
|---|---|---|---|---|---|---|---|
| 1 | *p*-Et$C_6H_4$ | **c** | THF | 36 | 20 | 30 | 62 |
| 2 | *p*-Et$C_6H_4$ | **c** | THF | 24 | −25 | 33 | 76 |
| 3 | *p*-Et$C_6H_4$ | **c** | MeCN | 24 | 0 | 50 | 78 |
| 4 | *p*-Et$C_6H_4$ | **c** | MeCN | 24 | −20 | 64 | 86 |
| 5 | *p*-Et$C_6H_4$ | **c** | DMF | 24 | −20 | 55 | 93 |
| 6 | *p*-Et$C_6H_4$ | **c** | DMF | 24 | −40 | 50 | 96 |
| 7 | *p*-Cl$C_6H_4$ | **e** | THF | 24 | 0 | 71 | 42 |
| 8 | *p*-Cl$C_6H_4$ | **e** | THF | 24 | −20 | 65 | 63 |
| 9 | *p*-Cl$C_6H_4$ | **e** | MeCN | 24 | −30 | 80 | 81 |
| 10 | *p*-Cl$C_6H_4$ | **e** | DMF | 24 | −30 | 51 | 95 |

[a] Yields of isolated products.

In the reaction of other *N*-(arylidene)-4-methylbenzenesulfonamides with MVK in the presence of TQO as Lewis base, similar results were obtained under the optimized reaction conditions (Table 3). For various *N*-(arylidene)-4-methylbenzenesulfonamides, Baylis–Hillman adducts **1** were obtained with high *ee* values(90–99%) and moderate to good yields (55–80%; Table 3, entries 1–5). The reaction of *N*-(*p*-nitrobenzylidene)-4-methylbenzenesulfonamide, *N*-furan-2-ylmethylene-4-methylbenzenesulfonamide, and 4-methyl-*N*-

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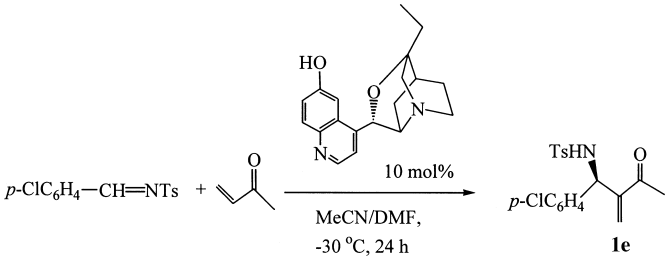
Table 2. Baylis–Hillman reactions of *N*-(*p*-chlorobenzylidene)-4-methylbenzenesulfonamide (1.0 equiv) with MVK in the presence of a chiral Lewis base (10 mol%).




| Entry | MeCN/DMF | Yield of **1e** [%][a] | *ee* value [%] | Absolute configuration |
|---|---|---|---|---|
| 1 | 5:1 | 76 | 78 | *R* |
| 2 | 4:1 | 78 | 90 | *R* |
| 3 | 1:1 | 68 | 93 | *R* |
| 4 | 1:2 | 66 | 93 | *R* |

[a] Yields of isolated products.

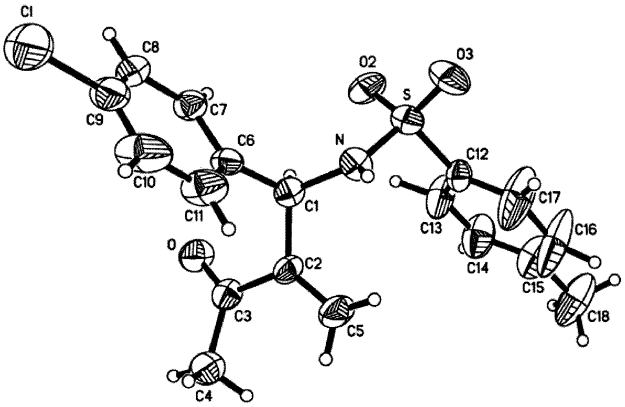
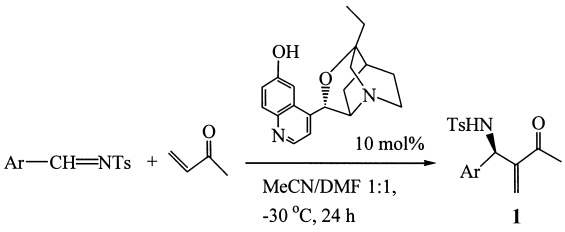



Figure 1. Crystal structure of **1e**.

Table 3. Baylis–Hillman reactions of *N*-(benzylidene)-4-methylbenzenesulfonamide (1.0 equiv) with MVK in the presence of a chiral Lewis base (10 mol%).

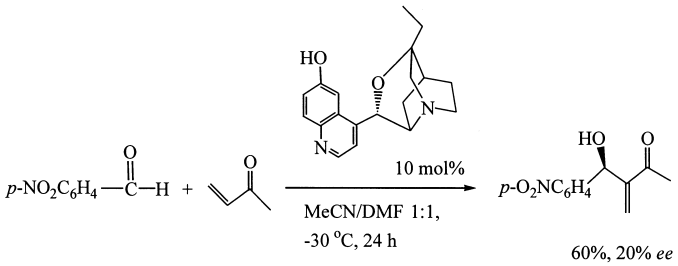



| Entry | Ar | **1** | Yield of **1** [%][a] | *ee* value [%] | Absolute configuration |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | **a** | 80 | 97[b] | *R* |
| 2 | *p*-$MeC_6H_4$ | **b** | 76 | 96 | *R* |
| 3 | *p*-$EtC_6H_4$ | **c** | 74 | 96 | *R* |
| 4 | *p*-$MeOC_6H_4$ | **d** | 64 | 99[c,d] | *R* |
| 5 | *m*-$FC_6H_4$ | **f** | 55 | 90 | *R* |
| 6 | *p*-$NO_2C_6H_4$ | **g** | 60 | 74[e] | *R* |
| 7 | 2-furyl | **h** | 58 | 73[d] | *R* |
| 8 | $C_6H_5$–CH=CH | **i** | 54 | 46[d] | *R* |

[a] Yields of isolated products. [b] In DMF, 57% yield, 96% *ee*. [c] In DMF, 59% yield, 99% *ee*. [d] The reaction mixture was stirred for 36 h. [e] In DMF, no imine Baylis–Hillman adduct was formed because the imine decomposed rapidly.

(3-phenylallylidene)benzenesulfonamide with MVK under the same reaction conditions gave **1g–i** with moderate *ee* values (entries 6–8). No formation of adduct **1g** was observed in DMF at −40 °C, because *N*-(4-nitrobenzylidene)-4-methylbenzenesulfonamide decomposes rapidly in DMF under these conditions.

The reaction of *p*-nitrobenzaldehyde with MVK under the same conditions gave the Baylis–Hillman adduct in only 20% *ee* with 60% yield of isolated product (Scheme 1). Thus, the use of sulfone-protected imines as substrates is important for achieving high enantioselectivity in Baylis–Hillman reactions with MVK as acceptor, although high enantioselectivities have been achieved in the reactions of 1,1,1,3,3,3-hexafluoroisopropyl acrylate with aldehydes.[2a]




Scheme 1. Baylis–Hillman reaction of *p*-nitrobenzaldehyde with MVK in the presence of TQO (10 mol%).

On the other hand, the reactions of *N*-tosylated imines with methyl acrylate under the same conditions were sluggish, and most *N*-tosylated imines decomposed during the reaction in DMF or MeCN. However, with DABCO as Lewis base in dichloromethane at 0 °C, the reaction proceeded smoothly to give the Baylis–Hillman adducts **2** in good yields. Moreover, in the presence of the chiral Lewis base TQO, products **2** were obtained in 58–87% yield with 70–83% *ee* (Table 4). Similar enantioselectivities were obtained when the reactions were carried out at −20 °C. The results are summarized in Table 4. In addition, the Baylis–Hillman reaction of an *N*-tosylated imine with acrylonitrile afforded adduct **3** in 35% yield with 55% *ee* in $CH_2Cl_2$, and in 34% yield with 68% *ee* in THF, under the same conditions as for methyl acrylate (Scheme 2).

To expand the scope and explore the limitations of this novel catalytic, asymmetric aza-Baylis–Hillman reaction, we tried to synthesize aliphatic *N*-tosylated imines as starting materials. However, we found that many of these are very labile, even when stored below −20 °C. We used literature procedures[7] to prepare the aliphatic *N*-tosylated imines **4** and **5**, which must be used immediately for the reaction. The attempted catalytic

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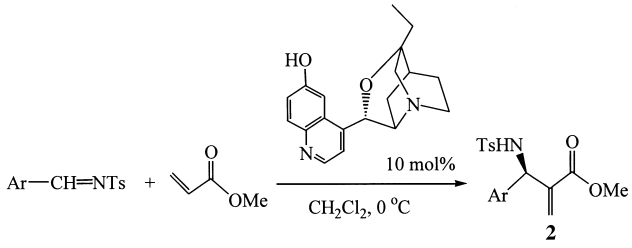
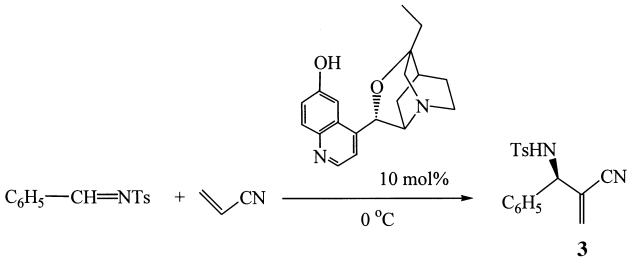
Table 4. Baylis–Hillman reactions of *N*-(benzylidene)-4-methylbenzenesulfonamide (1.0 equiv) with methyl acrylate in the presence of a chiral Lewis base (10 mol %).




**2**

| Entry | Ar | **2** | Yield of **2** [%][a] | *t* [h] | *ee* [%] | Absolute configuration |
|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | **a** | 62 | 72 | 83 | *R* |
| 2 | *p*-$MeC_6H_4$ | **b** | 67 | 72 | 80 | *R* |
| 3 | *p*-$EtC_6H_4$ | **c** | 62 | 72 | 82 | *R* |
| 4 | *p*-$MeOC_6H_4$ | **d** | 64 | 72 | 70 | *R* |
| 5 | *p*-$ClC_6H_4$ | **e** | 60 | 36 | 77 | *R* |
| 6 | *m*-$FC_6H_4$ | **f** | 87 | 32 | 83 | *R* |
| 7 | *p*-$NO_2C_6H_4$ | **g** | 58 | 35 | 72 | *R* |
| 8 | 2,3-$Cl_2C_6H_3$ | **h** | 58 | 38 | 71 | *R* |

[a] Yields of isolated products.




**3**

Scheme 2. Baylis–Hillman reaction of *N*-(benzylidene)-4-methylbenzenesulfonamide with acrylonitrile in $CH_2Cl_2$ (55 % *ee*, 35 % yield) and THF (68 % *ee*, 34 % yield).

asymmetric Baylis–Hillman reaction of **4** or **5** with MVK in the presence of TQO gave many unidentified products, and the Baylis–Hillman adduct was not formed (Scheme 3).

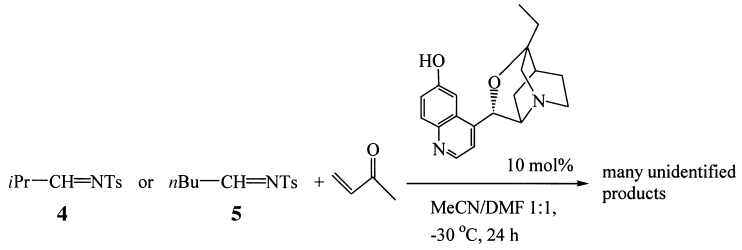
Note that (+)-quinidine and (−)-quinine showed no catalytic activity for this reaction. The hydroxy group on the quinolyl ring is also crucial, because the reaction became sluggish and gave the product with only about 10 % *ee* in very low yield when O-methylated TQO was used as chiral Lewis base. Thus, the structure of the Lewis base plays an important role in this reaction. Scheme 4 shows a possible mechanism, based on that proposed by Hatakeyama et al.[2a] We believe that the key factor is intramolecular hydrogen bonding between the phenolic OH group and the nitrogen-centered anion, stabilized by a sulfonyl group to give a relatively rigid transition state. The steric interaction of the C(O)Me group with the aromatic group in this stabilized transition state causes the formation of the Baylis–Hillman adduct with *R* configuration.

In conclusion, we have achieved the thus far highest *ee* values for Baylis–Hillman reactions involving MVK or methyl acrylate as acceptor. Moreover, this is the first case of highly enantioselective Baylis–Hillman reactions of imines with α,β-unsaturated ketones. Efforts are underway to elucidate the mechanistic details of this reaction and to disclose its scope and limitations.

## *Experimental Section*

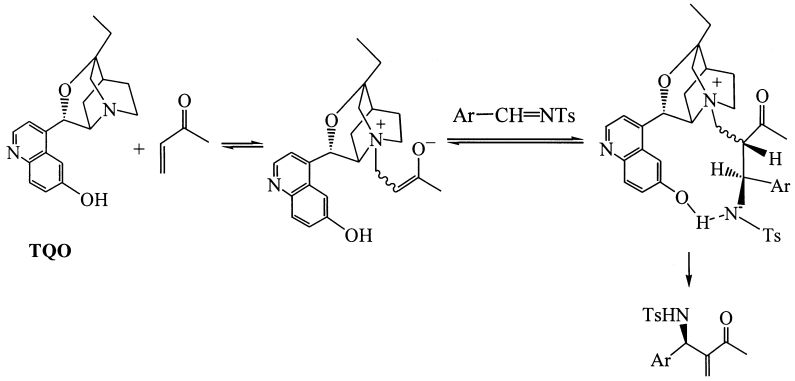
Melting points were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. $^1$H NMR spectra were recorded on a Bruker AM-300 spectrometer. Mass spectra were recorded on an HP-5989 instrument. *N*-Tosylimines were prepared according to literature procedures.[8] All solid compounds reported here gave satisfactory C,H,N microanalyses (Carlo-Erba 1106 analyzer). Commercially obtained reagents were used without further purification. All reactions were monitored by TLC on Huanghai plates coated with $GF_{254}$ silica gel. Flash column chromatography was carried out on 200–300 mesh silica gel under pressure. The optical purities of the Baylis–Hillman adducts were determined by HPLC analysis on a chiral stationary phase (Daicel Co. Chiralcel OD, AS, and OJ; eluent, 95:5 hexane/2-propanol; flow rate, 1.0 mL min$^{-1}$; detection, 254 nm light). The absolute configuration of the major enantiomer of **1e** was determined by X-ray crystallography, and the others were subsequently assigned according to the sign of the specific rotation.

Typical TQO-catalyzed Baylis–Hillman reaction of methyl vinyl ketone (MVK) with *N*-(*p*-ethylbenzenesulfonyl)benzaldimine: MVK (41 μL, 0.5 mmol) was added to a solution of *N*-(*p*-ethylbenzenesulfonyl)benzaldimine (72 mg, 0.25 mmol) and TQO (8.0 mg, 0.025 mmol) in $CH_3CN$/DMF (1:1, 1.0 mL) at −30 °C. The reaction mixture was stirred at −30 °C for 24 h. After the reaction was completed, the solvent was removed under reduced pressure, and the residue purified by flash column chromatography ($SiO_2$, EtOAc/petroleum ether 1:5) to yield **1c** (69 mg, 74 %) as a colorless




**4** **5**

Scheme 3. Baylis–Hillman reaction of aliphatic imines with MVK in the presence of TQO (10 mol %).




**TQO**

Scheme 4. A plausible reaction mechanism for the catalytic asymmetric Baylis–Hillman reaction of imines with MVK.

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solid (96% *ee*). M.p. 114 °C; $[\alpha]_D^{25} = -46.9°$ ($c = 1.00$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 1674\ cm^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$, TMS, 300 MHz): $\delta = 1.23$ (3H, t, $J = 7.6$ Hz, Me), 2.15 (3H, s, Me), 2.39 (3H, s, Me), 2.54 (2H, q, $J = 7.6$ Hz, $CH_2$), 5.20 (1H, d, $J = 6.1$ Hz, NH), 5.51 (1H, d, $J = 8.4$ Hz, CH), 6.09 (2H, s), 6.97 (2H, d, $J = 6.1$ Hz, Ar), 6.98 (2H, $J = 6.1$ Hz, Ar), 7.21 (2H, d, $J = 8.4$ Hz, Ar), 7.63 ppm (2H, d, $J = 8.4$ Hz); MS (EI): *m/z* (%): 358 [$M^+ - 1$] (0.5), 288 [$M^+ - 69$] (5.6), 202 [$M^+ - 155$] (100); Elemental analysis (%) calcd for $C_{20}H_{23}NO_3S$: C 67.20, H 6.49, N 3.92; found: C 67.04, H 6.42, N 3.74.

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[6] CCDC-167239 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk). Crystal data of **1e**: $C_{18}H_{18}ClNO_3S$; $M_r = 363.84$; $T = 293(2)$ K; monoclinic, space group $P2(1)$; $a = 8.513(3)$, $b = 12.076(4)$, $c = 9.767(3)$ Å, $\beta = 112.259(6)°$, $V = 929.3(5)$ Å$^3$; $Z = 2$; $\rho_{calcd} = 1.300\ Mg\,m^{-3}$; $F_{000} = 380$; final $R$ indices [$I > 2\sigma(I)$]: $R_1 = 0.0475$l, $R_2 = 0.0833$.

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# [(salen)Al]-Mediated, Controlled and Stereoselective Ring-Opening Polymerization of Lactide in Solution and without Solvent: Synthesis of Highly Isotactic Polylactide Stereocopolymers from Racemic D,L-Lactide

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Polylactides (PLAs) are among the most important synthetic biodegradable polymers investigated for biomedical and pharmaceutical applications such as controlled drug delivery, resorbable sutures, medical implants, and scaffolds for tissue engineering.[1] On the basis of annually renewable resources such as corn and sugar beets, PLAs are also promising degradable substitutes for petrochemical-based polyolefins.[2] The physical, mechanical, and degradation properties of PLAs are intimately dependent on the chain stereochemistry. For instance, isotactic poly(L-LA) (LA = lactide), a highly crystalline material with a $T_m \approx 170\,°C$, has excellent mechanical properties and degrades rather slowly, whereas atactic poly(D,L-LA) is amorphous and subject to a relatively fast degradation. Stereocontrol, therefore, is crucial in the synthesis of polylactides. Most catalysts, including stannous octoate, zinc lactate, and aluminum alkoxides, do not bias towards different enantiomers in the ring-opening polymerization of D,L-lactide, thereby furnishing PLAs with randomly distributed stereocenters.[3] Recently it was reported that a few single-site lactide-polymerization catalysts did show stereoselectivity. For example, [(bdi)ZnO*i*Pr] (bdi = β-diiminate) polymerized D,L-LA in such a way as to afford a heterotactic PLA, and chiral tris(pyrazolyl)borate magnesium complexes preferentially polymerized *meso*-LA in the presence of a mixture of *meso*-LA and D,L-LA (diastereoselectivity).[4]

It has long been a challenge to prepare PLAs with long isotactic sequences out of D,L-LA through isospecific polymerization (Scheme 1), since these stereoblock copolylactides are expected to be hard and strong as highly crystalline poly(L-LA)s but with varying degrees of crystallinity and degradation rates, depending on the average length of the isotactic blocks. So far, examples of isospecific lactide polymerization are limited to Schiff base aluminum alkoxide catalysts in $CH_2Cl_2$ or in toluene,[5] in which the binaphthyl Schiff base ligands impose the best stereochemical as well as molecular-weight control. However, the synthesis of the binaphthyl Schiff base ligand is time-consuming. Besides, solution polymerization with these catalysts is not a practically viable process. The following requirements must be satisfied for a catalyst to be industrially attractive:

1) The starting organic ligands should be commercially available and inexpensive.

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