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# Asymmetric Baylis–Hillman Reactions Promoted by Chiral Imidazolines

**Junye Xu, Yanyi Guan, Shihui Yang, Yurui Ng, Guangrong Peh, and Choon-Hong Tan*[a]**

**Abstract:** The coupling of electrophiles with activated alkenes by using tertiary amines or phosphines is generally known as the Baylis–Hillman reaction. It is a useful and atom-economical carbon–carbon bond-forming reaction that generates multifunctionalized products. This reaction is notoriously slow; yields are often low and substrate-dependent. The asymmetric reaction is still limited especially for unactivated olefins such as acrylates. Imidazolines have been developed as ligands in metal-catalyzed reactions and have also been used as privileged structures in diversity-oriented synthesis. A series of novel chiral imidazolines were prepared and used to develop asymmetric Baylis–Hillman reactions. These imidazolines promote the reactions of various aromatic aldehydes with unactivated acrylates. Enantiomeric excesses of up to 60% and high yields were obtained by using stoichiometric amounts of the promoter. Furthermore, the imidazolines are also suitable promoters for the reactions between aromatic aldehydes and alkyl vinyl ketones. Enantiomeric excesses of up to 78% and high yields were obtained with 50 mol% of an imidazoline with a chiral methylnaphthyl group. These chiral imidazolines are easily prepared from commercially available amino alcohols and can be easily recovered for reuse without loss of product enantioselectivity.

**Keywords:** asymmetric synthesis · Baylis–Hillman reaction · enantioselectivity · imidazoline · organocatalysis

## Introduction

The coupling of electrophiles with activated alkenes by using tertiary amines or phosphines is generally known as the Baylis–Hillman reaction.[1] It is a useful and atom-economical carbon–carbon bond-forming reaction that generates multifunctionalized products such as α-methylene-β-hydroxycarbonyl compounds. This reaction is notoriously slow; yields are often low and substrate-dependent. The development of a methodology that is applicable to a range of substrates is, therefore, much desired.

Many versions of the Baylis–Hillman reaction have been developed, but asymmetric examples are still limited; they have thus received considerable attention in the past few years.[2] An early attempt utilized a chiral pyrrolizidine,[3] and subsequently, a quinidine derivative, β-isocupreidine,[4] was found to be a successful catalyst for several Baylis–Hillman reactions, including that between 1,1,1,3,3,3-hexafluoroisopropyl acrylate and aldehydes or imines. Chiral phosphines,[5] Lewis acids,[6] bisthioureas,[7] and proline–peptide cocatalysts[8] were also observed to be good catalysts for asymmetric Baylis–Hillman reactions.

Recent developments include the use of 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (binol) derivatives as Brønsted acid catalysts,[9] as well as binol–amine[10a] and amine–thiourea[10b] compounds as bifunctional catalysts. Furthermore, several asymmetric intramolecular Baylis–Hillman reactions were also reported.[11] Alternative approaches to obtaining enantiomerically pure adducts include the use of chiral auxiliaries[12] and chiral ionic liquids.[13]

The commonly accepted mechanism of this reaction involves the conjugate addition of a nucleophile to generate an enolate, the attack of the enolate onto the aldehyde, and subsequent elimination to generate the product. However, the effect of the solvent, the rate-determining step, the effect of the p$K_a$ of the nucleophiles, and the role of hydrogen bonding are still under intense investigation for their implication in asymmetric Baylis–Hillman reactions.[14] Based on the accepted mechanism, several new extensions of the Baylis–Hillman reaction have been developed.[15]

Chiral imidazolidinones were developed by MacMillan and co-workers as highly enantioselective catalysts for a

[a] J. Xu, Y. Guan, S. Yang, Y. Ng, G. Peh, Prof. Dr. C.-H. Tan
Department of Chemistry
National University of Singapore
3, Science Drive, Singapore 117543 (Singapore)
Fax: (+65) 6779-1691
E-mail: chmtanch@nus.edu.sg

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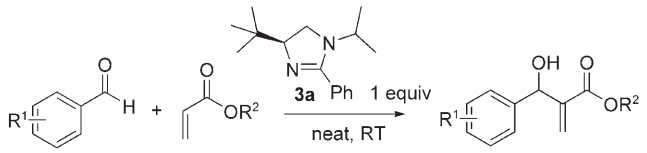
number of reactions, which include Diels–Alder, 1,3-dipolar cycloaddition, and Friedel–Crafts reactions.[16] Jørgensen reported a novel imidazoline catalyst that contains a carboxylic acid. This catalyst was shown to be effective for highly enantioselective Michael reactions.[17] Inspired by these examples, we turned our attention to another class of chiral imidazolines, the 1,2-disubstituted-4,5-dihydro-1*H*-imidazoles. These imidazolines were developed as possible ligands for enantioselective metal-catalyzed reactions.[18] Their similarities to oxazolines and the potential to tune their electronic properties with various 2-substituents make them appealing. The 4,5-dihydro-1*H*-imidazole is also a privileged structure in which many derivatives exhibit a wide variety of biological activities.[19] Diversity-orientated synthesis with 4,5-dihydro-1*H*-imidazole as a scaffold has also been attempted.[20] Recently, an anionic sulfonated analogue of 4,5-dihydro-1*H*-imidazole was found to act as a nucleophilic catalyst in a [2+2] cycloaddition between a ketene and imine.[21] Herein, we report the development of an asymmetric Baylis–Hillman reaction promoted by chiral imidazolines.

## Results and Discussion

### Reaction between Various Aldehydes and Acrylates Promoted by Chiral Imidazolines

The simple chiral imidazoline **3a** was easily prepared from the corresponding β-amino alcohol in good yield.[19] The reaction between 4-nitrobenzaldehyde and methyl acrylate was catalyzed, albeit slowly, by 10 mol% of **3a** (Table 1). The product **4a** was obtained in 21% yield with 51% enantiomeric excess after 14 days when no solvent was used. When a series of solvents such as THF, $CH_3CN$, dimethyl sulfoxide (DMSO), MeOH, and $CH_2Cl_2$ were tested, it was found that these conditions were inferior in terms of both the yield and enantiomeric excess with respect to neat conditions. However, when toluene was used, there was a slight improvement in enantioselectivity, although the reaction rate decreased. Neither microwaves nor high pressure improved the enantioselectivity or conversion of this reaction. The use of hydrogen-bonding donors as additives, such as thioureas and phenols, or changes to the temperature of the reaction, both increasing and decreasing, also did not improve the reaction. As far as we know, few examples of the asymmetric Baylis–Hillman reaction between aldehydes and unactivated acrylates have been reported,[5a,e,6] and this reaction is recognized as one of the slowest owing to its combination of substrates.

Table 1. Reaction of various aldehydes and acrylates in the presence of imidazoline **3a**.




1 2 4

| Entry | $R^1$ | $R^2$ | Product | *t* [days] | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|---|---|
| 1 | 4-$NO_2$ | Me | **4a** | 10 | 90 | 50 |
| 2[c] | 4-$NO_2$ | Me | **4a** | 12 | 89 | 54 |
| 3[d] | 4-$NO_2$ | *n*Bu | **4b** | 14 | 50 | 41 |
| 4 | 4-$NO_2$ | Bn | **4c** | 5 | 89 | 48 |
| 5 | 3-$NO_2$ | Bn | **4d** | 4 | 73 | 47 |
| 6 | 2-$NO_2$ | Bn | **4e** | 4 | 72 | 14 |
| 7 | 4-CN | Bn | **4f** | 4 | 63 | 48 |
| 8 | 2-Cl-5-$NO_2$ | Bn | **4g** | 4 | 82 | 31 |

[a] Yield of isolated product. [b] Chiral HPLC analysis, **4a** determined to be *R*.[4a] [c] Recovered **3a**. [d] Incomplete reaction. Bn = benzyl.

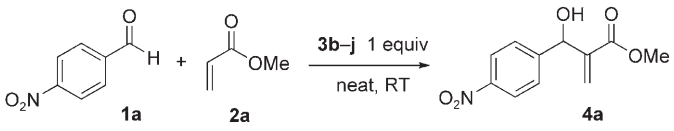
To make the reaction useful, one equivalent of **3a** was used, which increased the yield of the reaction dramatically to 90% (yield of isolated product, 100% conversion). The enantiomeric excess was also maintained at a satisfactory level (Table 1, entry 1). The use of a stoichiometric amount of the imidazoline did not disadvantage the reaction as it can be easily recovered through a simple acid–base workup for reuse without loss of activity (Table 1, entry 2). However, the reaction still required a long time for completion. Subsequently, we surveyed various aldehydes and acrylates with one equivalent of **3a** under neat conditions. We examined *tert*-butyl acrylate, *n*-butyl acrylate (Table 1, entry 3), and benzyl acrylate (Table 1, entry 4), all of which gave similar levels of enantioselectivity to methyl acrylate. Both *tert*-butyl acrylate and *n*-butyl acrylate produced much slower reactions, whereas benzyl acrylate allowed the reaction to complete in half the time. With benzyl acrylate, it was found that the promoter worked well with electron-deficient aromatic aldehydes (Table 1, entries 5–8). In general, *para* and *meta* substituents led to a slightly better enantioselectivity compared to *ortho* substituents. Alkyl and aromatic aldehydes with electron-donating substituents suffered from a low rate of reaction.

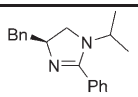
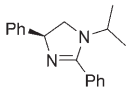
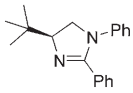
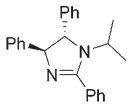
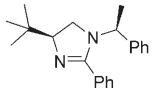
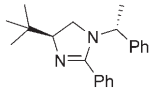
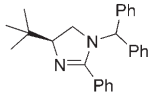
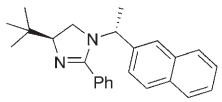
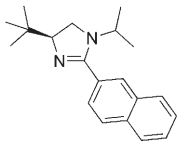
### Reaction between 4-Nitrobenzaldehyde and Methyl Acrylate Promoted by Various Chiral Imidazolines

To investigate and understand how various substituents contribute to the asymmetric induction, we tested various chiral imidazolines (Table 2). Modifications at the C4 position from *tert*-butyl (**3a**; Table 1, entry 1) to benzyl (**3b**; Table 2, entry 1) and phenyl (**3c**; Table 2, entry 2) decreased the enantioselectivity, thus showing that a bulky substituent is necessary for a high level of enantioselectivity. Next, we found that **3e**, with a *trans*-diphenyl configuration at C4 and C5, turned out to be a slightly better promoter than **3c**. The effects of various substitutions at N1 were studied through a collection of chiral imidazolines. An aliphatic group at the N1 position was found to be crucial as the presence of a phenyl group (Table 2, entry 3) resulted in an ineffective promotor. The usefulness of an isopropyl substitution at N1 (Table 2, entry 4) led us to install the chiral methylbenzyl groups (Table 2, entries 5 and 6) and the methylenediphenyl group (Table 2, entry 7). The improvements in enantioselectivity produced by these changes were marginal. These results show that the configuration of the chiral center of the

Table 2. Reaction of 4-nitrobenzaldehyde and methyl acrylate in the presence of imidazolines **3b–j**.




| Entry | Promoter | | *t* [days] | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|---|
| 1[c] |  | **3b** | 9 | 38 | 11 |
| 2 |  | **3c** | 4 | 100 | 16 |
| 3 |  | **3d** | 14 | no reaction | – |
| 4 |  | **3e** | 14 | 88 | 28 |
| 5 |  | **3f** | 11 | 90 | 59 |
| 6 |  | **3g** | 18 | 69 | 55 |
| 7 |  | **3h** | 17 | 68 | 58 |
| 8 |  | **3i** | 11 | 84 | 60 |
| 9[c] |  | **3j** | 5 | 38 | 53 |

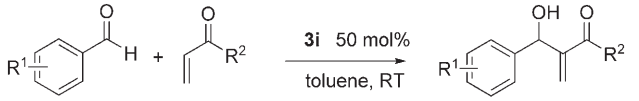
[a] Yield of isolated product. [b] Chiral HPLC analysis. [c] Incomplete reaction.

methylbenzyl group (Table 2, entries 5 and 6) does not influence the effectiveness of the imidazolines. However, we observed that by increasing the size of the N1 substituent, the rate of reaction was decreased. The use of the chiral methylnaphthyl group (Table 2, entry 8) gave the best result: 84% yield and 60% *ee*. Imidazoline **3i** was then used to repeat some of the experiments in Table 1 (entries 5–8). In general, the enantioselectivity increased moderately by around 10%, but the reaction time doubled. Finally, we modified the aryl group at C2 to a bulkier naphthyl group (Table 2, entry 9), but no improvement was observed. The introduction of both *para*- and *ortho*-phenols at the C2 position, in an attempt to provide possible activation of the aldehyde through hydrogen bonding, proved futile. We speculated that the protonation of the N3 amine group[22] by the phenols prevented the initial addition to the acrylate.

## Reaction between Various Aldehydes and Alkyl Vinyl Ketones Promoted by Chiral Imidazolines

The imidazolines were also suitable promoters for the reaction between aldehydes and alkyl vinyl ketones. This reaction proceeded at a much higher rate, and toluene was the most-suitable solvent for the reaction. Preliminary studies showed that **3i** gave the most-promising results and, thus, was used as the promoter in the subsequent survey. With 50 mol% of **3i**, the reaction between methyl vinyl ketone and 4-nitrobenzaldehyde was completed in 3 days (Table 3, entry 1). Similarly, the reaction with 3-nitrobenzaldehyde was completed in 3 days in 96% yield and 65% *ee* (Table 3, entry 2). The promoter **3i** was recovered and reused for the same experiment (Table 3, entry 3; second cycle). This process was repeated once more (Table 3, entry 4; third cycle), and it was found that the enantioselectivity of the product remained unchanged. However, the yields were slightly affected. In both cycles, >95% of the promotor was recovered. 4-Cyanobenzaldehyde (Table 3, entry 5) and 4-(trifluoromethyl) benzaldehyde (Table 3, entry 6) were also attempted and gave moderate yields and *ee*. The reactions between ethyl vinyl ketone and aldehydes were also examined; they were slightly slower than the corresponding reactions of methyl vinyl ketone. However, high enantioselectivity (77% *ee*) and yields of up to 89% were allowed when the experiments were conducted at −20°C (Table 3, entries 7 and 8). We speculated that bulky alkyl vinyl ketones may improve the enantioselectivity further. Thus, we prepared cyclohexyl vinyl ketone, which was not previously explored for the Baylis–Hillman reaction. They gave moderate to good *ee* and yields with several aldehydes, including 3-nitrobenzaldehyde, 4-nitrobenzaldehyde, and 4-cyanobenzaldehyde (Table 3, entries 9–11).

Table 3. Reaction of aldehydes with vinyl ketones in the presence of 50 mol% of imidazoline **3i**.




| Entry | $R^1$ | $R^2$ | Product | *t* [days] | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|---|---|
| 1 | 4-$NO_2$ | Me | **6a** | 3 | 75 | 59 |
| 2 | 3-$NO_2$ | Me | **6b** | 3 | 96 | 65 |
| 3[c] | 3-$NO_2$ | Me | **6b** | 3 | 71 | 65 |
| 4[d] | 3-$NO_2$ | Me | **6b** | 4 | 79 | 68 |
| 5[e] | 4-CN | Me | **6c** | 4 | 59 | 54 |
| 6[e] | 4-$CF_3$ | Me | **6d** | 4 | 71 | 47 |
| 7[f] | 4-$NO_2$ | Et | **6e** | 13 | 89 | 77 |
| 8[f] | 3-$NO_2$ | Et | **6f** | 13 | 60 | 75 |
| 9 | 4-$NO_2$ | Cy | **6g** | 8 | 69 | 78 |
| 10 | 3-$NO_2$ | Cy | **6h** | 9 | 63 | 68 |
| 11 | 4-CN | Cy | **6i** | 10 | 75 | 69 |

[a] Yield of isolated product. [b] Chiral HPLC analysis, **6a** determined to be *R*[4d]. [c] Recovered **3i**, second cycle. [d] Recovered **3i**, third cycle. [e] Incomplete reaction. [f] Reaction at −20°C. Cy = cyclohexyl.

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## Conclusions

We have developed a new asymmetric Baylis–Hillman reaction based on a series of chiral imidazolines, which promote the reaction between aromatic aldehydes and unactivated acrylates. Few examples[5a,e,6] of this combination of substrates have been reported so far. The reaction between aromatic aldehydes and alkyl vinyl ketones also gave good yields and enantioselectivities. Useful Baylis–Hillman reactions can therefore be developed as the imidazoline can be easily recycled. We are currently using the benzyl imidazoline hexafluorophosphate salt[22] as a model to improve the rate as well as the enantioselectivity of this reaction.

## Experimental Section

*General*

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker ACF300 (300 MHz), DPX300 (300 MHz), or AMX500 (500 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm). The residual solvent peak was used as an internal reference. Low-resolution (LR) mass spectra were obtained on a VG Micromass 7035 spectrometer in EI mode, a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL-T mass spectrometer in FAB mode. All high-resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. Infrared spectra were recorded on a BIO-RAD FTS 165 FTIR spectrometer. Enantiomeric excess was measured by chiral HPLC analysis on a set of Jasco HPLC units, which included a Jasco DG-980-50 degasser, an LG-980-02 ternary gradient unit, a PU-980 Intelligient HPLC pump, UV-975 Intelligient UV/Vis detectors, and an AS-950 Intelligient sampler. Optical rotations were recorded on a Jasco DIP-1000 polarimeter. Melting points were determined on a BÜCHI B-540 melting-point apparatus. Analytical thin-layer chromatography (TLC) was performed with Merck precoated TLC plates, silica gel 60F-254, layer thickness 0.25 mm. Flash chromatography separations were performed on Merck 60-mesh (0.040–0.063 mm) silica gel. Toluene was distilled from sodium/benzophenone and stored under $N_2$ atomosphere. THF was freshly distilled from sodium/benzophenone before use. All other reagents and solvents were of commercial grade and were used as supplied without further purification, unless otherwise stated.

*Syntheses*

General procedure for synthesis of **3a–j**: All chiral imidazolines (**3a–j**) were synthesized with minor modifications of a reported protocol.[19] For characterization of **3g–h**, **3j**, and **4g** and references for the reported compounds **3d**, **4a–c**, **4g**, **6a–b**, and **6d–f**, see the Supporting Information.

**3a**: Pale-yellow oil. $R_f$=0.50 ($CH_2Cl_2$/MeOH=10:1); $[\alpha]_D^{25}=-37.5$ ($c$=6.22 in $CHCl_3$); IR (film): $\tilde{\nu}$=2954, 2868, 1596, 1497 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$, 300 K): $\delta$=7.32–7.41 (m, 5H, arom CH), 3.78 (dd, $^3J_{H,H}$=11.1, 9.2 Hz, 1H, CH), 3.69 (sept, $^3J_{H,H}$=6.5 Hz, 1H, CH), 3.33 (dd, $^3J_{H,H}$=11.1, 9.7 Hz, 1H, CH), 3.16 (dd, $^3J_{H,H}$=9.7, 9.2 Hz, 1H, CH), 1.07 (d, $^3J_{H,H}$=6.5 Hz, 3H, $CH_3$), 0.93 (s, 9H, *t*Bu), 0.92 ppm (d, $^3J_{H,H}$=6.5 Hz, 3H, $CH_3$); $^{13}$C NMR (500 MHz, $CDCl_3$, 300 K): $\delta$=165.4 (N=C–N), 132.4 (arom C), 129.1 (arom CH), 128.2 (arom CH), 128.1 (2C, arom CH), 128.0 (arom CH), 73.3 (CH), 46.5 ($CH(CH_3)_2$), 43.8 ($CH_2$), 34.3 (C*t*Bu), 25.9 (*t*Bu), 20.7 ($CH_3$), 19.1 ppm ($CH_3$); LRMS (FAB): $m/z$=245.1 $[M+H]^+$; HRMS (FAB): $m/z$ calcd for $[C_{16}H_{24}N_2+H]^+$: 245.2018; found: 245.2014.

**3b**: Yellow oil. $R_f$=0.65 ($CH_2Cl_2$/MeOH=4:1); $[\alpha]_D^{25}=+4.7$ ($c$=0.23 in $CHCl_3$); IR (film): $\tilde{\nu}$=1613, 1591 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$, 300 K): $\delta$=7.14–7.32 (m, 10H, arom CH), 4.32–4.39 (m, 1H, CH), 3.63 (sept, $^3J_{H,H}$=6.9 Hz, 1H, CH), 3.36 (t, $^3J_{H,H}$=9.9 Hz, 1H, CH), 3.05–3.13 (m, 2H, $CH_2$), 2.75 (dd, $^3J_{H,H}$=13.4, 8.3 Hz, 1H, CH), 0.94 (d, $^3J_{H,H}$=6.9 Hz, 3H, $CH_3$), 0.78 ppm (d, $^3J_{H,H}$=6.9 Hz, 3H, $CH_3$); $^{13}$C NMR (500 MHz, $CDCl_3$, 300 K): $\delta$=165.5 (N=C–N), 137.2 (arom C), 130.7 (arom CH), 129.9 (arom CH), 128.6 (arom CH), 128.3 (arom CH), 128.1 (arom CH), 126.4 (arom CH), 61.5 (CH), 46.8 ($CH_2$), 41.3 ($CH_2$), 25.3 (CH), 20.2 ($CH_3$), 19.6 ppm ($CH_3$); LRMS (FAB): $m/z$=279.1 $[M+H]^+$; HRMS (FAB): $m/z$ calcd for $[C_{19}H_{22}N_2+H]^+$: 279.1861; found: 279.1866.

**3c**: Colorless oil. $R_f$=0.45 (hexane/ethyl acetate=1:1); $[\alpha]_D^{25}=-37.8$ ($c$=0.66 in $CHCl_3$); IR (film): $\tilde{\nu}$=2975, 2934, 1644, 1621 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=7.25–7.26 (m, 10H, arom CH), 5.18 (dd, $^3J_{H,H}$=11.2, 8.8 Hz, 1H, CH), 3.84–3.94 (m, 2H, $CH_2$), 3.34 (t, $^3J_{H,H}$=9.2 Hz, 1H, CH), 1.13 (d, $^3J_{H,H}$=6.6 Hz, 3H, $CH_3$), 1.01 ppm (d, $^3J_{H,H}$=6.6 Hz, 3H, $CH_3$); $^{13}$C NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=166.8 (N=C–N), 144.8 ( arom C), 131.6 (arom CH), 129.7 (arom CH), 128.5 (arom CH), 128.4 (arom CH), 128.2 (arom CH), 126.9 (arom CH), 126.6 (arom CH), 66.9 (CH), 51.2 (CH), 46.8 ($CH_2$), 20.6 ($CH_3$), 19.6 ppm ($CH_3$); LRMS (FAB): $m/z$=279.1 $[M+H]^+$; HRMS (FAB): $m/z$ calcd for $[C_{18}H_{20}N_2+H]^+$: 265.1705; found: 265.1700.

**3e**: Pale-yellow oil. $R_f$=0.45 (hexane/ethyl acetate=1:1); $[\alpha]_D^{25}=+1.1$ ($c$=0.10 in $CHCl_3$); IR (film): $\tilde{\nu}$=3020, 2934, 2401, 2097, 1615, 1216 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=7.80–7.83 (m, 2H, arom CH), 7.25–7.51 (m, 13H, arom CH), 4.92 (d, $^3J_{H,H}$=6.8 Hz, 1H, CHPh), 4.51 (d, $^3J_{H,H}$=6.8 Hz, 1H, CHPh), 4.01 (sept, $^3J_{H,H}$=6.8 Hz, 1H, $CH(CH_3)_2$), 0.95 (d, $^3J_{H,H}$=6.8 Hz, 3H, $CH_3$), 0.82 ppm (d, $^3J_{H,H}$=6.8 Hz, 3H, $CH_3$); $^{13}$C NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=167.5 (N=C–N), 145.1 (arom C), 143.9 (arom C), 130.7 (arom CH), 128.9 (arom CH), 128.7 (arom CH), 128.6 (arom CH), 127.6 (arom CH), 127.3 (arom CH), 126.3 (arom CH), 69.1 (CH), 48.4 (CH), 22.6 ($CH_3$), 19.6 ppm ($CH_3$); LRMS (FAB): $m/z$=341.2 $[M+H]^+$; HRMS (FAB): $m/z$ calcd for $[C_{24}H_{24}N_2+H]^+$: 341.2018; found: 341.2026. The stereochemistry of **3e** was determined based on reference [19].

**3f**: Pale-yellow oil; $R_f$=0.40 ($CH_2Cl_2$/MeOH=10:1); $[\alpha]_D^{25}=-4.7$ ($c$=18.20 in $CHCl_3$); IR (film): $\tilde{\nu}$=2959, 2869, 1593, 1495 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=7.56–7.59 (m, 2H, arom CH), 7.42–7.45 (m, 3H, arom CH), 7.23–7.31 (m, 3H, arom CH), 7.10–7.13 (m, 2H, arom CH), 4.87 (q, $^3J_{H,H}$=7.0 Hz, 1H, CH), 3.81 (dd, $^3J_{H,H}$=11.5, 9.4 Hz, 1H, CH), 3.37 (dd, $^3J_{H,H}$=11.5, 9.4 Hz, 1H, CH), 2.85 (t, $^3J_{H,H}$=9.4 Hz, 1H, CH), 1.54 (d, $^3J_{H,H}$=7.0 Hz, 3H, $CH_3$), 0.75 ppm (s, 9H, *t*Bu); $^{13}$C NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=165.2 (N=C–N), 140.3 (arom C), 132.3 (arom C), 129.6 (arom CH), 128.5 (arom CH), 128.3 (arom CH), 128.2 (arom CH), 127.4 (arom CH), 127.2 (arom CH), 127.0 (arom CH), 125.7 (arom C), 73.6 (CH), 53.3 (CH), 44.6 ($CH_2$), 34.2 (C*t*Bu), 25.9 (*t*Bu), 17.3 ppm ($CH_3$); LRMS (FAB): $m/z$=307.2 $[M+H]^+$; HRMS (FAB): $m/z$ calcd for $[C_{21}H_{26}N_2+H]^+$: 307.2174; found: 307.2174.

**3i**: White solid. M.p.: 112.7–112.9 °C; $R_f$=0.65 ($CH_2Cl_2$/MeOH=4:1); $[\alpha]_D^{25}=+7.9$ ($c$=4.28 in $CHCl_3$); IR (film): $\tilde{\nu}$=2954, 2869, 1615, 1594, 1409 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=7.43–7.85 (m, 12H, arom CH), 4.99 (q, $^3J_{H,H}$=7.0 Hz, 1H, CH), 3.80 (m, 1H, CH), 3.23 (t, $^3J_{H,H}$=9.6 Hz, 1H, CH), 3.09 (t, $^3J_{H,H}$=10.5 Hz, 1H, CH), 1.54 (d, $^3J_{H,H}$=7.0 Hz, 3H, $CH_3$), 0.97 ppm (s, 9H, *t*Bu); $^{13}$C NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=165.3 (N=C–N), 139.0 (arom C), 133.2 (arom C), 132.5 (arom C), 132.3 (arom C), 129.5 (arom CH), 128.5 (arom CH), 128.2 (2C, arom CH), 127.9 (arom CH), 127.5 (arom CH), 126.2 (arom CH), 125.9 (arom CH), 125.5 (arom CH), 124.9 (arom CH), 73.7 (CH), 53.3 (CH), 44.9 ($CH_2$), 34.4 (C*t*Bu), 26.0 (*t*Bu), 16.2 ppm ($CH_3$); LRMS (FAB): $m/z$=357.3 $[M+H]^+$; HRMS (FAB): $m/z$ calcd for $[C_{26}H_{28}N_2+H]^+$: 357.2321; found: 357.2324.

Typical experimental procedure for Baylis–Hillman reaction between aldehydes and acrylates promoted by chiral imidazolines: Promoter **3a** (24.4 mg, 0.10 mmol, 1 equiv) was added to an oven-dried vial. This was followed by **1a** (15.1 mg, 0.10 mmol) and **2a** (0.10 mL). The reaction mixture was stirred at room temperature and monitored by TLC. Upon completion or after the indicated reaction time, the reaction was quenched by adding HCl solution (2 M, 1.0 mL), and the product was extracted with ethyl acetate (2.0 mL). NaOH (2 M, 1.0 mL) was added to aqueous layer, which was then extracted with $CH_2Cl_2$ (2×2.0 mL) to recover **3a**. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate as eluent

  

to give the desired product. The enantiomeric excess was determined by HPLC analysis with a chiral column.

**4d**: 47% *ee*, colorless oil. $R_f$=0.15 (hexane/ethyl acetate=4:1); IR (film): $\tilde{\nu}$=3498, 3020, 1712, 1531, 1351, 1216 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=8.22 (s, 1H, arom CH), 8.11 (dd, $^3J_{H,H}$=8.4, 1.1 Hz, 1H, arom CH), 7.70 (d, $^3J_{H,H}$=7.7 Hz, 1H, arom CH), 7.48 (t, $^3J_{H,H}$=8.0 Hz, 1H, arom CH), 7.24–7.34 (m, 5H, arom CH), 6.46 (s, 1H, =CH), 5.95 (s, 1H, =CH), 5.64 (s, 1H, CH), 5.14 (s, 2H, $CH_2$), 3.05 ppm (br s, 1H, OH); $^{13}C$ NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=165.6 (C=O), 148.2 (arom C), 143.5 (arom CH), 141.0 (C=$CH_2$), 135.0 (arom C), 132.7 (arom CH), 129.3 (arom CH), 128.5 arom CH), 128.4 (arom CH), 128.1 (arom CH), 127.4 (arom CH), 122.7 (arom CH), 121.5 (arom CH), 72.3 (CHOH), 66.9 ppm ($CH_2$); LRMS (ESI): $m/z$=348.5 $[M+Cl]^-$; HRMS (ESI): $m/z$ calcd for $[C_{17}H_{15}NO_5+Cl]^-$: 348.0639; found: 348.0640; HPLC (Chiralcel OD-H column (Diacel)): hexane/2-propanol=95:5, flow rate=1.0 mL $min^{-1}$, $\lambda$=254 nm, $t_R$=22.9 (major), 33.7 min (minor).

**4e**: 14% *ee*, pale-yellow oil. $R_f$=0.15 (hexane/ethyl acetate=4:1); IR (film): $\tilde{\nu}$=3469, 3020, 1718, 1527, 1350, 1217 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=7.9 (dd, $^3J_{H,H}$=8.4, 1.1 Hz, 1H, arom CH), 7.72 (dd, $^3J_{H,H}$=7.7, 1.1 Hz, 1H, arom CH), 7.57–7.63 (dt, $^3J_{H,H}$=7.7, 1.1 Hz, 1H, arom CH), 7.41–7.47 (m, 1H, arom CH) 7.22–7.34 (m, 5H, arom CH), 6.43 (s, 1H, =CH), 6.21 (s, 1H, =CH), 5.78 (s, 1H, CH), 5.15 (dd, $^3J_{H,H}$=22.0, 12.2 Hz, $CH_2$), 3.24 ppm (br s, 1H, OH); $^{13}C$ NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=165.6 (C=O), 148.2 (arom C), 140.6 (C=$CH_2$), 136.1 (arom C), 135.3 (arom C), 133.4 (arom CH), 128.8 (arom CH), 128.6 (arom CH), 128.5 (arom CH), 128.2 (arom CH), 128.0 (arom CH), 126.8 (arom CH), 124.6 (arom CH), 67.6 (CHOH), 66.8 ppm ($CH_2$); LRMS (ESI): $m/z$=336.1 $[M+Na]^+$; HRMS (ESI): $m/z$ calcd for $[C_{17}H_{15}NO_5+Na]^+$: 336.0848; found: 336.0855: HPLC (Chiralcel OD-H column (Diacel)): hexane/2-propanol=95:5, flow rate=1.0 mL $min^{-1}$, $\lambda$=254 nm, $t_R$=23.4 (minor), 29.9 min (major).

**4f**: 48% *ee*, colorless oil. $R_f$=0.12 (hexane/ethyl acetate=4:1); IR (film): $\tilde{\nu}$=3473, 3020, 2231, 1716, 1630, 1500, 1456, 1317 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=7.58 (d, $^3J_{H,H}$=8.4 Hz, 2H, arom CH), 7.47 (d, $^3J_{H,H}$=8.4 Hz, 2H, arom CH), 7.23–7.35 (m, 5H, arom CH), 6.43 (s, 1H, =CH), 5.91 (s, 1H, =CH), 5.58 (s, 1H, CH), 5.14 (s, 2H, $CH_2$), 3.15 ppm (br s, 1H, OH); $^{13}C$ NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=165.6 (C=O), 146.6 (arom C), 141.1 (C=$CH_2$), 135.1 (arom C), 132.1 (arom CH), 128.5 (arom CH), 128.4 (arom CH), 128.1 (arom CH), 127.2 (arom CH), 127.1(arom CH), 118.6 (CN), 111.3 (arom C–CN), 72.5 (CHOH), 66.8 ppm ($CH_2$); LRMS (ESI): $m/z$=328.5 $[M+Cl]^-$; HRMS (ESI): $m/z$ calcd for $[C_{18}H_{15}NO_3+Cl]^-$: 328.0740; found: 328.0741; HPLC (Chiralcel OD-H column (Diacel)): hexane/2-propanol=95:5, flow rate=1.0 mL $min^{-1}$, $\lambda$=254 nm, $t_R$=28.5 (major), 36.6 min (minor).

Typical experimental procedure for Baylis–Hillman reaction between aldehydes and alkyl vinyl ketones promoted by chiral imidazolines: Methyl vinyl ketone (30.0 μL, 0.36 mmol, 16 equiv) was added to a solution of 4-nitrobenzaldehyde (3.3 mg, 0.02 mmol) and **3i** (4.0 mg, 0.01 mmol, 50 mol%) in toluene (0.1 mL) at the indicated temperature. Upon completion or after the indicated reaction time, the reaction mixture was purified directly by column chromatography with hexane/ethyl acetate as eluent to yield the product (3.6 mg, 75% yield) and the recovered catalyst.

**6c**: 54% *ee*, colorless oil. $R_f$=0.30 (hexane/ethyl acetate=2:1); IR (film): $\tilde{\nu}$=3466, 3020, 2230, 1674, 1217 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=7.63 (d, $^3J_{H,H}$=8.4 Hz, 2H, arom CH), 7.49 (d, $^3J_{H,H}$=8.4 Hz, 2H, arom CH), 6.25 (s, 1H, =CH), 6.01 (s, 1H, =CH), 5.62 (s, 1H, CHOH), 2.34 ppm (s, 3H, $CH_3$); $^{13}C$ NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=200.0 (C=O), 149.1 (C=$CH_2$), 147.0 (arom C), 132.1 (arom CH), 127.4 (arom CH), 127.1 (arom CH), 118.7 (CN), 111.3 (arom C), 72.1 (CHOH), 26.3 ppm ($CH_3$); LRMS (FAB): $m/z$=202.1 $[M+H]^+$; HRMS (FAB): $m/z$ calcd for $[C_{12}H_{11}NO_2+H]^+$: 202.0868; found: 202.0866; HPLC (Chiralcel AS-H column (Diacel)): hexane/2-propanol=90:10, flow rate=0.75 mL $min^{-1}$, $\lambda$=254 nm, $t_R$=33.4 (major), 40.5 min (minor).

**6g**: 78% *ee*, colorless oil. $R_f$=0.50 (hexane/ethyl acetate=2:1); IR (film): $\tilde{\nu}$=3445, 3021, 2936, 1665, 1523, 1349, 1216 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=8.18 (d, $^3J_{H,H}$=8.7 Hz, 2H, arom CH), 7.53 (d, $^3J_{H,H}$=8.7 Hz, 2H, arom CH), 6.22 (s, 1H, =CH), 5.99 (s, 1H, =CH), 5.62 (d, $^3J_{H,H}$=5.8 Hz, 1H, CH), 3.49 (d, $^3J_{H,H}$=5.8 Hz, 1H, OH), 2.93–2.99 (m, 1H, CHCy), 1.60–1.75 (m, 5H, Cy), 1.13–1.31 ppm (m, 5H, Cy); $^{13}C$ NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=206.2 (C=O), 149.1 (arom C), 147.5 (C=$CH_2$), 128.4 (arom C), 127.1 (arom CH), 125.8 (arom C), 123.5 (arom C), 73.2 (CHOH), 45.5 (CHCy), 29.2 (Cy), 29.1 (Cy), 25.7 (Cy), 25.6 (Cy), 25.5 ppm (Cy); LRMS (ESI): $m/z$=288.5 $[M-H]^-$; HRMS (ESI): $m/z$ calcd for $[C_{16}H_{19}NO_4-H]^-$: 288.1236; found: 288.1228; HPLC (Chiralcel AD-H column (Diacel)): hexane/2-propanol=95:5, flow rate=0.75 mL $min^{-1}$, $\lambda$=254 nm, $t_R$=24.8 (major), 27.8 min (minor).

**6h**: 68% *ee*, colorless oil. $R_f$=0.45 (hexane/ethyl acetate=2:1); IR (film): $\tilde{\nu}$=3413, 1020, 2934, 1532 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=8.20 (s, 1H, arom CH), 8.11–8.13 (m, 1H, arom CH), 7.72 (d, $^3J_{H,H}$=7.6 Hz, 1H, arom CH), 7.50 (t, $^3J_{H,H}$=8.2 Hz, 1H, arom CH), 6.24 (s, 1H, =CH), 6.02 (s, 1H, =CH), 5.62 (s, 1H, CHOH), 3.49 (br s, 1H, OH), 2.95–2.99 (m, 1H, CHCy), 1.66–1.77 (m, 5H, Cy), 1.14–1.31 ppm (m, 5H, Cy); $^{13}C$ NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=206.3 (C=O), 147.4 (arom CH), 148.2 (C=$CH_2$), 144.1 (arom C), 132.5 (arom CH), 129.3 (arom CH), 125.8 (arom CH), 122.5 (arom CH), 121.2 (arom CH), 73.1 (CHOH), 45.5 (CHCy), 29.2 (Cy), 29.1 (Cy), 25.7 (Cy), 25.6 (Cy), 25.5 ppm (Cy); LRMS (FAB): $m/z$=289.1 $[M]^+$; HRMS (FAB): $m/z$ calcd for $[C_{16}H_{19}NO_4]^+$: 289.1314; found: 289.1322; HPLC (Chiralcel AD-H column (Diacel)): hexane/2-propanol=95:5, flow rate=1.0 mL $min^{-1}$, $\lambda$=254 nm, $t_R$=17.5 (minor), 24.8 min (major).

**6i**: 69% *ee*, colorless oil. $R_f$=0.40 (hexane/ethyl acetate=2:1); $^1H$ NMR (300 MHz, $CDCl_3$, 300 K): $\delta$=7.61 (d, $^3J_{H,H}$=8.4 Hz, 2H, arom CH), 7.47 (d, $^3J_{H,H}$=8.4 Hz, 2H, arom CH), 6.19 (s, 1H, =CH), 5.96 (s, 1H, =CH), 5.58 (s, 1H, CHOH), 2.92–2.98 (m, 1H, CHCy), 1.67–1.75 (m, 5H, Cy), 1.13–1.34 ppm (m, 5H, Cy); $^{13}C$ NMR (500 MHz, $CDCl_3$, 300 K): $\delta$=206.2 (C=O), 147.6 (C=$CH_2$), 147.1 (arom C), 132.1 (arom CH), 127.0 (arom CH), 125.5 (arom CH), 118.7 (CN), 111.3 (arom C), 73.3 (CHOH), 45.5 (CHCy), 29.2 (Cy), 29.1 (Cy), 25.7 (Cy), 25.6 (Cy), 25.5 ppm (Cy); IR (film): $\tilde{\nu}$=3439, 3020, 2936, 2231, 1663, 1216 $cm^{-1}$; LRMS (EI): $m/z$=268.1 $[M-H]^-$; HRMS (EI): $m/z$ calcd for $[C_{17}H_{18}NO_2]^-$: 268.1338; found: 268.1336; HPLC (Chiralcel OJ-H column (Diacel)): hexane/2-propanol=90:10, flow rate=0.75 mL $min^{-1}$, $\lambda$=254 nm, $t_R$=16.6 (minor), 20.7 min (major).

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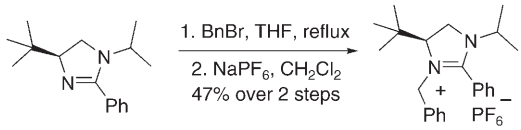
[22] We were able to alkylate the catalyst **3a** with benzyl bromide. A strong NOE was observed between the benzylic protons and those of the *tert*-butyl group, whereas none was observed for the isopropyl group.

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