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Organocatalyzed regioselective and enantioselective synthesis of 1,4- and 1,2-dihydropyridines

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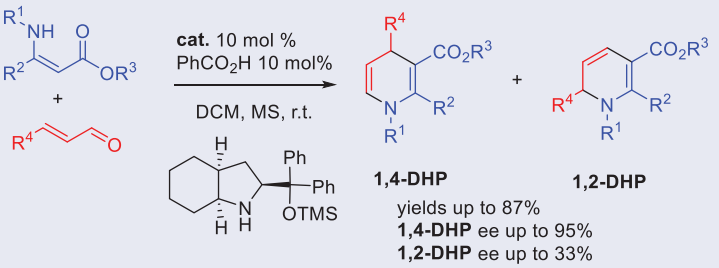
ABSTRACT

Herein, we introduce one of the first examples of asymmetric organocatalyzed synthesis of 1,2-dihydropyridines, affording enantioselective access to and partially solving regioselectivity challenges in the synthesis of dihydropyridines. We demonstrate that through modification of organocatalysts both 1,2- and 1,4-dihydropyridines (1,2- and 1,4-DHPs) can be obtained with high regioselectivity (ratio of 1,2-DHP/1,4-DHP from 95/5 to 0/100) and enantioselectivity (33% ee for 1,2-DHPs and up to 98% ee for 1,4-DHPs) in good yields (up to 87%).

GRAPHICAL ABSTRACT



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KEYWORDS
Asymmetric synthesis; chiral secondary amine; dihydropyridine; enantioselective organocatalysis

Introduction

Dihydropyridines (DHPs) are an interesting structural motif in organic chemistry due to their biological activity.[1–3] A perusal of the literature reveals that 1,4 dihydropyridines (1,4-DHPs) exhibit interesting pharmacological and biological properties. They can be active against calcium channels[4,5] find application in the treatment of cardiovascular disorders,[6] and present vasodilating activity.[7] Moreover, 1,4-dihydropyridines are NADH mimics[8,9] and can be used as hydride donors in a broad range of asymmetric transformations.[10–12] Different methods leading to enantiomerically enriched 1,4-

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DHPs, including diastereoselective cyclizations,[13,14] reductions of pyridines,[15–18] and a chemoenzymatic approach,[19] have been described.

1,2-DHPs are less studied compared to 1,4-DHPs; however, they are an important scaffold for the preparation of 2-azabicyclo[2.2.2]octanes (isoquinuclidines)[20] and can be used as synthetic intermediates for the synthesis of oseltamivir phosphate (Tamiflu).[21–23] A well-established route to the chiral ring system of oseltamivir that can be found currently in the literature is the Diels–Alder reaction of 1,2-dihydropyridines with dienophiles.[21–23] The majority of the published research into the synthesis of 1,2-DHPs focuses on one of three approaches: condensation reactions,[24] nucleophilic addition to pyridines and pyridinium salts,[25–38] or pericyclic reactions.[39–51] While organometallic compounds are common catalysts for these syntheses, organocatalysts have not been studied. Herein we report the asymmetric organocatalyzed synthesis of both 1,2-DHPs and 1,4-DHPs in good yields and in moderate to high enantiomeric excess.

Results and discussion

The investigation began with the reaction of methyl-3-(benzyl amino) acrylate **1** and (E)-cinnamaldehyde **2** in the presence of a simple chiral secondary amine, L-proline **5**. A mixture of 1,4-DHP and 1,2-DHP was formed in moderate yield (58%) with a regioisomeric ratio of nearly 1:1, in stark contrast to previous research in which only 1,4-DHPs were observed,[39,52,53] necessitating an expansion of the scope of the investigation to include regioselectivity as well as enantioselectivity.

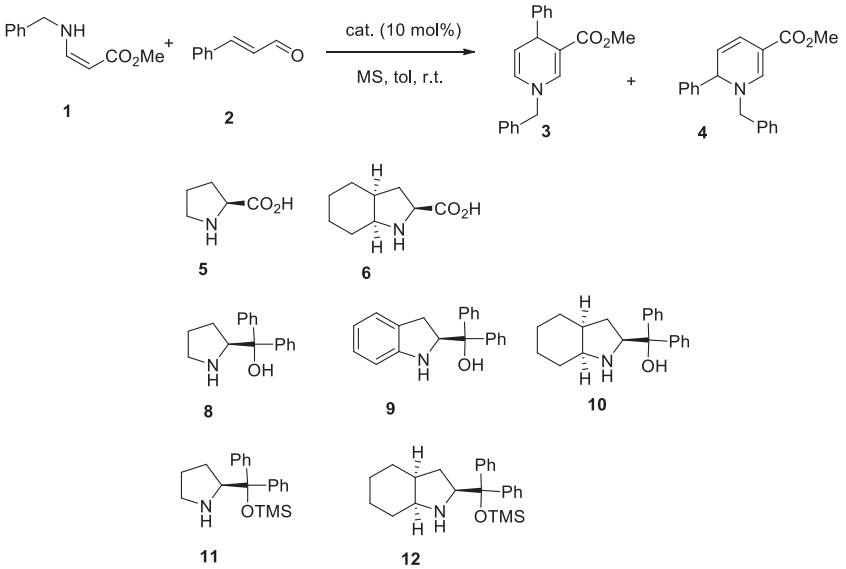
Continuing the study, catalysts **8–12** were prepared according to procedures outlined by Chan and coworkers[34] and a screening of a modest library of catalysts was embarked upon. Catalyst screening was carried out in the presence of 3Å molecular sieve under an argon atmosphere using toluene or dichloromethane as the solvent. The addition of benzoic acid (BA) as a co-catalytic additive was also investigated.

It was found that the reaction was highly dependent on the identity of the catalyst used. The influence of the catalyst was then examined in the same model reaction between (Z)-methyl-3-(benzyl amino) acrylate 1 and (E)-cinnamaldehyde 2 (Scheme 1). The 1,2-DHP/1,4-DHP ratios were determined from ^{1}H NMR spectra of the crude reaction mixtures. The results are shown in Table 1.

The amino acids **5** and **6** led to undesirable regioisomeric ratios with low enantioselectivity (Table 1, entries 1–2). Amino acid-derived catalysts bearing alcohol functionality such as **8, 9**, and **10** favored the 1,2-DHP with good regioselectivity. Of the catalysts that provide the 1,2-DHP as the major product, **10** gave the best result in terms of enantioselectivity with 33% ee for the 1,2-DHP and 16% ee for the 1,4-DHP (Table 1, entry 5) (Figure 1).

Catalysts **8**, **9**, and **10** led to the formation of solely the 1,2-DHP regioisomer; such reversal of the selectivity could result from the iminium intermediate. To further investigate this notion the iminium ion **9b** was synthesized (Scheme 2) from the ammonium tetrafluoroborate salt **9a** and cinnamaldehyde following procedures described by Seebach et al.[54–56]

Crystals of **9b** suitable for X-ray analysis were grown by vapor diffusion crystallization in acetonitrile/diethyl ether mixtures. As shown in Figure 2, the $^{+}$N=C bond



Scheme 1. The synthesis of 1,2-dihydropyridines and 1,4-dihydropyridines.

Table 1. Catalyst screening in the synthesis of 1,2-dihydropyridines and 1,4-dihydropyridines.

Entry	Catalyst	Solvent	Temp.	Yield, %	**4**/**3** ratio	ee **4**, %	ee **3**, %
1	5	Tol	r.t.	58	39/61	1	9
2	6	Tol	r.t.	42	50/50	2	5
3	8[a]	Tol	r.t.	57	90/10	5	11
4	9[a]	Tol	r.t.	79	90/10	8	0
5	10[a]	Tol	r.t.	73	95/5	33	16
6	11[a]	Tol	r.t.	56	37/63	4	85
7	12[a]	Tol[b]	r.t.	53	50/50	20	94
8	12[a]	Et_2O[c]	r.t.	87	49/51	6	79
9	12[a]	DCM[c]	r.t.	73	50/50	6	95
10	12	DCM[c]	r.t.	21	61/39	15	93
11	12[a]	DMF[d]	r.t.	37	50/50	2	49
12	12[a]	Tol[e]	0 °C	43	67/34	3	75
13	10	DCM	rt	81	90/10	3	27
14	10	THF	rt	70	96/4	0	0
15	10	CH_3CN	rt	56	98/2	0	0
16[b]	10	Tol	−20 °C	34	70/30	8	25

[a]10 mol% benzoic acid (BA) was used as co-catalyst (entries 5, 6, 7, 8, 9);
[b]reaction time: 5 days;
[c]reaction time: 2 days;
[d]reaction time: 3 days;
[e]reaction time: 8 days.

adopts a (*Z*)-configuration. The predominance of the (*Z*)-isomer might be explained by the minimization of steric interactions between the alkenyl and aryl hydrogens, which are more pronounced in the case of the (*E*)–isomer (Scheme 3).[57]

The X-ray structure of **9b** reveals a clear *gauche* orientation, which places the hydroxyl group *synclinal endo* over the pyrrolidine ring (N–C–C–O torsion angle of –57°). This preferential conformation might be attributed to a stabilizing hyperconjugation interaction or simply a minimization of steric interactions with the phenyl groups. A consequence of this interaction is to direct the phenyl group over one face of the

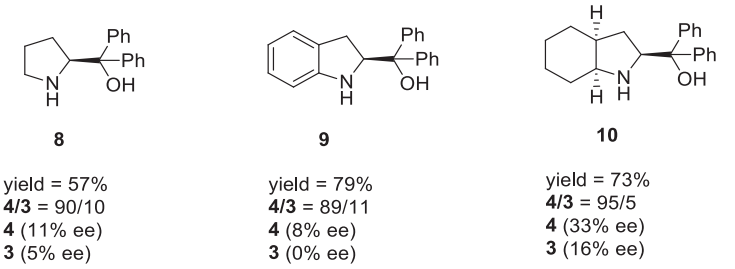
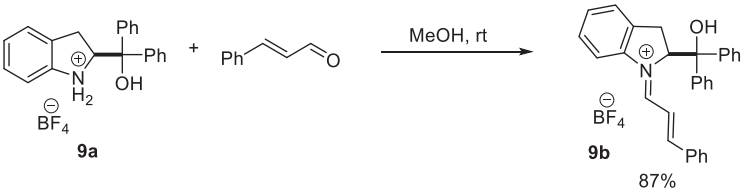


Figure 1. Catalysts **8, 9,** and **10**.



Scheme 2. Synthesis of the iminium ion **9b**.

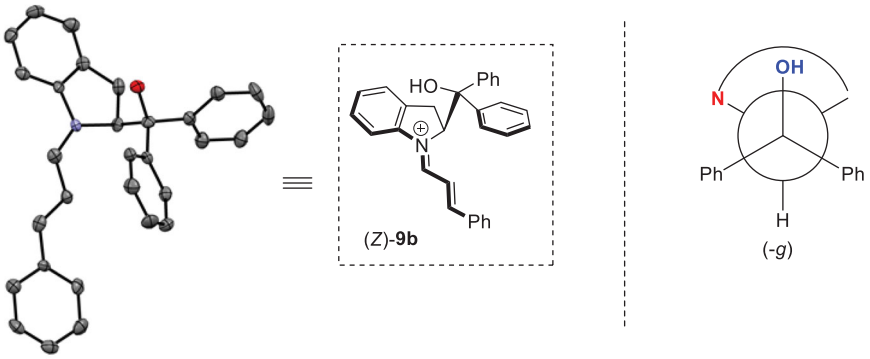
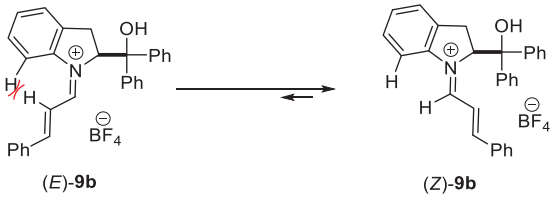


Figure 2. X-ray structure of the iminium ion **9b**.



Scheme 3. Steric interactions in the selective (*Z*)-iminium ion formation.

π–system, thus directing an incoming nucleophile to the opposite *Si* face. NMR spectroscopy showed that the conformations of **9b** observed in the crystals also dominate in $CDCl_3$ solution. Similar conformational effects have previously been observed during studies of the iminium ion derived from cinnamaldehyde and 2-(fluorodiphenylmethyl)-pyrrolidine, as reported by Gilmour et al.[58,59]

The reaction catalyzed by the silyl ether pyrrolidine **11** led to moderate regioselectivity (63/37) favoring the formation of the 1,4-isomer with good enantioselectivity (85%

Table 2. The screening of enaminoester in the synthesis of 1,2- and 1,4-dihydropyridines.

Entry	Enaminoester	Yield, %	1,2-/1,4- ratio	ee 1,2-,%	ee 1,4-,%
1	1a	63	0/100	–	38
2	1b	53	0/100	–	15
3	1c	73	49/51	6	95
4	1d	75	0/100	–	0

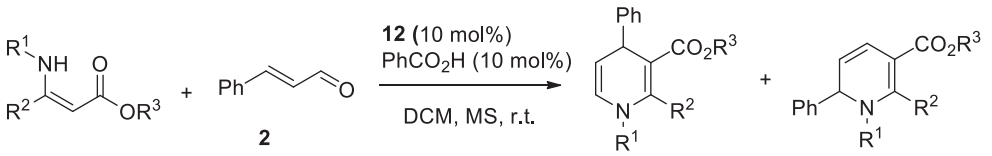
ee). The best result in terms of enantioselectivity was obtained with catalyst **12** providing the 1,4-DHP in an excellent 94% ee, with the caveat of no regioselectivity (Table 1, entry 7).

Prolinol type catalysts all favored the formation of the 1,2-DHP, but the enantioselectivities remained low. Diphenylprolinols **8** and **9** provided good regioselectivity but were inefficient as enantioselective catalysts in the screening reaction. Although (S)-diphenylprolinol-TMS ether **12** gave the 1,4-DHP as the major product with 93% ee in 21% yield after 5 days of reaction (Table 1, entry 10), the selectivity (up to 95%) and yield (up to 73% in 2 days) were improved when benzoic acid (BA) was introduced as a co-catalyst (Table 1, entry 9). Attempts to further optimize the reaction were made by screening solvents and reducing temperature. The use of dichloromethane as a solvent improved the selectivity further, affording the desired 1,4-DHP in 73% yield and 95% ee in shorter reaction time. Lowering the reaction temperature 0 °C decreased the yield (43% in 8 days) and reduced the enantiomeric excess of the 1,4-DHP to 72% ee (Table 1, entry 12).

Catalyst **10** (Table 1, entries 13–16), which led to good regioselectivity in favor of the 1,2-DHP isomer and promising ee's, was first selected as the catalyst with which to evaluate the influence of the solvent and temperature for condition optimization. Increasing the polarity of the solvent led to higher regioselectivity (Table 1, entries 13–15). The reaction in acetonitrile led to the *quasi*-exclusive formation of the 1,2-regioisomer; however, with no enantioselectivity (Table 1, entry 15). The reaction in toluene at room temperature remained the best in terms of enantioselectivity (entry 6). Disappointingly, reducing the temperature to −20 °C (entry 16) decreased both the regio- and enantio-selectivity.

With optimized reaction conditions in hand (Table 1, entry 9) the scope of the methodology was explored by testing a library of α,β-unsaturated aldehydes, and enaminoesters in the reaction (Table 2). The reaction smoothly undergoes a cascade cyclization or 6π-electrocyclizaton to afford dihydropyridines in good yields and regioselectivities and modest to high enantioselectivities (up to 98% ee for 1,4-DHP and 16% ee for 1,2-DHP).

The steric hindrance of the enaminoester appears to play an important role in the regioselectivity of the process. Substrates bearing an isopropyl or a *tert*-butyl group led to the formation of the 1,4-DHP exclusively. The enantioselectivity is also highly influenced by the substituent on the nitrogen atom, substrates bearing *N*-*tert*-butyl substitution led to better enantiomeric excess than the sister compound bearing *N*-isopropyl substitution (38% ee vs. 15% ee, Table 2, entries 1–2). The identity of the R^1 group (Scheme 4) also has a strong influence on the course of the reaction, with the enaminoester **1c**, bearing a benzyl group, leading to lower regioselectivity but much higher enantioselectivity (entry 3). Introducing β-methyl substitution, **1d** (Scheme 4), resulted in the restoration of 1,4-DHP exclusive regioselectivity at the cost of providing the



1a, R^1=$C(CH_3)_3$, R^2=H, R^3=CH_3
1b, R^1=$CH(CH_3)_2$, R^2=H, R^3=CH_3
1c, R^1=$PhCH_2$, R^2=H, R^3=CH_3
1d, R^1=$PhCH_2$, R^2=CH_3, R^3=CH_3

Scheme 4. The screening of enaminoesters in the synthesis of 1,2- and 1,4-dihydropyridines.

Table 3. The screening of aldehydes in the synthesis of dihydropyridines.

Entry	Aldehyde	Catalyst	Co-catalyst	Yield,%	1,2-/1,4- ratio	ee 1,2-, %	ee 1,4-, %
1	2a	12	BA	73	49/51	6	95
2	2b	12	BA	21	54/46	16	98
3	2c	12	BA	79	7/93	–	83
4	2d	12	BA	84	5/95	1	80
5	2e	12	BA	81	10/90	4	97
6	2f	12	BA	70	0/100	–	86
7	2g	12	BA	57	0/100	–	55
8	2h	12	BA	44	0/100	–	18
9	2i	12	BA	NR	–	–	–
10	2k	12	Sal	NR	–	–	–

NR: no reaction (entry 7, 8); AB: benzoic acid (10 mol%); Sal: salicylic acid (10 mol%).

product as a racemate (Table 2, entry 4); the steric influence of the methyl group may be an influential factor leading to this observation.

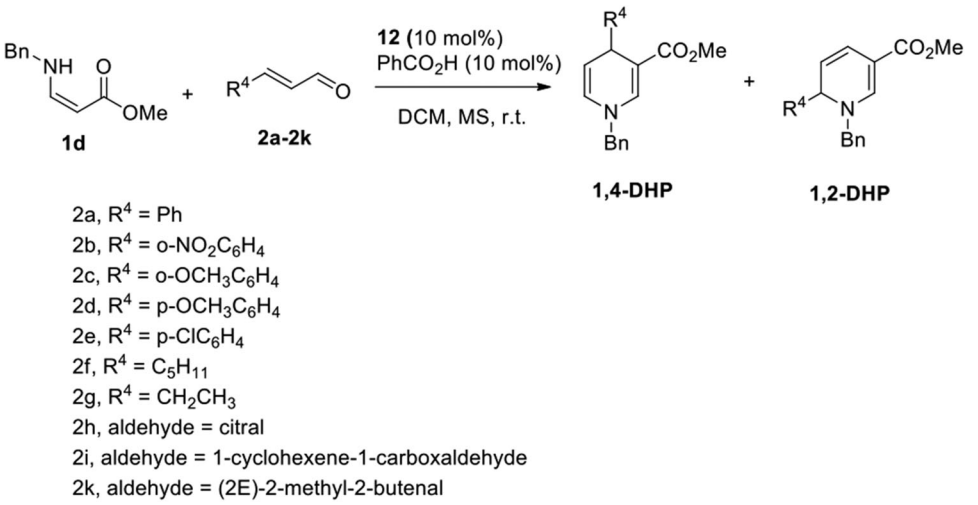
To further explore the scope of the method various α,β-unsaturated aldehydes were investigated (Table 3). Both aromatic and aliphatic aldehydes reacted smoothly, affording 1,4-DHPs with good yields and enantioselectivities (up to 98% ee).

Electron donating substitutions at the aryl ring of the enal had little effect on the yields and enantioselectivities but provided high regioselectivity favoring the formation of 1,4-DHPs (Table, entries 2–4). Aliphatic aldehydes (Table 3, entries 6–8) led to the exclusive formation of 1,4-DHPs at high enantiomeric excess (up to 86% ee), similarly to the results published by Kanger et al.[39](Scheme 5).

The aldehydes bearing aryl substituents generally preferred formation of the 1,4-regioisomer with good to excellent enantioselectivities of up to 98% ee (entries 1–5). With aldehydes bearing substituents at the α-position no reaction occurred (entries 9–10), this might be explained by the steric hindrance exerted by the substituent. In most cases, the 1,4-DHPs were the major compounds and obtained with high enantiomeric excesses, while the 1,2-DHPs were the minor compounds obtained with low enantiomeric excesses (up to 16% ee).

Conclusion

The development of atom efficient and metal-free asymmetric syntheses is an important goal in the green chemistry century. Progress toward an organocatalyzed enantioselective synthetic methodology that expands the synthetic space available for



Scheme 5. The screening of aldehydes in the synthesis of dihydropyridines.

enantiomerically enriched dihydropyridines to include both 1,2- and 1,4-dihydropyridine regioisomers provides the potential for new and green synthetic routes to both prospective and known pharmacologically and biologically active compounds. We have developed the first organocatalyzed synthesis of 1,2-dihydropyridines with high regioselectivity and up to 33% ee and the organocatalytic synthesis of 1,4-dihydropyridines with high regioselectivity and high enantioselectivity (up to 98%). These reactions proceeded in mild condition and products were obtained in very good yields as mixtures of regioisomers.

Experimental part

General information

All reactions were carried out under an argon atmosphere with dried, freshly distilled solvents under anhydrous conditions unless otherwise noted. Merck silica gel plates (60 F-254) using UV light as visualizing agent and phosphomolybdic acid and heat as developing agents. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography.

General procedure A for the preparation of β-enaminoesters

The amine (1.3 mmol, 1.3 eq.) in water (2.6 ml) was added to methyl propiolate (1.0 mmol, 1.0 eq.) and the reaction mixture was stirred at room temperature for 15 minutes. EtOAc (2.0 mL) was then added to the reaction mixture and the organic phase was extracted with EtOAc (2.0 mL × 3). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under vacuum. The crude residue was purified by column chromatography on silica (cyclohexane/EtOAc).

General procedure B for the preparation of β-enaminoesters in the presence of lewis acid

A dried round-bottomed flask was charged with activated molecular sieve, $La(OTf)_3$ (5 mol%), dichloromethane (5 mL), the dicarbonyl derivative (1 mmol, 1 eq.) and the primary amine (1.5 mmol, 1.5 eq.). The reaction mixture was stirred at room temperature until completion by TLC analysis. The solution was then filtered through celite, and concentrated under vacuum. The crude residue was purified on silica gel by flash chromatography (EtOAc/cyclohexane)

General procedure C for the preparation of dihydropyridines in the presence of benzoic acid as a brønsted acid

To a dried Schlenk's tube charged molecular sieve was added dichloromethane (5 ml), benzoic acid (0.10 mmol, 10 mol%), α,β-unsaturated aldehyde (1.5 mmol, 1.5 eq.) and the enaminoester (1 mmol, 1.5 eq.) under argon. The mixture was allowed to stir at room temperature for 8–24 hours. After filtration on Celite, the solvent was removed under reduced pressure. The residue was purified by column chromatography (cyclohexane/EtOAc = 10: 1 – 20:1 or pentane/EtOAc 20:1 – 30/1) to afford the 1,2-dihydropyridine and the 1,4-dihydropyridine.

General procedure D for the preparation of dihydropyridines in the presence of 10 mol% of lewis acid

(**D1**) A Schlenk's tube under argon was charged with sodium sulfate (150 mg), the Lewis acid catalyst (0.05 mmol, 5 mol%), dichloromethane (10 ml), the enaminoester (1 mmol, 1 eq.) and the unsaturated aldehyde (1.2 mmol, 1.2 eq.). The solution was stirred at room temperature until completion by TLC analysis. The solution was then filtered through a Celite pad, and concentrated under vacuum. The crude residue was purified on silica gel by flash chromatography (petroleum ether/diethyl ether).

(**D2**) Molecular sieves (M.S.) were added to a Schlenk's tube and dried under vacuum. $La(OTf)_3$ (0.10 mmol, 10 mol%) was added, followed by dichloromethane (10 ml), the α,β-unsaturated aldehyde (1 mmol, 1.5 eq.) and the enaminoester (1 mmol, 1.0 eq.). The mixture was allowed to stir at room temperature for 8 to 24 hours. After filtration on Celite, the solvent was removed under reduced pressure. The residue was purified by column chromatography (cyclohexane/EtOAc = 10: 1 – 20:1 or pentane/EtOAc 20:1 – 30/1) to afford the 1,4-dihydropyridine.

General procedure E for the preparation of enantioenriched dihydropyridines in the presence of L-proline type derivatives as the catalyst

Molecular sieves were added into a Schlenk's tube and dried under vacuum.

The catalyst (0.10 mmol, 10 mol %) and co-catalyst (0.010 mmol, 10 mol%) were added, followed by dichloromethane (10 ml), the α,β-unsaturated aldehyde (1.5 mmol, 1.5 eq.) and the enaminoester (1.0 mmol, 1.0 eq.) The reaction mixture was allowed to stir at room temperature for 1 to 2 days. After filtration on Celite, the solvent was

removed under reduced pressure. The residue was purified by column chromatography to afford a mixture of 1,2- dihydropyridine and 1,4-dihydropyridine. Both regioisomers were isolated with column chromatography where practical.

Full experimental detail, including ^{1}H and ^{13}C NMR spectra of all compounds and HPLC chromatography traces are available via the "Supplementary Content" section of this article's webpage.

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References

[1] Isambert, N.; Lavilla, R. Heterocycles as Key Substrates in Multicomponent Reactions: The Fast Lane towards Molecular Complexity. *Chemistry*. **2008**, *14*, 8444–8454. DOI: 10.1002/chem.200800473.

[2] Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. Synthesis of Pyridine and Dihydropyridine Derivatives by Regio- and Stereoselective Addition to N-Activated Pyridines. *Chem. Rev.* **2012**, *112*, 2642–2713. DOI: 10.1021/cr200251d.

[3] Suryavanshi, P. A.; Sridharan, V.; Maiti, S.; Menéndez, J. C. Fully Diastereoselective Synthesis of Polysubstituted, Functionalized Piperidines and Decahydroquinolines Based on Multicomponent Reactions Catalyzed by Cerium(IV) Ammonium Nitrate. *Chemistry*. **2014**, *20*, 8791–8799. DOI: 10.1002/chem.201402607.

[4] Faruk Khan, M. O.; et al. Isoquinuclidines: A Review of Chemical and Pharmacological Properties. In *Studies in Natural Products Chemistry*; Attaur, R., Ed.; Elsevier: Amsterdam, 2008; pp 753–787

[5] Hubert, C.; Moreau, J.; Batany, J.; Duboc, A.; Hurvois, J.-P.; Renaud, J.-L. Brønsted Acid-Catalyzed Synthesis of Pyransvia a Formal [3 + 3] Cycloaddition. *Adv. Synth. Catal.* **2008**, *350*, 40–42. DOI: 10.1002/adsc.200700375.

[6] Moreau, J.; Hubert, C.; Batany, J.; Toupet, L.; Roisnel, T.; Hurvois, J.-P.; Renaud, J.-L. Metal-Free Brønsted Acid Catalyzed Formal [3 + 3] Annulation. Straightforward Synthesis of Dihydro-2H-Chromenones, Pyranones, and Tetrahydroquinolinones. *J. Org. Chem.* **2009**, *74*, 8963–8973. DOI: 10.1021/jo901238y.

[7] Boschi, D.; Caron, G.; Visentin, S.; Di Stilo, A.; Rolando, B.; Fruttero, R.; Gasco, A. Searching for Balanced Hybrid NO-Donor 1,4-Dihydropyridines with Basic Properties. *Pharm. Res.* **2001**, *18*, 987–991. DOI: 10.1023/A:1010992412549.

[8] Thu Pham, H.; Chataigner, I.; Renaud, aJ-L. New Approaches to Nitrogen Containing Heterocycles: Enantioselective Organocatalyzed Synthesis of Dihydropyridines (DHP's), Quinolizidine Derivatives and Dihydropyrimidine(DHPM's.) *COC*. **2012**, *16*, 1754–1775. DOI: 10.2174/138527212802651322.

[9] Moreau, J.; Duboc, A.; Hubert, C.; Hurvois, J.-P.; Renaud, J.-L. Metal-Free Brønsted Acids Catalyzed Synthesis of Functional 1,4-Dihydropyridines. *Tetrahedron Lett.* **2007**, *48*, 8647–8650. DOI: 10.1016/j.tetlet.2007.10.040.

[10] Kaur, V. R.; Christian, B.; Jean-Luc, R. Lewis Acid-Catalyzed Sequential Transformations: Straightforward Preparation of Functional Dihydropyridines. *Adv. Synth. Catal.* **2006**, *348*, 2571–2574.

[11] Lavilla, R. Recent Developments in the Chemistry of Dihydropyridines. *J. Chem. Soc, Perkin Trans.* **2002**, *1*, 1141–1156. DOI: 10.1039/b101371h.

[12] Saini, A.; Kumar, S.; Sandhu, J. S. Hantzsch Reaction: Recent Advances in Hantzsch 1,4-Dihydropyridines. *J. Sci. Ind. Res.* **2008**, *67*, 95–111.

[13] Zhang, X.; Staples, R. J.; Rheingold, A. L.; Wulff, W. D. Catalytic Asymmetric α-Iminol Rearrangement: New Chiral Platforms. *J. Am. Chem. Soc.* **2014**, *136*, 13971–13974. DOI: 10.1021/ja5065685.

[14] Ingle, G. K.; Liang, Y.; Mormino, M. G.; Li, G.; Fronczek, F. R.; Antilla, J. C. Chiral Magnesium BINOL Phosphate-Catalyzed Phosphination of Imines: Access to Enantioenriched α-Amino Phosphine Oxides. *Org. Lett.* **2011**, *13*, 2054–2057. DOI: 10.1021/ol200456y.

[15] Larson, S. E.; Li, G.; Rowland, G. B.; Junge, D.; Huang, R.; Woodcock, H. L.; Antilla, J. C. Catalytic Asymmetric Aza-Darzens Reaction with a Vaulted Biphenanthrol Magnesium Phosphate Salt. *Org. Lett.* **2011**, *13*, 2188–2191. DOI: 10.1021/ol200407r.

[16] David, T.; Gabriela, M.-A.; Fernando, G.-T. A Convenient Domino Access to Substituted Alkyl 1,2-Dihydropyridine-3-Carboxylates from Propargyl Enol Ethers and Primary Amines. *Chem. A Eur. J.* **2010**, *16*, 428–431.

[17] Zhang, Z.; Antilla, J. C. Enantioselective Construction of Pyrroloindolines Catalyzed by Chiral Phosphoric Acids: total Synthesis of (-)-Debromoflustramine B. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 11778–11782. DOI: 10.1002/anie.201203553.

[18] Wang, H.; Jain, P.; Antilla, J. C.; Houk, K. N. Origins of Stereoselectivities in Chiral Phosphoric Acid Catalyzed Allylborations and Propargylations of Aldehydes. *J. Org. Chem.* **2013**, *78*, 1208–1215. DOI: 10.1021/jo302787m.

[19] Zhang, Z.; Zheng, W.; Antilla, J. C. Highly Enantioselective Catalytic Benzoyloxylation of 3-Aryloxindoles Using Chiral VAPOL Calcium Phosphate. *Angew. Chem. Int. Ed. Engl.* **2011**, *50*, 1135–1138. DOI: 10.1002/anie.201006595.

[20] Silva, A.; Silva, E.; Rocha, D. Diels–Alder Reactions of 1,2-Dihydropyridines: An Efficient Tool for the Synthesis of Isoquinuclidines. *Synthesis.* **2018**, *50*, 1773–1782. DOI: 10.1055/s-0037-1609418.

[21] Li, G.; Liang, T.; Wojtas, L.; Antilla, J. C. An Asymmetric Diels-Alder Reaction Catalyzed by Chiral Phosphate Magnesium Complexes: highly Enantioselective Synthesis of Chiral Spirooxindoles. *Angew. Chem. Int. Ed. Engl.* **2013**, *52*, 4628–4632. DOI: 10.1002/anie.201209295.

[22] Nimmagadda, S. K.; Zhang, Z.; Antilla, J. C. Asymmetric One-Pot Synthesis of 1,3-Oxazolidines and 1,3-Oxazinanes via Hemiaminal Intermediates. *Org. Lett.* **2014**, *16*, 4098–4101. DOI: 10.1021/ol501789c.

[23] Liang, T.; Li, G.; Wojtas, L.; Antilla, J. C. Chiral Metal Phosphate Catalysis: highly Asymmetric hetero-Diels-Alder Reactions. *Chem. Commun. (Camb.)* **2014**, *50*, 14187–14190. DOI: 10.1039/c4cc06520d.

[24] Ingle, G.; Mormino, M. G.; Antilla, J. C. Lithium BINOL Phosphate Catalyzed Desymmetrization of meso-Epoxides with Aromatic Thiols. *Org. Lett.* **2014**, *16*, 5548–5551. DOI: 10.1021/ol502527q.

[25] Groenendaal, B.; Ruijter, E.; Orru, R. V. A. 1-Azadienes in Cycloaddition and Multicomponent Reactions towards N-Heterocycles. *Chem. Commun.* **2008**, *44*, 5474–5489. DOI: 10.1039/b809206k.

[26] Girling, P. R.; Kiyoi, T.; Whiting, A. Mannich-Michael versus formal aza-Diels-Alder approaches to piperidine derivatives. *Org. Biomol. Chem.* **2011**, *9*, 3105–3121. DOI: 10.1039/c0ob00996b.

[27] Duttwyler, S.; Chen, S.; Lu, C.; Mercado, B. Q.; Bergman, R. G.; Ellman, J. A. Regio- and Stereoselective 1,2-Dihydropyridine Alkylation/Addition Sequence for the Synthesis of Piperidines with Quaternary Centers. *Angew. Chem. Int. Ed. Engl.* **2014**, *53*, 3877–3880. DOI: 10.1002/anie.201310517.

[28] J, M. J.; A, B. J.; B, C. A. Copper-Catalyzed Direct Alkenylation of N-Iminopyridinium Ylides. *Angew. Chem. Int. Ed.* **2010**, *49*, 1115–1118.

[29] Richard, V.; Ipouck, M.; Mérel, D. S.; Gaillard, S.; Whitby, R. J.; Witulski, B.; Renaud, J.-L. Iron(II)-Catalysed [2 + 2+2] Cycloaddition for Pyridine Ring Construction. *Chem. Commun. (Camb.)* **2014**, *50*, 593–595. DOI: 10.1039/c3cc47700b.

[30] Weding, N.; Hapke, M. Preparation and Synthetic Applications of Alkene Complexes of Group 9 Transition Metals in [2 + 2+2] Cycloaddition Reactions. *Chem. Soc. Rev.* **2011**, *40*, 4525–4538. DOI: 10.1039/c0cs00189a.

[31] Domínguez, G.; Pérez-Castells, J. Recent Advances in [2 + 2+2] Cycloaddition Reactions. *Chem. Soc. Rev.* **2011**, *40*, 3430–3444. DOI: 10.1039/c1cs15029d.

[32] Hao, W.; et al. Synthesis of Substituted 1,2-Dihydropyridines from Propargyl Vinyl Ethers and Allenic Vinyl Ethers by Gold-Catalyzed Claisen Rearrangement and 6π-Aza-Electrocyclization. *Adv. Synth. Catal.* **2010**, *352*, 2450–2454.

[33] Gross, K. M. B.; Jun, Y. M.; Beak, P. Asymmetric Deprotonations: Lithiation of N-(tert-Butoxycarbonyl)Indoline with sec-Butyllithium/(−)-Sparteine. *J. Org. Chem.* **1997**, *62*, 7679–7689. DOI: 10.1021/jo9708856.

[34] Ren-Shi, L.; et al. Highly Efficient Asymmetric Michael Reaction of Aldehydes to Nitroalkenes with Diphenylperhydroindolinol Silyl Ethers as Organocatalysts. *Adv. Synth. Catal.* **2009**, *351*, 2449–2459.

[35] Bhaskar Kanth, J. V.; Periasamy, M. Convenient Method for the Synthesis of Chiral α,α-Diphenyl-2-Pyrrolidinemethanol. *Tetrahedron.* **1993**, *49*, 5127–5132. DOI: 10.1016/S0040-4020(01)81877-9.

[36] Sibi, M. P.; Manyem, S. Lanthanide Lewis Acid-Mediated Enantioselective Conjugate Radical Additions. *Org. Lett.* **2002**, *4*, 2929–2932. DOI: 10.1021/ol026327h.

[37] Li, K.; Zhou, Z.; Wang, L.; Chen, Q.; Zhao, G.; Zhou, Q.; Tang, C. Asymmetric Carbonyl Reduction with Borane Catalyzed by Chiral Phosphinamides Derived from l-Amino Acid. *Tetrahedron Asym.* **2003**, *14*, 95–100. DOI: 10.1016/S0957-4166(02)00789-9.

[38] Randive, N. A.; Kumar, V.; Nair, V. A. A Facile Approach to Substituted Acrylates by Regioselective and Stereoselective Addition of Thiols and Amines to an Alkynyl Ester in Water. *Monatsh. Chem.* **2010**, *141*, 1329–1332. DOI: 10.1007/s00706-010-0399-9.

[39] Noole, A.; Borissova, M.; Lopp, M.; Kanger, T. Enantioselective Organocatalytic Aza-Ene-Type Domino Reaction Leading to 1,4-Dihydropyridines. *J. Org. Chem.* **2011**, *76*, 1538–1545. DOI: 10.1021/jo200095e.

[40] Choudhary, S.; Pawar, A. P.; Yadav, J.; Sharma, D. K.; Kant, R.; Kumar, I. One-Pot Synthesis of Chiral Tetracyclic Dibenzo[b, f][1,4]oxazepine-Fused 1,2-Dihydropyridines (DHPs) under Metal-Free Conditions. *J. Org. Chem.* **2018**, *83*, 9231–9239. DOI: 10.1021/acs.joc.8b01232.

[41] Auria-Luna, F.; Marqués-López, E.; Gimeno, M. C.; Heiran, R.; Mohammadi, S.; Herrera, R. P. Asymmetric Organocatalytic Synthesis of Substituted Chiral 1,4-Dihydropyridine Derivatives. *J. Org. Chem.* **2017**, *82*, 5516–5523. DOI: 10.1021/acs.joc.7b00176.

[42] Kobayashi, T.; Hatano, S.; Tsuchikawa, H.; Katsumura, S. A Novel Strategy for the Synthesis of 2-Arylpyridines Using One-Pot 6π-Azaelectrocyclization. *Tetrahedron Lett.* **2008**, *49*, 4349–4351. DOI: 10.1016/j.tetlet.2008.05.048.

[43] Sydorenko, N.; Hsung, R. P.; Vera, E. L. Torquoselective 6pi-Electron Electrocyclic Ring Closure of 1-Azatrienes Containing Acyclic Chirality at the C-Terminus. *Org. Lett.* **2006**, *8*, 2611–2614. DOI: 10.1021/ol060932t.

[44] Francisco, P.; et al. Cycloaddition Reactions of Neutral 2-Azadienes with Enamines – Regiospecific Synthesis of Highly Substituted Dihydropyridines and Pyridines. *Eur. J. Org. Chem.* **2001**, *2001*, 2115–2122.

[45] Colby, D. A.; Bergman, R. G.; Ellman, J. A. Synthesis of Dihydropyridines and Pyridines from Imines and Alkynes via C-H activation. *J. Am. Chem. Soc.* **2008**, *130*, 3645–3651. DOI: 10.1021/ja7104784.

[46] Duttwyler, S.; Lu, C.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. Highly Diastereoselective Synthesis of Tetrahydropyridines by a C–H Activation-Cyclization-Reduction Cascade. *J. Am. Chem. Soc.* **2012**, *134*, 4064–4067. DOI: 10.1021/ja2119833.

[47] Liu, H.; Zhang, Q.; Wang, L.; Tong, X. PPh3-Catalyzed [2 + 2 + 2] and [4 + 2] Annulations: synthesis of Highly Substituted 1,2-Dihydropyridines (DHPs). *Chem. Commun. (Camb.)* **2010**, *46*, 312–314. DOI: 10.1039/b915825a.

[48] Yamakawa, T.; Yoshikai, N. Annulation of α,β-Unsaturated Imines and Alkynes via Cobalt-Catalyzed Olefinic C-H Activation. *Org. Lett.* **2013**, *15*, 196–199. DOI: 10.1021/ol303259m.
[49] Harschneck, T.; Kirsch, S. F. One-Pot Synthesis of 1,2-Dihydropyridines: Expanding the Diverse Reactivity of Propargyl Vinyl Ethers. *J. Org. Chem.* **2011**, *76*, 2145–2156. DOI: 10.1021/jo102545m.
[50] Binder, J. T.; Kirsch, S. F. Synthesis of Highly Substituted Pyrroles via a Multimetal-Catalyzed Rearrangement-Condensation-Cyclization Domino Approach. *Org. Lett.* **2006**, *8*, 2151–2153. DOI: 10.1021/ol060664z.
[51] Suhre, M. H.; Reif, M.; Kirsch, S. F. Gold(I)-Catalyzed Synthesis of Highly Substituted Furans. *Org. Lett.* **2005**, *7*, 3925–3927. DOI: 10.1021/ol0514101.
[52] Kumar, A.; Maurya, R. A. Organocatalysed Three-Component Domino Synthesis of 1,4-Dihydropyridines Under Solvent Free Conditions. *Tetrahedron.* **2008**, *64*, 3477–3482. DOI: 10.1016/j.tet.2008.02.022.
[53] Franke, P. T.; Johansen, R. L.; Bertelsen, S.; Jørgensen, K. A. Organocatalytic Enantioselective One-Pot Synthesis and Application of Substituted 1,4-Dihydropyridines-Hhantzsch Ester Analogues. *Chem Asian J.* **2008**, *3*, 216–224. DOI: 10.1002/asia.200700360.
[54] Seebach, D.; Grošelj, U.; Badine, M. D.; W. Bernd, S.; Beck, A. K. Isolation and X-Ray Structures of Reactive Intermediates of Organocatalysis with Diphenylprolinol Ethers and with Imidazolidinones. *Helv. Chim. Acta*. **2008**, *91*, 1999–2034.
[55] Grošelj, U.; Seebach, D.; Badine, D. M.; Schweizer, W. B.; Albert K. B.; Krossing, I.; Klose P.; Hayashi Y.; Uchimaru, T. Structures of the Reactive Intermediates in Organocatalysis with Diarylprolinol Ethers. *Helv. Chim. Acta*. **2009**, *92*, 1225–1259.
[56] Sami, L.; Roland, A.; Herbert, M. How Does Electrostatic Activation Control Iminium-Catalyzed Cyclopropanations? *Angew. Chem. Int. Ed*. **2009**, *48*, 5034–5037.
[57] Kunz, R. K.; MacMillan, D. W. C. Enantioselective Organocatalytic Cyclopropanations. The Identification of a New Class of Iminium Catalyst Based upon Directed Electrostatic Activation. *J. Am. Chem. Soc.* **2005**, *127*, 3240–3241. DOI: 10.1021/ja042774b.
[58] E, Z. L.; Christof, S.; Ryan, G. Fluorine Conformational Effects in Organocatalysis: An Emerging Strategy for Molecular Design. *Angew. Chem. Int. Ed.* **2011**, *50*, 11860–11871.
[59] Christof, S.; et al. Theoretical and X-Ray Crystallographic Evidence of a Fluorine-Imine Gauche Effect: An Addendum to Dunathan's Stereoelectronic Hypothesis. *Chem. Eur. J.* **2011**, *17*, 8850–8857.