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Highly enantioselective synthesis of alkyl-pyridines derivatives through a Michael-Michael-aldol cascade reaction

Marta Meazza,^[a] Michael Potter,^[a] Mateusz B. Pitak,^[b] Simon J. Coles,^[b] Andrea Mazzanti,^[c] and Ramon Rios*^[a]

Introduction

Alkylazaarenes¹ and, more concretely, *ortho* substituted pyridines are common 3-D scaffolds in Medicinal Chemistry and Agrochemistry. As it is shown in Figure 1, the alkylazaarene moiety is present in several natural and pharmaceutical compounds such as GlyT-1 inhibitor **1** or a DPP-IV inhibitor **2** (Figure 1).²

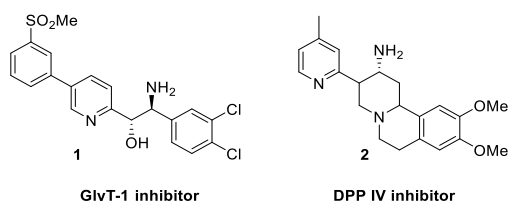
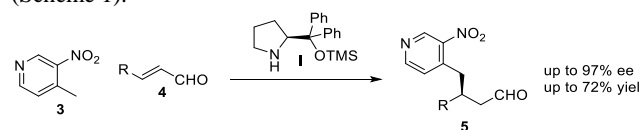


Figure 1. Pharmaceutical active compounds containing azaarenes

Despite the utility and interest of these compounds, very few enantioselective methodologies have been developed for the synthesis of chiral derivatives with an asymmetric carbon in the pseudo benzylic position. Almost all the examples reported are based on achiral reactions that usually require harsh reaction conditions such as (super)stoichiometric strong bases such as LiHMDS³ obviously limiting their use.

To our knowledge, there are few examples in the literature in which the α pseudobenzylic position of an azaarene can be activated in an enantioselective fashion with mild conditions. Two general strategies have been reported using electron-withdrawing substituents either in the azaarene ring or in the benzylic position. For example, Melchiorre and co-workers reported two single examples of the activation of 2- and 4-methyl pyridines bearing a

nitroaryl substituent with moderate results.⁴ On the other hand using an electronwithdrawing group in the azaarene ring, Lar recently reported the use of Metal Lewis acid for the activation of the pseudobenzylic α positions of the azaarenes. By using chiral palladium complexes, methyl azarenes react with nitrostyrenes or imines obtaining the final products in good yield and excellent enantioselectivities.⁵ Wei Wang and co-worker reported the addition of methyl nitropyridines to enals with excellent yields and enantioselectivities. Unfortunately 2-methyl-5-nitropyridines did not give good results under these conditions (Scheme 1).⁶



Scheme 1. Wang's methodology for the synthesis of azaarene derivatives

Our research group, interested in the enantioselective activation of benzylic and "pseudo benzylic" positions, developed a synergistic approach based on the concurrent activation of the azaarene with a metal Lewis acid and of the nucleophile with an organocatalyst with good results. However, when we tried to apply this synergistic approach to 2-methyl-pyridine derivatives, very low yields were obtained. It should be noticed that in all the previous examples one of the limitations has been the generation of quaternary α -stereocenters, only tertiary stereocenters have been synthesized.⁸

In order to address these difficulties and at the same time generate a nucleophile strong enough to synthesize quaternary stereocenters, we propose the use of a nitrile group to increase the nucleophilicity of the compounds, thus allowing their double functionalization in a cascade fashion (Figure 2).

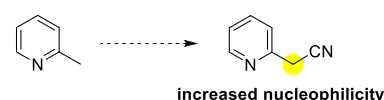


Figure 2. Proposed strategy

We envisioned that the use of these compounds, in combination with the activation of enals by a secondary amine, could lead to the synthesis of highly functionalized 2-substituted-pyridine derivatives. The reaction happens *via* an organocascade⁹ reaction consisting in a double Michael addition to α,β -unsaturated aldehydes, followed by an intramolecular aldol reaction, in a

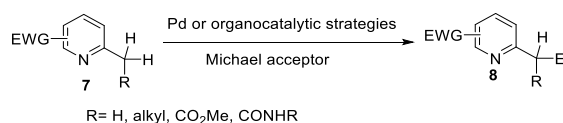
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similar fashion to the one developed by Jørgensen and coworkers and subsequently explored by our research group (Figure 3).¹⁰

Previous strategies: tertiary stereocenters



This work: quaternary stereocenter through a domino cascade reaction

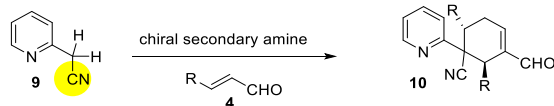


Figure 3: Enantioselective strategies for the synthesis of α -substituted pyridines

Results and Discussion

In an initial screening we tested the reaction between cinnamaldehyde **4a** and 2-pyridineacetonitrile **9a**. As it is shown in Table 1, the reaction performs well in CHCl_3 , benzene and CH_2Cl_2 , giving the final product in good conversions and moderate to good diastereoselectivities and excellent enantioselectivities (entries 1, 2 and 7; Table 1). When EtOAc or toluene were used as solvents, similar conversions and enantioselectivities but lower diastereoselectivities have been found (entries 3 and 5; Table 1). THF and MeOH gave complex mixtures with degradation products, however the final compound was obtained in good diastereo- and enantioselectivities. Besides, when the reaction was run in DMF no product was obtained. Next, we decided to study the effect of different acid additives. The reaction gave similar results with *m*-F benzoic acid (only slightly lower diastereoselectivities). When TFA or no acid was used, no reaction was observed. This is in agreement with our previous works in which it was found that the use of a benzoic acid derivative is crucial for the formation of the final compound.

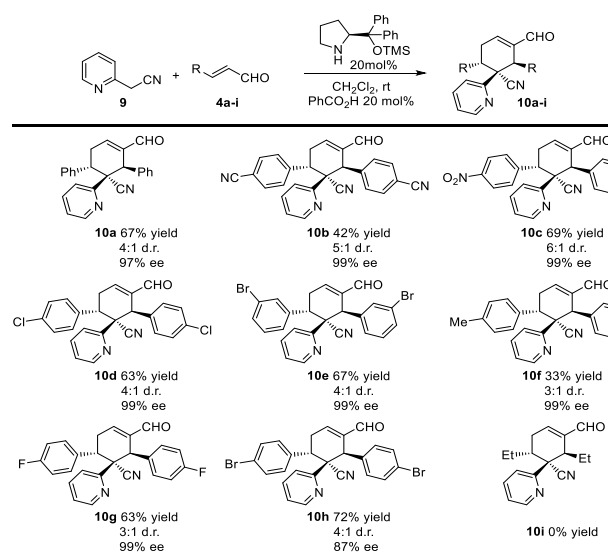
Table 1. Reaction optimization

Entry	Solvent	Additive	Conversion ^[a]	d.r. ^[b]	ee ^[c]
1	CHCl_3	PhCO_2H	60	3:1	>90
2	CH_2Cl_2	PhCO_2H	67	4:1	>90
3	EtOAc	PhCO_2H	64	2:1	>90
4	DMF	PhCO_2H	-	-	-
5	Toluene	PhCO_2H	62	2:1	>90
6	THF	PhCO_2H	CM	4:1	>90
7	Benzene	PhCO_2H	69	3:1	>90
8	MeOH	PhCO_2H	CM	-	-
9	CH_2Cl_2	TFA	-	-	-
10	CH_2Cl_2	<i>m</i> $\text{FC}_6\text{H}_4\text{CO}_2\text{H}$	66	3:1	>90
11	CH_2Cl_2	-	-	-	-

[a] Determined by ^1H -NMR analysis of crude reaction; CM = complex mixtures [b]

Determined by ^1H -NMR analysis of crude reaction; [c] Determined by Chiral HPLC analysis of the crude reaction

Once we had the optimized reaction conditions in hand, we decided to study the scope of the reaction in terms of the enal. As it is shown in Scheme 2, the reaction performs well with *p*-substituted aromatic enals. For example, *p*-nitro and *p*-cyano substituted render the final products in excellent yields (3 new C-C bonds are formed), very good diastereo- and excellent enantioselectivities (**10b** and **10c**). Halogen substituted enals like *p*-Cl, *p*-F, *p*-Br or *m*-Br render the final compounds again in excellent yields, excellent enantioselectivities but slightly lower diastereoselectivities (**10d**, **10e**, **10g** and **10h**). When an electron donating substituent such as *p*-methyl was used, lower yields were obtained but still good enantioselectivities (**10f**). However, when an aliphatic aldehyde like pentenal was used, the reaction rendered complex mixtures (Scheme 2).



Scheme 2. Reaction scope

The relative configuration of the major diastereomer of the compound **10a** was ascertained by X-ray crystallographic analysis (figure 4):

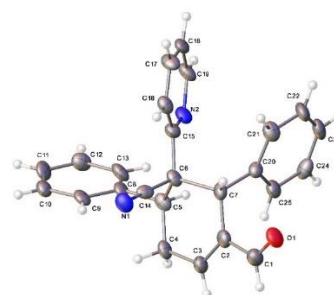


Figure 4. Molecular structure of **10a**. Displacement ellipsoids – 50% probability.¹¹

The absolute configuration of the major diastereomers of **10c** and **10e** was determined to be *4R,5S,6R* (using (*R*)-**1** as catalyst) by TD-DFT simulation of the Electronic Circular Dichroism (ECD) spectra (Figure 5 and SI).¹²

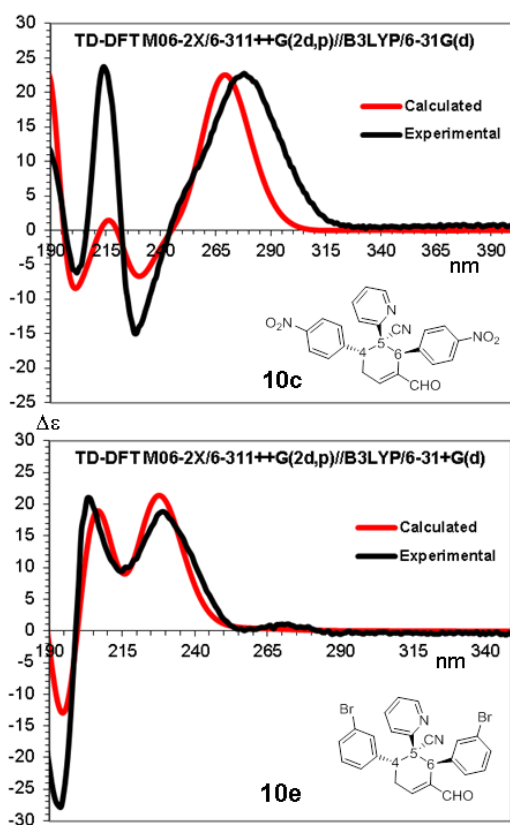
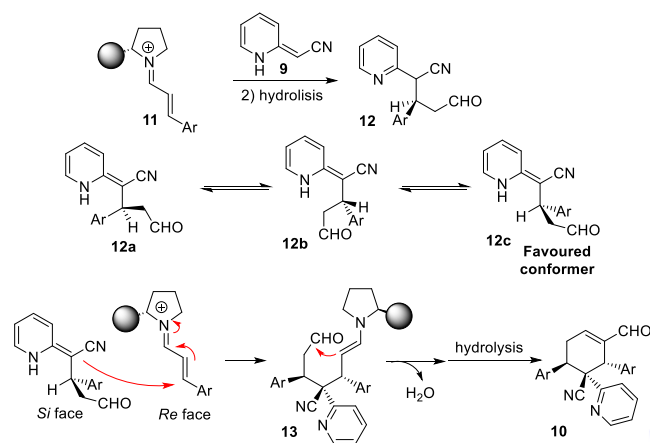


Figure 5. TD-DFT simulations (red traces) of the experimental ECD spectra (black traces) of the major diastereoisomer of **10c** and **10e**. Simulations were obtained at the M06-2X/6-311++G(2d,p)//B3LYP/6-31G(d) level of theory. Further details and simulations are reported in ESI.

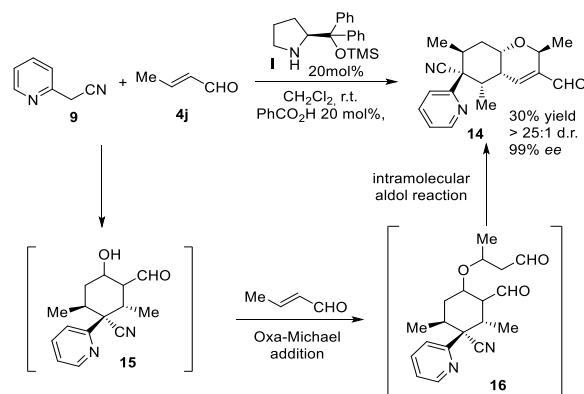
The absolute configuration and diastereoselectivity of the major diastereomer is in agreement with the mechanism proposed and with the previous works done with this type of catalyst, where the stereochemistry at the β -position of the enal is perfectly controlled by the catalyst (**I**).¹³

These results are in accordance with the following proposed mechanism. First **9** reacts with the iminium form of the enal with the Jørgensen-Hayashi catalyst, furnishing the intermediate **12**. Next the “enamine” form of the intermediate **12** could adopt several conformations: as it is shown in Scheme 3, the “enamine” adopts the conformer **12c** in order to relieve the strain in the allylic system, with the hydrogen of the chiral center lying in the same plane of the pyridine ring. The subsequent Michael addition, therefore, will occur preferentially on the face of the enamine opposite to the bulky aryl ring (*Si* face). Regarding the enal, again the enantiocontrol is determined by the catalyst **I**. After a Michael addition, the enamine intermediate **13** undergoes an intramolecular aldol reaction followed by dehydration to render the final compound **10** (Scheme 3).



Scheme 3. Proposed reaction mechanism

Surprisingly, when crotonaldehyde was used, the reaction only rendered one identifiable product in moderate yield and in totally diastereo- and enantioselective fashion (99% *ee* and only one diastereomer detected in the NMR of the crude). We determined that a quintuple cascade reaction takes place affording compound **14** (Scheme 4). We propose that after the first cascade reaction leading to the aldol intermediate **15**, instead of the dehydration, the alcohol undergoes an oxo-Michael addition to third molecule of crotonaldehyde leading to **16**. This intermediate after an intramolecular aldol reaction followed by dehydration renders the final compound **14** (Scheme 4).



Scheme 4. Proposed reaction sequence

The relative configuration of product **14** was determined by X-ray analysis (Figure 6).

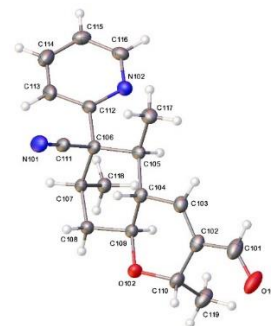
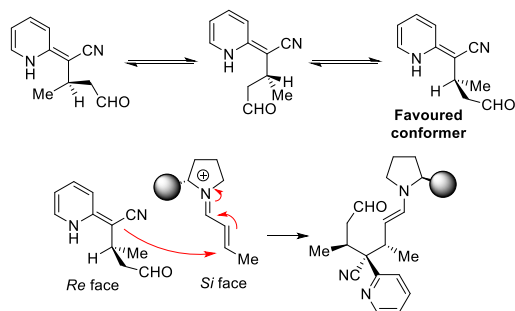


Figure 6. Molecular structure of **14**. Displacement ellipsoids – 50% probability.¹⁴

Remarkably compound **14**, obtained from the quintuple cascade reaction, shows an opposite configuration in the cyano pyridine position. This can be easily explained by the same mechanism. In the case of crotonaldehyde the attack takes place from the *Re* face of the first Michael product. In this case, the methyl presents a

lower steric hindrance than the CH_2CHO , which is shielding the *Si* face and leading to the opposite configuration at this center (Scheme 5).



Scheme 5. Proposed reaction mechanism

Conclusion

In summary, we developed a new methodology for the synthesis of pyridine derivatives based on a triple cascade reaction catalyzed by chiral secondary amines. The resulting cyclohexenes (3 C-C bond were formed) were obtained in good yields, good diastereoselectivities and excellent enantioselectivities. Studies towards the development of new methodologies for the synthesis of azaarene derivatives are ongoing in our laboratory.

Experimental Section

General Procedure

2-(pyridin-2-yl)acetonitrile (0.2 mmol, 1 equiv), the α,β -unsaturated aldehyde (3 equiv), the Jørgensen-Hayashi catalyst (20 mol%), benzoic acid (20 mol%) and DCM (2 ml) were added to a 6 mL vial. The crude mixture was stirred at room temperature for 48 hours and the reaction was checked by NMR. The crude mixture was washed with aqueous sodium bicarbonate (40 mL). The aqueous phase was extracted with ethyl acetate (3x20 mL), the organic phases collected and dried over MgSO_4 and the solvent removed *in vacuo*. The reaction mixture was then purified by flash chromatography (hexane/EtOAc).

Supporting Information

(1*R*,2*S*,3*R*)-6'-formyl-2'-(pyridin-2-yl)-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-carbonitrile (10a) major diastereomer. ^1H NMR (400 MHz, CDCl_3) δ 9.56 (s, 1H), 8.35 (ddd, J = 4.7, 1.6, 0.8 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.32 (t, J = 3.7 Hz, 1H), 7.22 (td, J = 7.8, 1.8 Hz, 1H), 7.18 – 7.03 (m, 6H), 6.96 (ddd, J = 7.5, 4.8, 0.9 Hz, 1H), 6.61 (dd, J = 7.4, 3.8 Hz, 3H), 4.61 (bs, 1H), 3.95 (dd, J = 9.4, 7.8 Hz, 1H), 3.22 – 3.12 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 191.6, 154.6, 149.6, 148.9, 140.9, 139.9, 136.0, 135.7, 131.1, 129.7, 129.0, 128.8, 128.7, 128.1, 127.9, 127.4, 123.3, 122.7, 122.1, 52.8, 51.2, 39.6, 35.4. The enantiomeric excess was determined by HPLC using a Chiralpak ID column (hexane/*i*PrOH = 80:30, flow rate 1.0 mL/min, λ = 254 nm): t_r (S) = 37.0, t_r (R) = 27.2, 97% (R) *ee*. $[\alpha]_D^{19}$ = -56.0° (c = 1.0, CHCl_3) (S catalyst). HRMS m/z (ESI-) Exact mass calculated for $\text{C}_{25}\text{H}_{19}\text{N}_2\text{O}$ [M-H] $^-$: 363.1503, found: 363.1502.

(1*R*,2*R*,3*R*)-6'-formyl-2'-(pyridin-2-yl)-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-carbonitrile (10a) minor diastereomer. ^1H NMR (400 MHz, CDCl_3) δ 9.53 (s, 1H), 8.52 (ddd, J = 4.9, 1.8, 0.8 Hz, 1H), 7.55 (td, J = 7.8, 1.9 Hz, 1H), 7.39 (d, J = 3.8 Hz, 5H), 7.23 (dd, J = 7.7, 3.6 Hz, 3H), 7.18 (d, J = 7.7 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 6.79 (d, J = 7.4 Hz, 2H), 4.61 (s, 1H), 3.72 (t, J = 8.1 Hz, 1H), 2.92 (dd, J = 7.7, 3.2 Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 192.0, 155.5, 148.9, 148.9, 141.2, 139.0, 137.6, 136.3, 131.1, 130.2, 129.8, 129.0, 128.6, 128.3, 128.2, 128.1, 124.3, 123.2, 120.9, 54.4, 46.3, 43.9, 30.2. HRMS m/z (ESI-) Exact mass calculated for $\text{C}_{25}\text{H}_{19}\text{N}_2\text{O}$ [M-H] $^-$: 363.1503, found: 363.1501.

(1*R*,2*S*,3*R*)-6'-formyl-2'-(pyridin-2-yl)-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2',4,4''-tricarbonitrile (10b). Major diastereomer. Yield 42%. Dark red solid. Column eluent: 3:1 (Hexane/EtOAc). Melting point range: 162–165 °C. IR: 2961 cm^{-1} ($\text{HC}=\text{C}$ stretch), 2228 cm^{-1} (nitrile stretch), 1684 cm^{-1} ($\text{C}=\text{O}$ aldehyde stretch), 1607 cm^{-1} (aliphatic $\text{C}=\text{C}$ stretch), 1504 cm^{-1} , 1486 cm^{-1} (aromatic $\text{C}=\text{C}$ stretch). ^1H NMR (400 MHz, CDCl_3) δ 9.53 (s, 1H), 8.50–8.49 (m, 1H), 7.66 – 7.64 (m, 2H), 7.47 – 7.45 (m, 4H), 7.35 – 7.28 (m, 3H), 7.21 – 7.19 (m, 1H), 6.88 – 6.86 (m, 2H), 4.68 (s, 1H), 3.65 (dd, J = 8.9, 6.1 Hz, 1H), 3.08 – 2.97 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 191.3, 154.2, 149.2, 143.9, 142.5, 140.3, 137.0, 132.3, 132.0, 130.8, 130.3, 128.5, 123.9, 123.8, 120.0, 118.6, 118.4, 112.3, 112.2, 53.5, 45.5, 44.9, 29.9. The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/*i*PrOH = 70:30, flow rate 1.0 mL/min, λ = 265 nm): t_r (S) = 38.3, t_r (R) = 41.1, 99% (R) and 99% (S) *ee*. $[\alpha]_D^{19}$ = -135.4° (c = 0.4, CHCl_3) (S catalyst). HRMS m/z (ESI-) Exact mass calculated for $\text{C}_{27}\text{H}_{13}\text{N}_4\text{O}$ [M-H] $^-$: 409.1095, found: 409.1093.

(1*R*,2*S*,3*R*)-6'-formyl-4,4''-dinitro-2'-(pyridin-2-yl)-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-carbonitrile (10c). Major diastereomer. Yield 69%. Red solid. Column chromatography eluent: 3:1 (hexane/EtOAc). Melting point range: 170–175 °C. IR: 2962 cm^{-1} ($\text{HC}=\text{C}$ stretch), 2160 cm^{-1} (nitrile stretch), 1686 cm^{-1} ($\text{C}=\text{O}$ aldehyde stretch), 1603 cm^{-1} (aliphatic $\text{C}=\text{C}$ stretch), 1520 cm^{-1} , 1468 cm^{-1} (aromatic $\text{C}=\text{C}$ stretch). ^1H NMR (400 MHz, CDCl_3) δ 9.57 (s, 1H), 8.52–8.51 (m, 1H), 8.22 (t, J = 8.8 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H), 7.69–7.64 (m, 1H), 7.52 (d, J = 8.7 Hz, 2H), 7.41–7.37 (m, 2H), 7.33–7.29 (m, 2H), 6.93 (d, J = 6.6 Hz, 1H), 4.77 (s, 1H), 3.73 (d, J = 8.9, 6.0 Hz, 1H), 3.16 – 3.05 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 191.1, 154.1, 149.3, 149.0, 147.9, 147.8, 145.8, 144.5, 140.5, 137.2, 130.9, 130.5, 124.1, 123.8, 123.8, 120.0, 53.5, 45.3, 45.0, 30.16. The enantiomeric excess was determined by HPLC using a Chiralpak IB column (hexane/*i*PrOH = 70:30, flow rate 1.0 mL/min, λ = 265 nm): t_r (S) = 29.6, t_r (R) = 31.8, 99% (R) and 99% (S) *ee*. $[\alpha]_D^{19}$ = -235.8° (c = 0.5, CHCl_3) (S catalyst). HRMS m/z (ESI-) Exact mass calculated for $\text{C}_{25}\text{H}_{17}\text{N}_4\text{O}_5$ [M-H] $^-$: 453.1204, found: 453.1206.

(1*R*,2*S*,3*R*)-4,4''-dichloro-6'-formyl-2'-(pyridin-3-yl)-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-carbonitrile (10d). Major diastereomer. Yield 63%. Yellow solid. Column chromatography eluent: 3:1 (hexane/EtOAc). Melting point range: 139–142 °C. IR: 2922 cm^{-1} , 2852 cm^{-1} ($\text{HC}=\text{C}$ stretch), 2222 cm^{-1} (nitrile stretch), 1686 cm^{-1} ($\text{C}=\text{O}$ aldehyde stretch), 1586 cm^{-1} (aliphatic $\text{C}=\text{C}$ stretch), 149 cm^{-1} , 1468 cm^{-1} (aromatic $\text{C}=\text{C}$ stretch). ^1H NMR (400 MHz, CDCl_3) δ 9.52 (s, 1H), 8.53–8.49 (m, 1H), 7.62–7.57 (m, 1H), 7.36–7.34 (m, 3H), 7.30–7.28 (m, 2H), 7.16–7.14 (m, 4H), 6.72–6.70 (m, 2H), 4.58 (s, 1H), 3.61 (dd, J = 9.5, 6.4 Hz, 1H), 2.97–2.84 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 191.7, 154.9, 149.0, 148.9, 140.1, 137.3, 136.6, 135.8, 134.3, 134.2, 131.4, 131.0, 128.8, 128.4, 124.1, 123.5, 120.1, 54.1, 45.4, 43.6, 29.8. The enantiomeric excess was determined by HPLC using Chiralpak IB column (hexane/*i*PrOH = 90:10, flow rate 1.0 mL/min, λ = 265 nm): (S) = 14.7, t_r (R) = 18.6, 99% (R) and 99% (S) *ee*. $[\alpha]_D^{19}$ = +97.0° (c = 0.4, CHCl_3) (S catalyst). HRMS m/z (ESI-) Exact mass calculated for $\text{C}_{25}\text{H}_{17}\text{Cl}_2\text{N}_2\text{O}$ [M-H] $^-$: 431.0723, found: 431.0722.

(1*R*,2*S*,3*R*)-3,3''-dibromo-6'-formyl-2'-(pyridin-2-yl)-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-carbonitrile (10e). Major diastereomer. Yield 45%. Light orange solid. Column chromatography eluent: 3:1 (hexane/EtOAc). Melting point range: 166–168 °C. IR: 3015 cm^{-1} , 2923 cm^{-1} ($\text{HC}=\text{C}$ stretch), 1687 cm^{-1} ($\text{C}=\text{O}$ aldehyde stretch), 1587 cm^{-1} (aliphatic $\text{C}=\text{C}$ stretch), 1427 cm^{-1} , 1428 cm^{-1} (aromatic $\text{C}=\text{C}$ stretch). ^1H NMR (400 MHz, CDCl_3) δ 9.53 (s, 1H), 8.54–8.52 (m, 1H), 7.66–7.60 (m, 1H), 7.49–7.44 (m, 2H), 7.40 – 7.27 (m, 4H), 7.25–7.24 (m, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.10–7.06 (m, 1H), 6.81–6.78 (m, 2H), 4.56 (s, 1H), 3.59 (dd, J = 10.1, 6.0 Hz, 1H), 2.94–2.88 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 191.6, 154.8, 149.1, 148.9, 141.1, 140.5, 139.6, 136.5, 132.6, 131.5, 131.3, 130.1, 129.8, 129.2, 128.1, 124.2, 123.6, 122.7, 122.1, 120.3, 53.9, 45.7, 43.8, 30.0. The enantiomeric excess was determined by HPLC using a Chiralpak IB column (hexane/*i*PrOH = 90:10, flow rate 1.0 mL/min, λ = 265 nm): t_r (S) = 16.1, t_r (R) = 22.7, 99% (R) and 99% (S) *ee*. $[\alpha]_D^{19}$ = +11.7° (c = 0.7, CHCl_3) (S catalyst). HRMS m/z (ESI-) Exact mass calculated for $\text{C}_{25}\text{H}_{17}\text{Br}_2\text{N}_2\text{O}$ [M-H] $^-$: 518.9713, found: 518.9713.

(1*R*,2*S*,3*R*)-6'-formyl-4,4''-dimethyl-2'-(pyridin-2-yl)-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-carbonitrile (10f). Major diastereomer. Yield 33%. Brown oil. Column chromatography eluent: 3:1 (hexane/EtOAc). IR: 2921 cm^{-1} ($\text{HC}=\text{C}$ stretch), 2323 cm^{-1} (nitrile stretch), 1690 cm^{-1} ($\text{C}=\text{O}$ aldehyde stretch), 1587 cm^{-1} , 1573 cm^{-1} (aliphatic $\text{C}=\text{C}$ stretch), 1468 cm^{-1} , 1431 cm^{-1} (aromatic $\text{C}=\text{C}$ stretch). ^1H NMR (400 MHz, CDCl_3) δ 9.53 (s, 1H), 8.52–8.51 (m, 1H), 7.56–7.53 (m, 1H), 7.25 – 7.19 (m, 2H), 7.12–7.10 (m, 3H), 6.99–6.97 (m, 3H), 6.69–6.67 (m, 3H), 4.55 (s, 1H), 3.70–3.66 (m, 1H), 2.88–2.85 (m, 2H), 2.36 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 191.9, 155.5, 148.7, 148.6, 141.1, 137.7, 137.6, 136.0, 135.9, 134.5, 129.9, 129.5, 129.2, 128.7, 124.2, 122.9, 122.0, 54.4, 45.9, 43.3, 30.1, 21.2, 21.0. The enantiomeric excess was determined by HPLC using a Chiralpak IB column (hexane/*i*PrOH = 90:10, flow rate 1.0 mL/min, λ = 250 nm): t_r (S) = 10.7, t_r (R) = 15.1, 99% (R) and 99% (S) *ee*. $[\alpha]_D^{18}$ = +16.3° (c = 0.5, CHCl_3) (R catalyst). HRMS m/z (ESI-) Exact mass calculated for $\text{C}_{25}\text{H}_{23}\text{N}_2\text{O}$ [M-H] $^-$: 391.1816, found: 391.1817.

(1'R,2'S,3'R)-4,4''-difluoro-6'-formyl-2'-(pyridin-2-yl)-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-carbonitrile (10g). Major diastereomer. Yield 63%. Yellow oil. Column chromatography eluent: 3:1 (hexane/EtOAc). IR: 3055 cm⁻¹, 2928 cm⁻¹ (HC=C stretch), 2356 cm⁻¹ (nitrile stretch), 1685 cm⁻¹ (C=O aldehyde stretch), 1603 cm⁻¹, 1588 cm⁻¹ (aliphatic C=C stretch), 1508 cm⁻¹, 1468 cm⁻¹ (aromatic C=C stretch). ¹H NMR (400 MHz, CDCl₃) δ 9.52 (s, 1H), 8.52–8.51 (m, 1H), 7.61–7.56 (m, 1H), 7.35–7.32 (m, 2H), 7.24–7.22 (m, 2H), 7.14–7.12 (m, 2H), 7.09–7.05 (m, 2H), 6.89–6.85 (m, 3H), 4.59 (s, 1H), 3.64 (dd, *J* = 9.6, 6.5 Hz, 1H), 2.96–2.87 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 190.6, 154.0, 147.8, 147.6, 139.9, 135.3, 130.5, 130.5, 130.2, 130.1, 123.1, 122.2, 119.6, 114.5, 114.3, 114.1, 113.9, 53.2, 44.2, 42.1, 29.2. ¹⁹F NMR (376 MHz, CDCl₃) δ -114.09, -114.22. The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/*i*PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm): *t*_r (S) = 30.6, *t*_r (R) = 35.7, 99% (R) and 99% (S) *ee*. [α]_D²¹ = -142.5° (c = 0.3, CHCl₃) (R catalyst). HRMS *m/z* (ESI-) Exact mass calculated for C₂₅H₁₇F₂N₂O [M-H]⁺: 399.1314, found: 399.1316.

(1'R,2'S,3'R)-4,4''-dibromo-6'-formyl-2'-(pyridin-2-yl)-1',2',3',4'-tetrahydro-[1,1':3',1''-terphenyl]-2'-carbonitrile (10h). Major diastereomer. Yield 35%. Yellow solid. Column chromatography eluent: 3:1 (hexane/EtOAc). Melting point range: 173–177 °C. IR: 3018 cm⁻¹, 2929 cm⁻¹ (HC=C stretch), 1685 cm⁻¹ (C=O aldehyde stretch), 1587 cm⁻¹ (aliphatic C=C stretch), 1488 cm⁻¹, 1432 cm⁻¹ (aromatic C=C stretch). ¹H NMR (400 MHz, CDCl₃) δ 9.54 (s, 1H), 8.81–8.76 (m, 1H), 7.59–7.56 (m, 2H), 7.42–7.40 (m, 3H), 7.30–7.28 (m, 2H), 7.20–7.17 (m, 2H), 7.03–7.00 (m, 2H), 4.50 (s, 1H), 3.95–3.90 (m, 1H), 3.14–3.11 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 190.1, 152.7, 148.4, 147.7, 141.7, 139.3, 137.6, 135.2, 133.8, 130.5, 130.1, 129.4, 128.8, 128.1, 122.0, 121.8, 121.0, 49.4, 37.8, 33.5, 28.7. The enantiomeric excess was determined by HPLC using a Chiralpak IE column (hexane/*i*PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm): *t*_r (S) = 32.7, *t*_r (R) = 48.4, 99% (R) and 99% (S) *ee*. [α]_D²¹ = -98.3° (c = 0.6, CHCl₃) (R catalyst). HRMS *m/z* (ESI-) Exact mass calculated for C₂₅H₁₇Br₂N₂O [M-H]⁺: 518.9713, found: 518.9711.

(4aR,5S,6R,7S,8aS)-3-formyl-2,5,7-trimethyl-6-(pyridin-2-yl)-4a,5,6,7,8a-hexahydro-2H-chromene-6-carbonitrile (14). Yellow solid. Column chromatography eluent: 5:1 (hexane/EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 1H), 8.61 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.78 (td, *J* = 7.8, 1.8 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.30–7.25 (m, 1H), 6.99 (bs, 1H), 4.74 (q, *J* = 6.7 Hz, 1H), 3.78–3.64 (m, 1H), 2.89 (dq, *J* = 12.7, 6.4 Hz, 1H), 2.63–2.47 (m, 2H), 2.34 (td, *J* = 12.6, 4.7 Hz, 1H), 1.99–1.89 (m, 1H), 1.43 (d, *J* = 6.7 Hz, 3H), 1.20 (d, *J* = 6.4 Hz, 3H), 0.72 (d, *J* = 7.4 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 192.2, 156.8, 149.1, 148.3, 145.5, 137.5, 123.1, 123.0, 122.0, 68.5, 65.5, 55.7, 45.3, 40.5, 36.4, 32.0, 19.0, 15.8, 14.6. The enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (hexane/*i*PrOH = 95:5, flow rate 1.0 mL/min, λ = 210 nm): *t*_r (S) = 20.2, *t*_r (R) = 21.7, 99% (R) and 99% (S) *ee*. [α]_D²⁰ = -22.4° (c = 0.8, CHCl₃) (R catalyst). HRMS *m/z* (ESI+) Exact mass calculated for C₁₉H₂₃N₂O₂ [M+H]⁺: 311.1754, found: 311.1754.

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Keywords: azaarenes • 2-substituted pyridine • enantioselective • Michael addition • cascade reaction • organocatalysis

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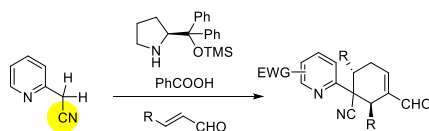
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Organocatalysis

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**Highly enantioselective synthesis of
alkylazaarenes derivatives through
a Michael-Michael-aldol cascade
reaction**



A new methodology for the synthesis of pyridine derivatives based on a triple cascade reaction catalyzed by chiral secondary amines. The resulting cyclohexenes (3 C-C bond were formed) were obtained in good yields, good diastereoselectivities and excellent enantioselectivity

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