Enantioselective One-pot Synthesis of Biaryl-substituted Amines by Combining Palladium and Enzyme Catalysis in Deep Eutectic Solvents

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This document contains 19 Figures and 7 Tables over 23 pages
1. General information

General methods

$^1$H-NMR and proton-decoupled $^{13}$C-NMR spectra (CDCl$_3$) were obtained using a Bruker DPX-300 ($^1$H, 300.13 MHz and $^{13}$C, 75.5 MHz) spectrometer using the $\delta$ scale (ppm) for chemical shifts. Calibration was made on the signal of the solvent ($^{13}$C: CDCl$_3$, 77.16; $^1$H: CDCl$_3$, 7.26). HPLC analyses to determine the degree of conversion were carried out in an Agilent RR1200 HPLC system, using a reversed phase column (Zorbax Eclipse XDB-C18, RR, 18 μm, 4.6 x 50 mm, Agilent). HPLC analyses to determine the ee were performed on a Hewlett Packard 1100 LC liquid chromatograph.
3. Inhibition studies

\[
\begin{align*}
4a & \quad + \quad \text{D-alanine} \\
\xrightarrow{\text{EX-STA}} & \\
5a
\end{align*}
\]

**Figure S1.** Effect of TPPTS.

**Table S1.** Effect of TPPTS.

| conc. TPPTS | mol % | c (%) |
|-------------|-------|-------|
| 2 mM        | 11    | 95 %  |
| 3 mM        | 17    | 74 %  |
| 4 mM        | 22    | 45 %  |

mol %: mole percent with respect to the starting biaryl ketone  
c (%): conversion of the formed amine in the reaction
**Figure S2.** Effect of Pd(TPPTS)$_2$Cl$_2$.

**Table S2.** Effect of Pd(TPPTS)$_2$Cl$_2$.

| conc. Pd(TPPTS)$_2$Cl$_2$ | mol % | c (%) |
|---------------------------|-------|-------|
| 0.18 mM                   | 1     | 81    |
| 0.36 mM                   | 2     | 70    |
| 0.54 mM                   | 3     | 67    |

**Figure S3.** Effect of PhB(OH)$_2$.

**Table S3.** Effect of PhB(OH)$_2$.

| conc. PhB(OH)$_2$ | mol % | c (%) |
|-------------------|-------|-------|
| 10 mM             | 54    | 95    |
| 20 mM             | 100   | 75    |
| 30 mM             | 160   | 72    |
Figure S4. Effect of aryl halide.

Table S4. Effect of aryl halide.

| conc. aryl halide | mol % | c (%) |
|------------------|-------|-------|
| 10 mM            | 54    | 95    |
| 20 mM            | 100   | 93    |
| 30 mM            | 160   | 93    |
3. Spectral data of biaryl amines

The identity of the resulting biaryl amines 5a-e was confirmed by comparison of their $^1$H-NMR spectra with those previously reported.[2]

1-((1,1'-biphenyl)-4-yl)ethanamine (5b)
Colorless oil; $^1$H NMR (300 MHz, CDCl$_3$) δ (ppm): 1.47 (d, $J$ 6.6 Hz, 3H), 1.85 (brs, NH$_2$), 4.21 (q, $J$ 6.6 Hz, 1H), 7.29-7.41 (m, 1H), 7.43-7.49 (m, 4H), 7.53-7.65 (m, 4H); $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 28.1 (CH$_3$), 53.5 (CH), 128.6 (CH), 129.5 (2CH), 129.6 (CH), 129.7 (2CH), 131.2 (2CH), 142.2 (C), 143.4 (C), 149.2 (C) MS (APCI$^+$, m/z): 198 [(M+H)$^+$, 100%]; [$\alpha$]$^1$D$^18$ +18.7 (c 0.5, CHCl$_3$), ee = 99% for (R)-5b.

1-((1,1'-biphenyl)-3-yl)ethanamine (5c)
Colorless oil; $^1$H NMR (300 MHz, CDCl$_3$) δ (ppm): 1.47 (d, $J$ 6.6 Hz, 3H), 1.78 (brs, NH$_2$), 4.21 (q, $J$ 6.6 Hz, 1H), 7.35-7.43 (m, 2H), 7.44-7.54 (m, 4H), 7.60-7.68 (m, 2H); $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 25.9 (CH$_3$), 51.5 (CH), 124.7 (CH), 125.8 (C), 127.2 (2CH), 127.3 (2CH), 128.8 (2CH), 128.9 (2CH), 141.5 (C), 148.3 (C). MS (APCI$^+$, m/z): 198 [(M+H)$^+$, 100%]; [$\alpha$]$^1$D$^18$ +25.2 (c 1.0, CHCl$_3$), ee >99% for (R)-5c.

1-((4-(pyridin-2-yl)phenyl)ethanamine (5d)
White gummy solid; $^1$H NMR (300 MHz, CDCl$_3$) δ (ppm): 1.42 (d, $J$ 6.6 Hz, 3H), 2.66 (brs, NH$_2$), 4.16 (q, $J$ 6.6 Hz, 1H), 7.16-7.21 (m, 1H), 7.45 (d, $J$ 8.1 Hz, 2H), 7.70-7.76 (m, 2H), 7.95 (d, $J$ 8.1 Hz, 2H), 8.68 (d, $J$ 4.8 Hz, 1H); $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 25.3 (CH$_3$), 51.1 (CH), 120.4 (CH), 121.9 (CH), 126.2 (2CH), 127.1 (2CH), 136.7 (CH), 138.1 (C), 147.9 (C), 149.6 (CH), 157.2 (C); MS (APCI$^+$, m/z): 199 [(M+H)$^+$, 100%]; [$\alpha$]$^1$D$^18$ +20.7 (c 1.3, CHCl$_3$), ee = 99% for (R)-5d.

1-((4-(pyridin-3-yl)phenyl)ethanamine (5a)
Colorless oil; $^1$H NMR (300 MHz, CDCl$_3$) δ (ppm): 1.43 (d, $J$ 6.6 Hz, 3H), 2.11 (brs, NH$_2$), 4.18 (q, $J$ 6.6 Hz, 1H), 7.34 (dd, $J$ 8.1 and 4.8 Hz, 1H), 7.45 (d, $J$ 8.1 Hz, 2H), 7.55 (d, $J$ 8.1 Hz, 2H), 7.87 (dt, $J$ 7.8 and 2.1 Hz, 1H), 8.56 (dd, $J$ 4.5 and 1.5 Hz, 1H), 8.83 (d, $J$ 1.2 Hz, 1H); $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 25.6 (CH$_3$), 50.9 (CH), 123.5 (CH), 126.5 (2CH), 127.2 (2CH), 134.3 (CH), 136.3 (C), 136.4 (C), 147.6 (C), 148.1 (CH), 148.2 (CH); MS (APCI$^+$, m/z): 199 [(M+H)$^+$, 100%]; [$\alpha$]$^1$D$^18$ +24.5 (c 1.0, CHCl$_3$), ee = 99% for (R)-5a.
1-(4-(pyridin-4-yl)phenyl)ethanamine (5e)

White gummy solid; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm): 1.41 (d, $J$ 6.6 Hz, 3H), 1.85 (brs, NH$_2$), 4.18 (q, $J$ 6.6 Hz, 1H), 7.40-7.48 (m, 4H), 7.60 (d, $J$ 8.1 Hz, 2H), 8.63 (d, $J$ 4.8 Hz, 1H); $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 25.7 (CH$_3$), 51.0 (CH), 121.5 (2CH), 126.5 (2CH), 127.1 (2CH), 136.6 (C), 148.1 (C), 148.8 (C), 150.2 (2CH); MS (APCI$^+$, m/z): 199 [(M+H)$^+$, 100%]; $[\alpha]_D^{18}$ +23.3 (c 1.0, CHCl$_3$), ee = 99% for (R)-5e.

4. Assignment of the absolute configuration

Optical rotations and retention times in HPLC analyses for each biaryl amine obtained by enzymatic transamination were compared with the ones obtained previously in the single bioamination, confirming the (R)-configuration of the amines unambiguously.$^{[2]}$ The data obtained for the amine 7 was compared with those in the literature.$^{[3]}$
5. HPLC analytical data

5.1. Analytical data for the determination of the degree of conversion (C) of the Suzuki cross-coupling reactions

HPLC Method for 4b,c (Method A): HPLC analyses were carried out in an Agilent chromatographic system, using a reversed phase column (Zorbax Eclipse XDB-C18, RR, 1.8 μm, 4.6 x 50 mm, Agilent) and acetonitrile (MeCN) and 0.1% trifluoroacetic acid (TFA) in water as solvents. Samples were eluted with three linear gradients from 10% to 60% MeCN for 5.70 min, followed by another from 60% to 100% MeCN for 0.5 min and a third gradient from 100% to 10% MeCN for 1.90 min, at a flow rate of 2 ml/min. Detection and spectral characterization of peaks were performed at 220 nm with a diode array detector and ChemStation Rev.B.03.01 software (Agilent).

HPLC Method for 4a,d,e (Method B): HPLC analyses were carried out in an Agilent chromatographic system, using a reversed phase column (Zorbax Eclipse XDB-C18, RR, 1.8 μm, 4.6 x 50 mm, Agilent) and acetonitrile (MeCN) and 0.1% triethylamine (Et₃N) in water as solvents. Samples were eluted with three linear gradients from 10% to 60% MeCN for 5.70 min, followed by another from 60% to 100% MeCN for 0.5 min and a third gradient from 100% to 10% MeCN for 1.90 min, at a flow rate of 1.50 ml/min. Detection and spectral characterization of peaks were performed at 278 nm with a diode array detector and ChemStation Rev.B.03.01 software (Agilent).

Table S5. Determination of C (%) in Suzuki cross-coupling reactions

| Method | Retention time (t_R, min) | Monoarylketone  | Biarylketone |
|--------|--------------------------|-----------------|--------------|
| B      | a                        | 2.9             | 4a           | 3.8          |
| A      | b                        | 4.5             | 4b           | 5.8          |
| A      | c                        | 4.8             | 4c           | 5.9          |
| B      | d                        | 2.7             | 4d           | 5.6          |
| B      | e                        | 2.8             | 4e           | 3.8          |
5.2. **Analytical data for the determination of the degree of conversion (C) of the bioamination reactions**

The methods described above, namely Method A and B, were also used for the determination of the conversion in the second step.

**Table S6. Determination of c (%) in bioamination reactions**

| Method | Retention time (tR, min) | Ketone | Amine |
|--------|--------------------------|--------|-------|
|        |                          | tR     | tR    |
| A      | 6                        | 3.2    | 7     |
| B      | 4a                       | 3.8    | 5a    |
| A      | 4b                       | 5.8    | 5b    |
| A      | 4c                       | 5.9    | 5c    |
| B      | 4d                       | 5.6    | 5d    |
| B      | 4e                       | 3.8    | 5e    |

5.3. **Analytical data for determination of enantiomeric excess**

HPLC conditions using a chiral column are shown in the following table. Assignment of the configuration for every peak is also included. Detection of peaks (UV absorption) was performed at 210 and 278 nm.

**Table S7. Chiral HPLC analysis of the resulting biaryl amines using Hexane/Propan-2-ol mixtures and 0.8 mL/min flow.**

| Compound | Column | Eluent (Hex/ i-PrOH) | T (°C) | tR (min) |
|----------|--------|-----------------------|--------|----------|
| 7a       | OD     | 96:4                  | 40     | 21.7 (S), 23.9 (R) |
| 5a<sup>b</sup> | AD-H   | 75:25                | 40     | 8.1 (S), 8.7 (R) |
| 5b<sup>b</sup> | AD-H   | 90:10                | 30     | 7.2 (R), 8.3 (S) |
| 5c<sup>b</sup> | AD-H   | 90:10                | 40     | 6.2 (R), 7.4 (S) |
| 5d<sup>b</sup> | AD-H   | 75:25                | 40     | 6.3 (R), 7.9 (S) |
| 5e<sup>b</sup> | AD-H   | 85:15                | 40     | 10.5 (R), 11.5 (S) |

<sup>a</sup> Derivatized as Acetamide-derivative <sup>b</sup> Derivatized as Boc-derivative.
6. Copy of chiral-HPLC chromatograms

Figure S5. Determination of enantiomeric excess of 5a.

(R)-5a in >99% ee after the chemoenzymatic cascade

Figure S6. Determination of the enantiomeric excess of 5b.

(R)-5b in >99% ee after the chemoenzymatic cascade
**Figure S7.** Determination of the enantiomeric excess of 5c.

(R)-5c in >99% ee after the chemoenzymatic cascade

**Figure S8.** Determination of enantiomeric excess of 5d.

(R)-5d in >99% ee after the chemoenzymatic cascade
Figure S9 Determination of the enantiomeric excess of 5e.

(R)-5e in >99% ee after the chemoenzymatic cascade
7. HPLC analysis for the determination of conversion in the one-pot process

Figure S10. In process HPLC monitoring for the sequential preparation of 5a
Figure S11. In process HPLC monitoring for the sequential preparation of 5b

first step

second step
Figure S12. In process HPLC monitoring for the sequential preparation of 5c.
Figure S13. In process HPLC monitoring for the sequential preparation of 5d
**Figure S14.** In process HPLC monitoring for the sequential preparation of 5e
8. Copy of NMR spectra

1-(4-(pyridin-3-yl)phenyl)ethanamine (5a)

Figure S15. $^1$H and $^{13}$C-NMR spectra of 5a in CDCl$_3$. 
1-((1,1'-biphenyl)-4-yl)ethanamine (5b)

Figure S16. $^1$H and $^{13}$C-NMR spectra of 5b in CDCl$_3$. 
1-((1,1'-biphenyl)-3-yl)ethanamine (5c)

Figure S17. $^1$H and $^{13}$C-NMR spectra of 5c in CDCl$_3$. 
1-(4-(pyridin-2-yl)phenyl)ethanamine (5d)

Figure S18. $^1$H and $^{13}$C-NMR spectra of 5d in CDCl$_3$. 
1-(4-(pyridin-4-yl)phenyl)ethanamine (5e)

Figure S19. $^1$H and $^{13}$C-NMR spectra of 5e in CDCl₃.
9. References

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