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Alkylation Amination of Biogenic Furans via Imine-to-Azaallyl Anion Umpolung

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Abstract: Starting from biogenic furfurals, an operationally simple and scalable condensation-umpolung-alkylation protocol was employed in the synthesis of racemic furfurylamines. Subsequent enzymatic kinetic resolution by o-transaminase or lipase biocatalysts allows for the preparation of functionalized heterocyclic building blocks from biogenic base chemicals in optically pure form.

Keywords: furfural, amines, umpolung, biocatalysis, transaminase

Furfurals are generally considered to be highly important intermediates in cellulosic and lignocellulosic biorefinery scenarios and thus represent key entities in potential post-fossil value chains.1 However, while strategies for the transformation of biogenic furans into fuels, polymers and basic bulk chemicals have lately attracted major scientific interest, their role as rich source of fine chemicals is yet considered an underdeveloped area.2 Nonetheless, with an increasing sensitivity for resource-consciousness also functionalizing approaches will gain in importance. Apart from being an attractive synthetic target itself, furans offer a broad spectrum of follow-up chemistry including cycloadditions,3 ring cleavage,4 and ring expansion reactions5 as well as serving as masked carboxylic acid derivatives.6 With our recent entrance into furan valorisation chemistry,7 we became interested in the direct conversion of furan-based aldehydes (1) from second generation biorefinery to synthetically useful functional building blocks. Inspired by the work of Walsh, Buchwald and others on the use of aldehyde-derived azaallyl anions as nucleophiles in C-C-coupling reactions,8 we designed a concise route for the synthesis of substituted furfurylamines exploiting this kind of reactivity umpolung (Scheme 1). Here, we envisaged that by condensation with an appropriate benzylic amine such as diphenylaminomethane, furfurylidene amines could be obtained that would serve as C-nucleophiles upon deprotonation and could be alkylated at the formerly aldehydic carbon. Hydrolysis of the thus formed benzophenone imine would finally liberate the desired α-branched primary amines (2). Using readily available amino donors and classical electrophilic alkylating agents, we imagined that such a protocol would represent a concise and well applicable alternative to traditional imine alkylation pathways.9

Scheme 1 Reactivity umpolung of furfurals through azaallyl anion formation

The general synthesis of α-benzhydrylimines has been previously reported in detail and usually comprises treatment of the carbonyl compound with diphenylmethyamine in aprotic solvents in the presence of dehydrating agents or with the azeotropic removal of water.10 Consequently, also the condensation of freshly distilled furfural (1a) with benzhydrylamine in dichloromethane or toluene with an excess of MgSO₄ proceeded smoothly and gave rise to the desired imine 3a in 90% and 87% yield, respectively (Table 1, entries 1–2). However, simply for practical reasons it seemed attractive to avoid solid desiccants or any other additive whatsoever. To our delight, condensation was taking place also in bench-grade ethanol in an open flask from where the so formed imine precipitated out of solution and was isolated in high purity by simple filtration and drying in vacuo in 93% yield (Table 1, entry 3). In the same way, a series of substituted furfurals derived from hydroxymethylfurfural (HMF) was reacted with benzhydrylamine. In all cases, very high yields were achieved without the necessity for further purification of the thus obtained aldimines 3b–3f (Table 1, entries 4–8).
electrophiles. Strikingly, replacement of tetrahydrofuran as solvent by N,N-dimethylformamide resulted in a dramatical rate acceleration (Table 2, entries 8). For other polar aprotic solvents such as acetonitrile or dimethylsulfoxide, this effect was less pronounced. Although, the regioselectivity in the DMF-based system was slightly diminished, the high absolute yield of 2a and the convenience of short reaction times (<15 min) at mild temperature convinced us to pursue our subsequent studies under these conditions.

Table 1 Imine formation: solvent screening and substrate scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Furural</th>
<th>Solvent</th>
<th>Additive</th>
<th>Yield [%]</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>1a</td>
<td>CH₂Cl₂</td>
<td>MgSO₄</td>
<td>3a, 90</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>1a</td>
<td>toluene</td>
<td>MgSO₄</td>
<td>3a, 87</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>1a</td>
<td>EtOH</td>
<td></td>
<td>3a, 93</td>
</tr>
<tr>
<td>4</td>
<td>CH₃</td>
<td>1b</td>
<td>EtOH</td>
<td></td>
<td>3b, 92</td>
</tr>
<tr>
<td>5</td>
<td>CH₂OMe</td>
<td>1c</td>
<td>EtOH</td>
<td></td>
<td>3c, 84</td>
</tr>
<tr>
<td>6</td>
<td>CH₂OMOM</td>
<td>1d</td>
<td>EtOH</td>
<td></td>
<td>3d, 86</td>
</tr>
<tr>
<td>7</td>
<td>CH₂OBn</td>
<td>1e</td>
<td>EtOH</td>
<td></td>
<td>3e, 91</td>
</tr>
<tr>
<td>8</td>
<td>CH₂OAc</td>
<td>1f</td>
<td>EtOH</td>
<td></td>
<td>3f, 93</td>
</tr>
</tbody>
</table>

*a Representative reaction conditions: 1a (100 mmol), benzhydrylamine (100 mmol), MgSO₄ (0–500 mmol), solvent (400 ml) at room temperature for 18 h.

With the furylimines in hand, we turned our attention to the envisioned formation and trapping of their correspondingazaallyl anions. Treatment of 3a with solid KOtBu (1.2 eq.) in dry THF at room temperature led to the immediate formation of a deep red solution that was further stirred for 15 min. To study the effect of the reaction temperature, the azaallyl anion solution was cooled down, followed by the dropwise addition of allyl bromide. The thus formed turquoise coloured suspension was stirred overnight at the indicated temperature (Table 2), then the reaction mixture was hydrolyzed by aqueous HCl for 2 h at room temperature. At ~78 °C, the allylation proceeded sluggishly and after 18 h low conversion and an almost statistical mixture of homoallylamine 2a and the undesired regioisomer 4a was obtained (Table 2, entry 1). With increasing temperature both yield and regioselectivity in favour of 2a increased (Table 2, entry 2) and optimal results were achieved by running the reaction at room temperature (Table 2, entry 3). In subsequent optimization rounds, KOtBu prevailed as base of choice. The use of other alkoxides such as KOtPr, LiOrBu or NaOrBu (Table 2, entry 4) resulted in comparable product ratios between 2a and 4a at slightly reduced yields. Stronger bases like potassium hexamethyldisilazide or n-butyllithium on the other hand did not allow for a productive allylation (Table 2, entry 5). A change of the electrophile from allyl bromide to allyl iodide had only marginal influence (Table 2, entry 6). We speculated that the sterical properties of the reactive electrophilic species might influence the regioselectivity of this transformation in a beneficial fashion. Thus, diallyl carbonate in combination with [allylPdCl₂] and bis(diarylphosphino)butane as catalyst was employed as allylation reagent (Table 2, entry 7), providing a bulky dppb-S⁺-allyl palladium complex as reactive entity. Though also the palladium-catalyzed allylic substitution of the in situ formed azaallyl anion proved to be efficient with a total yield of 83%, in contrast to our expectations the reaction turned out less selective as compared to the use of simple allyl halides as electrophiles. Strikingly, replacement of tetrahydrofuran as solvent by N,N-dimethylformamide resulted in a dramatical rate acceleration (Table 2, entries 8). For other polar aprotic solvents such as acetonitrile or dimethylsulfoxide, this effect was less pronounced. Although, the regioselectivity in the DMF-based system was slightly diminished, the high absolute yield of 2a and the convenience of short reaction times (<15 min) at mild temperature convinced us to pursue our subsequent studies under these conditions.

Table 2 Effect of base, temperature, solvent and electrophilic agent on the allylation of imine 3a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>T [°C]</th>
<th>Solvent</th>
<th>X</th>
<th>2a [%]</th>
<th>4a [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOtBu</td>
<td>−78</td>
<td>THF</td>
<td>Br</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>KOtBu</td>
<td>−20</td>
<td>THF</td>
<td>Br</td>
<td>46</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>KOtBu</td>
<td>25</td>
<td>THF</td>
<td>Br</td>
<td>51</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>NaOrBu</td>
<td>25</td>
<td>THF</td>
<td>Br</td>
<td>42</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>nBuLi</td>
<td>25</td>
<td>THF</td>
<td>Br</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>KOtBu</td>
<td>25</td>
<td>THF</td>
<td>I</td>
<td>51</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>KOtBu</td>
<td>25</td>
<td>THF</td>
<td>OAlloc</td>
<td>58</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td>KOtBu</td>
<td>0</td>
<td>DMF</td>
<td>Br</td>
<td>72</td>
<td>27</td>
</tr>
</tbody>
</table>

*a Reaction conditions: 3a (2.0 mmol), base (2.2 mmol), allylic electrophile (3.0 mmol), solvent (10 ml). Isolated yield of mixtures of 2a and 4a, ratios determined by 1H-NMR. b Reaction in presence of [allylPdCl₂] (2 mol%) and dppb (2.5 mol%). c Reaction time: 15 min.

Based on this optimized protocol, various imines were reacted with a series of electrophilic halides to yield a set of functionalized primary amines (Scheme 2). In all cases, the in situ formed azaallyl anions were quickly consumed after addition of the alkyl halides at 0 °C in DMF. After removal of the solvent in vacuo, the crude mixture of imines was hydrolyzed and bulb-to-bulb distillation delivered the pure amines 2a – 2l. On a 5-mmol-scale, the α-allylated furfurylamine 2a was obtained in 67% yield. In the same way, also simple electrophiles such as methyl iodide, ethyl bromide and butyl bromide gave rise to the corresponding amino products in 72% (2b), 62% (2c) and 80% (2d) yield, respectively. Notably, scale-up (25 mmol) of the imine methylation proceeded smoothly and 2b was obtained in this case in excellent 93%. Functionalized electrophiles proved to be well accepted by the method. Thus, both benzylated 2e as well as propargylated 2f could be isolated after bulb-to-bulb distillation in good yield. Moreover, also the 5-methylfurfurylidene amine 3b showed similar behaviour and the 2,5-disubstituted furfurylamines 2g and 2h were isolated in 70% and 73% yield, respectively. Unfortunately, protected HMF-derived imines proved to be much more troublesome as precursors in the azaallyl anion alkylation. While the...
methylether-functionalized amine 2i was still obtained in a low yield of 12%, all other tested imines suffered from pronounced decomposition under the previously employed alkylation conditions. Hence, further development of this method to allow for the preparation of the synthetically highly interesting HMF-derived amine products will be of great importance.

On the longer run, the ever-growing demand for optically pure chiral building blocks will serve as great motivation for the development of asymmetric variants of this method by means of e.g. chiral counterions or ligand-controlled transition metal-catalyzed procedures. In many cases, however, kinetic resolution has proved to be a very reliable and straightforward method for the preparation of enantiomerically enriched building blocks from readily accessible racemates. Based on our recent studies on the development of novel biocatalytic and chemoenzymatic synthetic approaches,11 we aimed to couple the described synthesis of furfuryleammines with subsequent enzyme-catalyzed solutions to obtain optically pure amino compounds. In the past years, transaminases have emerged as powerful and highly applicable catalyst family in the context of stereoselective amine synthesis.12 During the screening of a small commercial library of ω-transaminases, ATA 025 was identified as suitable biocatalyst for the oxidative kinetic resolution of 1-furfurylalkylamines. Incubation of amine rac-2a with pyruvate as amino acceptor in presence of ATA 025 and pyridoxal phosphate (PLP) resulted in a fast depletion of (R)-2a under the formation of acetylfuran as oxidation product and after 24 h, (S)-2a was isolated 45% yield in highly enantioenriched form (98% ee). Gratifyingly, another protein from the kit, ATA 251, showed opposite selectivity and could successfully be employed in the preparation of (R)-2a (46%, 99% ee). Hence, by the right choice of the biocatalyst both enantiomers are accessible via simple deaminative kinetic resolution. Alternatively, using lipases as enantiodiscriminating catalyst, an acylative kinetic resolution could be achieved. Here, lipase B from C. antarctica (Novozym 435) catalyzed the selective amidation of (R)-2b my means of isopropyl acerate as donor to give acetamide (R)-2b. In this approach, conserving also the chiral integrity of the resolution product, both enantiomers were obtained in almost enantiopure form ((S)-2a: 98% ee; (R)-enantiomer as acetamide (R)-5a: 99% ee).

Scheme 3 Oxidative and acylative kinetic resolution

In summary, a preparatively convenient, flexible and scalable route towards 1-furfurylalkylamines was developed. Using inexpensive furfurals and alkyl halides in combination with benzhydroxylamine as nitrogen source, a condensation-umpolung-alkylation protocol allows for the generation of up to gram quantities of a variety of synthetically interesting, substituted chiral furfurylamines. On the basis of subsequent enzymatic kinetic resolutions, either by ω-transaminase-catalyzed oxidation or lipase-catalyzed acylation, both (R)- and (S)-enantiomers are accessible in excellent optical purity. Currently, further optimization with regard to the transformation of hydroxymethylfurfural-derived imines as well as in-depth studies on the enzymatic resolution processes are ongoing work in our group.

Experimental section

All reactions carried out under argon atmosphere were performed with dry solvents using anhydrous conditions. Anhydrous THF was freshly distilled from sodium and benzophenone, anhydrous MeCN was distilled from CaH2, anhydrous DMF was obtained from Acros Organics. Lipase B from Candida antarctica was obtained from Sigma (L4777, Novozym 435, lipase acrylic resin from Candida antarctica), all aminotransferases tested (incl. ATA 025 and ATA 251) were obtained from Stem (96-7125, Codexis ATA Screening Kit). Commercially available reagents were used without further purification. All products were purified either by column chromatography over silica gel (Macherey-Nagel MN-Kieselgel 60, 40-60 μm, 240-400 mesh) or by recrystallization. Reactions were monitored by thin layer chromatography (TLC) carried out on precoated silica gel plates (Macherey-Nagel, TLC Silica gel 60 F254) using UV
light and KMnO₄-solution or Hanessian’s stain for visualization. Uncorrected melting points were measured on a Büchi melting point apparatus using open glass capillaries. ¹H-NMR and ¹³C-NMR spectra were recorded at room temperature on a Bruker AV-300 instrument. Chemical shifts are reported in parts per million (ppm) calibrated using residual non-deuterated solvents as internal reference (CDCl₃ at 7.26 ppm) (¹H-NMR) and 77.00 ppm (¹³C-NMR). Infrared spectra were recorded on a Shimadzu IRAffinity-1 FT-IR-spectrometer, absorption bands are reported in wave numbers [cm⁻¹]. High resolution mass spectrometry was performed on a Finnigan MAT 900 S by electrospray ionization or an Agilent 8940A GC-System using a Macherey-Nagel FS- Lipodex E (25 m x 0.25 mm), Ns, 1.4 ml min⁻¹; 65 °C (8 min) / 8 °C min⁻¹ (4.4 min) / 10 °C min⁻¹ (4 min) / 140 °C (15 min).

General procedure for the preparation of furfurylidene imines

At room temperature, benzhydrylamine (18.3 g, 100 mmol) in ethanol (400 mL) and the reaction mixture was stirred overnight. Product precipitation was observed in most cases and could be further promoted by ice-bath cooling or by adding a few drops of water. The solids were filtered off, washed with cold diethyl ether and recrystallized from ethanol to yield analytically pure imines.

**N-Furfurylidene-N-(diphenylmethyl)amine (3a)**

According to the general procedure, 3a (24.2 g, 92.6 mmol, 93%) was obtained as pale yellow crystals; mp 102 °C; Rf = 0.60 (cyclohexane/ethyl acetate, 3/1).

¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 8.18 (s, 1H), 7.52 (d, J = 1.4 Hz, 1H), 7.24-7.47 (m, 10H), 6.79 (d, J = 3.4 Hz, 1H), 6.46 (dd, J = 3.4 Hz, J = 1.7 Hz, 1H), 5.57 (s, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ [ppm] = 151.9, 149.8, 145.0, 143.4, 128.5, 127.9, 127.1, 114.5, 111.7, 78.1.

FT-IR (neat, ATR): ν [cm⁻¹] = 3435 (br w), 2877 (w), 2841 (w), 1645 (s), 1492 (m), 1483 (m), 1446 (m), 1390 (m), 1273 (m), 1102 (s), 933 (s), 879 (m), 854 (m), 759 (s), 732 (s), 707 (s), 696 (s), 657 (m).

GC-MS: M = 575 (5), m/z (% rel. intensity) = 275 (82, 55%), 232 (12), 198 (13), 167 (100), 152 (38), 128 (8), 115 (8), 104 (5), 99 (10), 79 (11), 51 (11).

Anal. calcd (%) for C₇₅H₇NO: C 78.67, H 6.29, N 5.08; found: C 78.87, H 6.29, N 5.05.

**N-5-(Methoxymethyl)furfurylidene-N-(diphenylmethyl)amine (3c)**

According to the general procedure, 3c (1.64 g, 5.37 mmol, 84%) was obtained as beige solid; mp 89 °C; Rf = 0.44 (cyclohexane/ethyl acetate, 3/1).

¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 8.14 (s, 1H), 7.31-7.33 (m, 8H), 7.20-7.25 (m, 2H), 6.80 (d, J = 3.3 Hz, 1H), 6.40 (d, J = 3.3 Hz), 5.59 (s, 1H), 4.44 (s, 2H), 3.37 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ [ppm] = 154.6, 152.0, 150.1, 143.3, 128.5, 128.0, 127.2, 114.7, 111.0, 77.8, 66.7, 58.3.

FT-IR (neat, ATR): ν [cm⁻¹] = 3105 (w), 3028 (w), 2860 (w), 1633 (s), 1525 (m), 1492 (m), 1446 (m), 1377 (m), 1294 (m), 1274 (m), 1193 (m), 1085 (s), 1035 (m), 1018 (m), 1001 (m), 954 (m), 935 (m), 821 (m), 786 (m), 759 (m), 723 (m), 694 (s), 657 (m).

GC-MS: M = 575 (4), m/z (% rel. intensity) = 305 (15, 56%), 274 (4), 260 (2), 232 (3), 207 (3), 196 (3), 180 (3), 167 (100), 152 (23), 139 (3), 128 (3), 115 (7), 104 (3), 91 (12), 77 (7), 65 (10), 51 (10).

Anal. calcd (%) for C₇₅H₇NO: C 78.69, H 6.27, N 4.58; found: C 78.47, H 6.31, N 4.52.

**N-5-(Methoxymethoxymethyl)furfurylidene-N-(diphenylmethyl)amine (3d)**

According to the general procedure, 3d (1.74 g, 5.19 mmol, 86%) was obtained as beige solid; mp 42 °C; Rf = 0.39 (cyclohexane/ethyl acetate, 3/1).

¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 8.15 (s, 1H), 7.31-7.33 (m, 3H), 7.20-7.25 (m, 2H), 6.60 (d, J = 3.3 Hz, 1H), 6.41 (d, J = 3.3 Hz, 5.59 (s, 1H), 4.68 (s, 2H), 4.58 (s, 2H), 3.39 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ [ppm] = 154.2, 152.1, 150.1, 143.3, 128.5, 128.0, 127.1, 114.7, 111.1, 95.7, 77.8, 66.7, 61.2, 55.5.

FT-IR (neat, ATR): ν [cm⁻¹] = 3105 (w), 2945 (w), 2860 (w), 1637 (s), 1492 (m), 1446 (m), 1367 (m), 1294 (m), 1276 (m), 1199 (m), 1145 (s), 1093 (m), 1026 (s), 997 (m), 979 (s), 800 (m), 748 (m), 671 (w).
935 (s), 921 (m), 785 (m), 758 (m), 748 (m), 696 (s), 655 (m).

GC-MS: t_R = 17.2 min; m/z (% rel. intensity) = 335 (33, M^+), 274 (14), 167 (100), 152 (16), 139 (2), 115 (3), 96 (2), 77 (2), 51 (2).

Anal. calcd (%) for C_{2}H_{6}NO: C 75.20, H 6.31, N 4.17; found: C 74.91, H 6.32, N 4.09.

N-5-(Benzyloxyethyl)furfurylidene-N-(diphenylmethyl)amine (3e)

According to the general procedure, 3e (2.42 g, 6.34 mmol, 91 %) was obtained as beige solid; mp 74 °C; R_f = 0.36 (cyclohexane/ethyl acetate, 3/1).

1^H-NMR (300 MHz, CDCl_3): δ [ppm] = 8.13 (s, 1H), 7.18-7.36 (m, 15H), 6.78 (d, J = 3.3 Hz, 1H), 6.39 (d, J = 3.3 Hz), 5.58 (s, 1H), 4.55 (s, 2H), 4.51 (s, 2H).

1^3C-NMR (75 MHz, CDCl_3): δ [ppm] = 154.6, 151.9, 150.0, 143.3, 137.8, 128.5, 128.0, 127.8, 127.1, 114.8, 111.0, 77.8, 72.4, 64.2.

FT-IR (neat, ATR): v [cm^{-1}] = 3026 (w), 2852 (w), 1635 (s), 1492 (m), 1446 (m), 1363 (m), 1276 (m), 1267 (m), 1215 (m), 1089 (s), 1070 (s), 1020 (s), 977 (m), 948 (s), 810 (m), 785 (m), 761 (m), 736 (s), 725 (m), 696 (s), 655 (m).

GC-MS: t_R = 19.4 min; m/z (% relative intensity) = 381 (10, M^+), 274 (2), 167 (100), 152 (16), 139 (2), 128 (2), 115 (3), 105 (3), 91 (24), 73 (17), 65 (12), 51 (2).

Anal. calcd (%) for C_{2}H_{6}NO: C 81.86, H 6.07, N 3.67; found: C 81.98, H 6.19, N 3.65.

General procedure for the preparation of furfurylamines

The corresponding imine (5.0 mmol) was dissolved in anhydrous N,N-dimethylformamide (25 mL). At 0 °C, potassium tert-butoxide (673 mg, 6.0 mmol) was added and the deep red solution was stirred for 5 min. After addition of the alkyl halide (7.5 mmol) stirring was continued for 15 min. The reaction mixture was diluted with water (15 mL) water and saturated sodium bicarbonate solution (25 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over MgSO_4 and concentrated under reduced pressure and excess N,N-dimethylformamide was removed in high vacuum. The residue was redissolved in methanol (25 mL) and hydrochloric acid (1 N, 25 mL) was added. The solution was stirred at room temperature for 2 h, then extracted with diethyl ether (3 x 50 mL). At 0 °C, the aqueous layer was brought to pH > 12 by addition of aqueous sodium hydroxide solution (5 N) and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over MgSO_4, volatiles were removed in vacuo and the crude product was purified by bulb-to-bulb distillation (40-140 °C, 0.3 mbar).

1-(2-Furyl)but-3-enylamine (2a)

According to the general procedure using allyl bromide (907 mg, 7.5 mmol), 2b (460 mg, 3.36 mmol, 67 %) was obtained as colourless liquid.

1^H-NMR (300 MHz, CDCl_3): δ [ppm] = 7.29 (dd, J = 1.8 Hz, J = 0.8 Hz, 1H), 6.25 (dd, J = 3.1, 1.8 Hz, 1H), 6.10-6.09 (m, 1H), 5.73 (ddt, J = 17.1 Hz, J = 10.0 Hz, J = 7.0 Hz, 1H), 5.13-5.04 (m, 2H), 3.96 (dd, J = 7.2 Hz, J = 5.8 Hz, 1H), 2.49-2.59 (m, 1H), 2.30-2.45 (m, 1H), 1.54 (br s, 2H).

1^3C-NMR (75 MHz, CDCl_3): δ [ppm] = 158.6, 141.3, 137.4, 117.8, 109.9, 104.3, 49.2, 40.9.

FT-IR (neat, ATR): v [cm^{-1}] = 3369 (br w), 3076 (w), 2978 (w), 2912 (br w), 1639 (w), 1600 (br w), 1506 (w), 1438 (w), 1359 (w), 1332 (w), 1147 (m), 1072 (br w), 1008 (s), 916 (br s), 883 (s), 846 (br s), 804 (s), 731 (s).

1-(2-Furyl)ethylamine (2b)

In analogy to the general procedure using imine 3a (6.53 g, 25 mmol), potassium tert-butoxide (3.37 g, 30 mmol) and isodomethane (5.30 g, 37.5 mmol), 2b (2.58 g, 23.2 mmol, 93 %) was obtained as colourless liquid.

1^H-NMR (300 MHz, CDCl_3): δ [ppm] = 7.32 (d, J = 1.6 Hz, 1H), 1.68 (dd, J = 3.2 Hz, J = 1.6 Hz, 1H), 6.08 (d, J = 3.2 Hz, 4.06 (q, J = 6.7 Hz, 1H), 1.53 (br s, 2H), 1.41 (d, J = 6.7 Hz, 3H).

1^3C-NMR (75 MHz, CDCl_3): δ [ppm] = 160.4, 141.3, 110.1, 103.3, 45.2, 22.2.

FT-IR (neat, ATR): v [cm^{-1}] = 2972 (w), 1583 (br m), 1506 (w), 1450 (br w), 1355 (br w), 1319 (w), 1147 (m), 1006 (m), 927 (m), 873 (br m), 806 (br m), 731 (s).

GC: Lipodox E, t_R(S)-2b) = 7.7 min; t_R(R)-2b) = 8.2 min.

1-(2-Furyl)propylamine (2c)

According to the general procedure using bromoethane (817 mg, 7.5 mmol), 2c (390 mg, 3.11 mmol, 62 %) was obtained as colourless liquid.

1^H-NMR (300 MHz, CDCl_3): δ [ppm] = 7.32 (dd, J = 1.8 Hz, J = 0.8 Hz, 1H), 6.29 (dd, J = 3.3 Hz, J = 1.8 Hz, 1H), 6.10 (d, J = 3.3 Hz, 1H), 3.82 (t, J = 6.7 Hz, 1H), 1.81 (ddq, J = 13.5 Hz, J = 7.3 Hz, J = 6.7 Hz, 1H), 1.68 (ddq, J = 13.5 Hz, J = 7.3 Hz, J = 6.7 Hz, 1H), 1.54 (br s, 2H), 0.91 (t, J = 7.3 Hz, 3H).
1H-NMR (300 MHz, CDCl₃): δ [ppm] = 5.98 (d, J = 2.9 Hz, 1H), 5.87 (d, J = 2.9 Hz, 1H), 3.76 (t, J = 6.8 Hz, 1H), 2.25 (s, 3H), 1.81 (ddq, J = 13.9 Hz, J = 7.3 Hz, J = 6.8 Hz, 1H), 1.67 (ddq, J = 13.9 Hz, J = 7.3 Hz, J = 6.8 Hz, 1H), 1.47 (br s, 2H), 0.93 (t, J = 7.3 Hz, 3H).

13C-NMR (75 MHz, CDCl₃): δ [ppm] = 157.4, 150.8, 105.7, 105.0, 51.4, 29.4, 13.6, 10.7.

FT-IR (neat, ATR): v [cm⁻¹] = 2962 (w), 2924 (w), 2875 (w), 1562 (br w), 1454 (br w), 1319 (br w), 1219 (m), 1018 (m), 960 (w), 877 (br m), 779 (s), 732 (w), 702 (w).

1-(5-Methyl-2-furyl)propylamine (2i)

According to the general procedure using 2-propanol (817 mg, 7.5 mmol), 2i (40 mg, 0.23 mmol, 12%) was obtained as colourless liquid.

1H-NMR (300 MHz, CDCl₃): δ [ppm] = 6.23 (d, J = 3.1 Hz, 1H), 6.06 (d, J = 3.1 Hz, 1H), 4.35 (s, 2H), 3.81 (t, J = 6.7 Hz, 1H), 3.35 (s, 3H), 1.82 (ddq, J = 6.7 Hz, J = 7.4 Hz, J = 13.2 Hz 1H), 1.68 (ddq, J = 6.7 Hz, J = 7.4 Hz, J = 13.2 Hz, 1H), 1.67 (br s, 2H), 0.92 (t, J = 7.4 Hz, 3H).

13C-NMR (75 MHz, CDCl₃): δ [ppm] = 159.9, 150.5, 110.0, 105.0, 66.6, 57.8, 51.5, 29.4, 10.6.

FT-IR (neat, ATR): v [cm⁻¹] = 2962 (w), 2929 (w), 2893 (w), 1598 (w), 1552 (w), 1492 (w), 1452 (w), 1377 (w), 1359 (w), 1190 (w), 1178 (w), 1085 (s), 1018 (m), 941 (m), 898 (br m), 788 (s), 752 (m), 700 (s).

Procedure for the transaminase-catalyzed kinetic resolution

ATA-025 (20 mg) or ATA-251 (10 mg) was added to a solution of rac-2b (200 mg, 1.79 mmol), sodium pyruvate (120 mg, 1.09 mmol) and pyridoxal-5-phosphate (10 mg, 0.04 mmol) in phosphate buffer (40 mL, 100 mM, pH 8.0) and the reaction mixture was stirred at 40 °C for 24 h (ATA-025) or 42 h (ATA-251), respectively, monitored by
GC. Aqueous sodium hydroxide (5 N, 15 mL) was added and the solution was extracted with ethyl acetate (3 x 50 mL). The solvent was removed in vacuo and the residue was redissolved in methanol (30 mL) and NaBH₄ (90 mg, 2.38 mmol) was added. After complete reduction of acetylfuran (monitored by TLC), hydrochloric acid (1N, 20 mL) was added and the solution was extracted with diethyl ether (3 x 75 mL). These extracts were discarded.

The aqueous layer was adjusted to pH 12 by addition of aqueous sodium hydroxide (5 N) and the extract with diethyl ether (3 x 75 mL). The combined organic extracts were dried over MgSO₄ and the volatiles were carefully removed in vacuo to yield the amines: ATA-025: (S)-2b (90 mg, 0.81 mmol, 45%, 98% ee); ATA-251: (R)-2b (91 mg, 0.82 mmol, 46%, 99% ee). Optical purity was determined by GC from the corresponding acetamide 5b after derivatization with acetic anhydride.

Procedure for the lipase-catalyzed kinetic resolution
Novozym 435 (10 mg, lipase B from C. antarctica) was added to a solution of 2b (200 mg, 1.79 mmol) and isopropyl acetate (0.32 mL, 2.7 mmol) in methyl tert-butyl ether (4 mL) and the reaction mixture was placed in an orbital shaker at 35 °C. After 26 h, another portion of Novozym 435 (20 mg) and isopropyl acetate (0.1 mL, 0.81 mmol) was added. After 48 h, the reaction mixture was mixed with hydrochloric acid (1N, 15 mL) and the aqueous phase was extracted with diethyl ether (3 x 40 mL). The combined organic extracts were dried over MgSO₄, filtered and the volatiles were removed in vacuo.

Acetamide (R)-5b was obtained as colourless solid (95 mg, 0.62 mmol, 35%, 99% ee); mp 47-49 °C; Rf = 0.22 (cyclohexane/ethyl acetate, 3/7). The aqueous layer was adjusted to pH 12 by addition of aqueous sodium hydroxide (5 N, 15 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic extracts were dried over MgSO₄ and the volatiles were carefully removed in vacuo.

(S)-2b was obtained as colourless liquid (80 mg, 0.72 mmol, 40%, 98% ee).¹³

³¹C-NMR (75 MHz, CDCl₃): δ [ppm] = 169.2, 155.5, 141.8, 110.2, 105.5, 42.9, 23.2, 19.6.

FT-IR (neat, ATR): ν [cm⁻¹] = 3271 (br m), 3066 (w), 2980 (w), 2935 (w), 1641 (br s), 1541 (br s), 1504 (s), 1448 (m), 1371 (s), 1307 (m), 1278 (m), 1232 (w), 1151 (s), 1124 (m), 1097 (w), 1074 (w), 1039 (w), 1008 (s), 966 (m), 921 (m), 808 (br m), 734 (br s), 666 (w), 566 (w), 534 (w), 490 (w), 435 (20 s), 3271 (br m), 30 435 (20 s), 3271 (br m), 30

GC: Lipodox E, ts((S)-5b) = 20.1 min; ts((R)-5b) = 20.9 min.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toe/synthesis.

References and Notes


(13) Due to the relatively high volatility, 2b was obtained as mixture with diethyl ether, compound ratios were determined by 1H-NMR. Complete removal of the ethereal solvent resulted also in substantial loss of the amine product.