Synthesis F. Blume et al. Paper

Alkylative Amination of Biogenic Furans through Imine-to-Azaallyl Anion Umpolung

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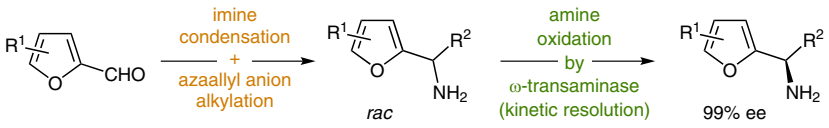
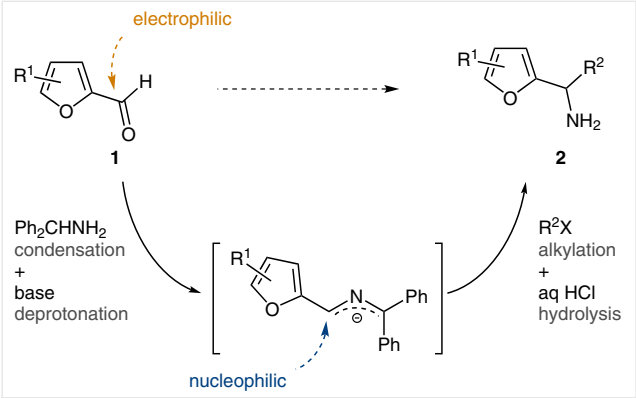


Received: 03.02.2015
Accepted after revision: 20.03.2015
Published online: 19.05.2015
DOI: 10.1055/s-0034-1380201; Art ID: ss-2015-t0084-op

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 ω-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 a rich source of fine chemicals is so far considered an underdeveloped area.[2] Nonetheless, with an increasing sensitivity for resource-intensive processes, functionalizing approaches are expected to 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 reactions[5] 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 into 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 that exploited 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 widely applicable alternative to traditional imine alkylation pathways.[9]

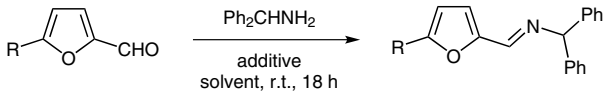


Scheme 1 Reactivity umpolung of furfurals through azaallyl anion formation

The general synthesis of *N*-benzhydrylimines has been previously reported in detail and usually comprises treatment of the carbonyl compound with diphenylmethylamine 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 $MgSO_4$ proceeded smoothly and gave rise to the desired imine **3a** in 90 and 87% yield, respectively (Table 1, entries 1 and 2). However, for practical reasons, it seemed attractive to avoid solid desiccants or any other additive. To our delight, condensation was also found to take place in bench-grade ethanol in an open flask from which the imine precipitated out of solution and was isolated in high purity by simple filtration and drying in vacuo in 93%

yield (entry 3). In the same way, a series of substituted furfurals derived from hydroxymethylfurfural (HMF) were allowed to react with benzhydrylamine. In all cases, very high yields were achieved without the necessity for further purification of the thus obtained aldimines **3b**–**f** (entries 4–8).

Table 1 Imine Formation: Solvent Screening and Substrate Scope[a]



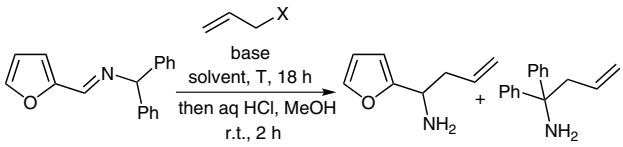
1a–f **3a–f**

Entry	R	Furfural	Solvent	Additive	3	Yield (%)
1	H	**1a**	CH_2Cl_2	$MgSO_4$	**3a**	90
2	H	**1a**	toluene	$MgSO_4$	**3a**	87
3	H	**1a**	EtOH	–	**3a**	93
4	Me	**1b**	EtOH	–	**3b**	92
5	CH_2OMe	**1c**	EtOH	–	**3c**	84
6	CH_2OMOM	**1d**	EtOH	–	**3d**	86
7	CH_2OBn	**1e**	EtOH	–	**3e**	91
8	CH_2OAc	**1f**	EtOH	–	**3f**	93

[a] Reaction conditions: **1a** (100 mmol), benzhydrylamine (100 mmol), $MgSO_4$ (0–500 mmol), solvent (400 mL), r.t., 18 h.

With the furylimines in hand, we turned our attention to the envisioned formation and trapping of their corresponding azaallyl anions. Treatment of **3a** with solid potassium *tert*-butoxide (1.2 equiv) in anhydrous tetrahydrofuran at room temperature led to the immediate formation of a deep-red solution that was further stirred for 15 minutes. To study the effect of the reaction temperature, the azaallyl anion solution was cooled and allyl bromide was added dropwise. The turquoise suspension thus formed was stirred overnight at the indicated temperature (Table 2), then the reaction mixture was hydrolyzed with aqueous HCl for two hours at room temperature. At –78 °C, the allylation proceeded sluggishly and, after 18 hours, low conversion and an almost statistical mixture of homoallylamine **2a** and the undesired regioisomer **4a** was obtained (entry 1). With increasing temperature, both yield and regioselectivity in favour of **2a** increased (entry 2) and optimal results were achieved by running the reaction at room temperature (entry 3). In subsequent optimisation rounds, potassium *tert*-butoxide prevailed as base of choice. The use of other alkoxides such as potassium isopropoxide, lithium *tert*-butoxide, or sodium *tert*-butoxide (entry 4) resulted in comparable product ratios between **2a** and **4a** in slightly reduced yields. Stronger bases such as potassium hexamethyldisilazide or *n*-butyllithium, on the other hand, did not allow a productive allylation (entry 5). A change in the electrophile from allyl bromide to allyl iodide had only a marginal influence (entry 6). We speculated that the steric properties of the reactive electrophilic species might influence the regioselectivity of this transformation in a beneficial fashion. Thus, diallyl carbonate in combination with $[allylPdCl]_2$ and bis(diphenylphosphino)butane as catalyst was employed as allylation reagent (entry 7), providing a bulky dppb-η^3-allylpalladium complex as reactive entity. Although the palladium-catalysed allylic substitution of the azaallyl anion formed in situ also proved to be efficient, with a total yield of 83%, in contrast to our expectations, the reaction turned out to be less selective than the use of simple allyl halides as electrophiles. Strikingly, replacement of tetrahydrofuran as solvent by *N*,*N*-dimethylformamide resulted in a dramatic rate acceleration (entries 8). For other polar aprotic solvents such as acetonitrile or dimethyl sulfoxide, this effect was less pronounced. Although the regioselectivity in the *N*,*N*-dimethylformamide-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**[a]



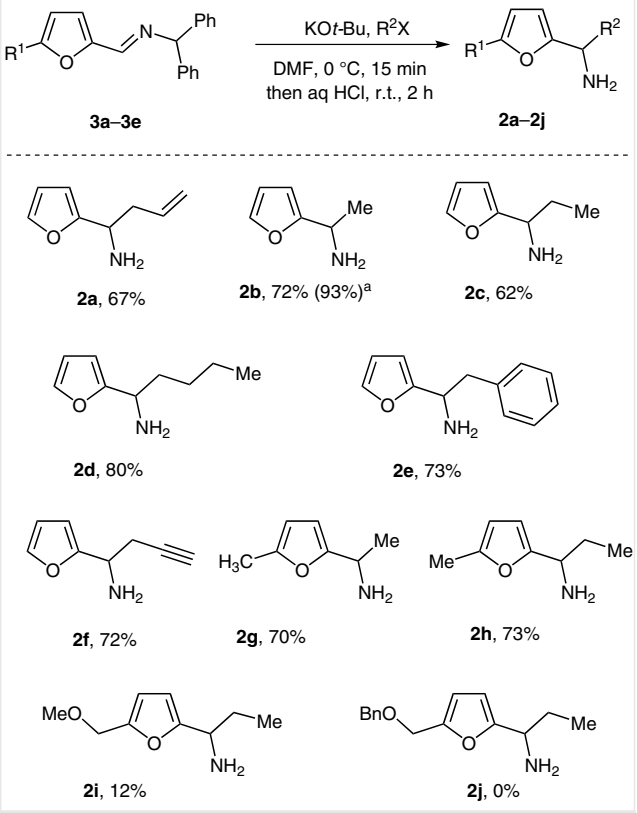
3a **2a** **4a**

Entry	Base	Temp (°C)	Solvent	X	**2a** (%)[b]	**4a** (%)[b]
1	*t*-BuOK	–78	THF	Br	16	12
2	*t*-BuOK	–20	THF	Br	46	22
3	*t*-BuOK	25	THF	Br	51	24
4	*t*-BuONa	25	THF	Br	42	16
5	*n*-BuLi	25	THF	Br	–	–
6	*t*-BuOK	25	THF	I	51	6
7[c]	*t*-BuOK	25	THF	OAlloc	58	25
8[d]	*t*-BuOK	0	DMF	Br	72	27

[a] Reaction conditions: **3a** (2.0 mmol), base (2.2 mmol), allylic electrophile (3.0 mmol), solvent (10 mL).
[b] Isolated yield of mixtures of **2a** and **4a**; ratios determined by ^1H NMR analysis.
[c] Reaction in the presence of $[allylPdCl]_2$ (2 mol%) and dppb (2.5 mol%).
[d] Reaction time: 15 min.

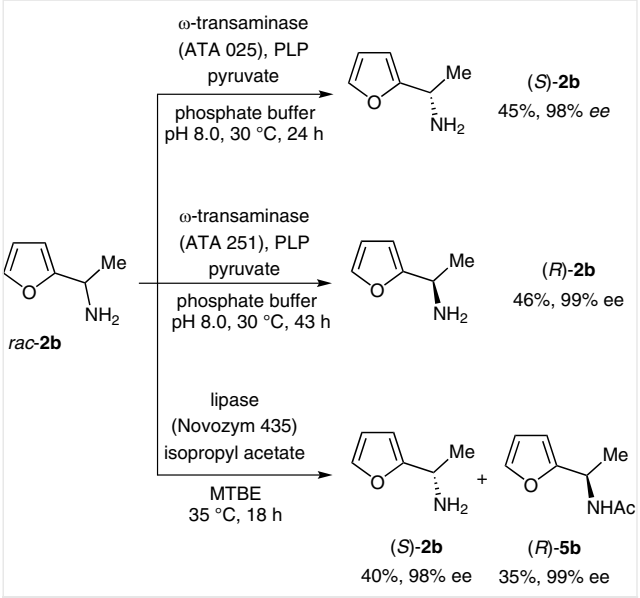
Based on this optimised protocol, various imines were reacted with a series of electrophilic halides to yield a set of functionalized primary amines (Scheme 2). In all cases, the azaallyl anions formed in situ were quickly consumed after addition of the alkyl halides at 0 °C in *N*,*N*-dimethylformamide. After removal of the solvent in vacuo, the crude mixture of imines was hydrolysed and bulb-to-bulb distillation delivered the pure amines **2a**–**i**. On a 5 mmol scale, the α-

allylated furfurylamine **2a** was obtained in 67% yield. In the same way, simple electrophiles such as methyl iodide, ethyl bromide, and butyl bromide also 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 an excellent yield of 93%. Functionalised electrophiles proved to be widely 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, 5-methylfurfurylidene amine **3b** also showed similar behaviour, and 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 prenucleophiles in the azaallyl anion alkylation. Whereas methyl ether functionalised 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.



Scheme 2 Substrate scope and limitations. [a] Yield on 25 mmol scale.

In the long 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, for example, chiral counterions or ligand-controlled transition-metal-catalysed 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 furfurylamines with subsequent enzyme-catalysed solutions to obtain optically pure amino compounds. Transaminases have emerged as a 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 a suitable biocatalyst for the oxidative kinetic resolution of 1-furylalkylamines. As shown in Scheme 3, incubation of amine *rac*-**2b** with pyruvate as amino acceptor in the presence of ATA 025 and pyridoxal phosphate (PLP) resulted in rapid depletion of (*R*)-**2b** and the formation of acetylfuran as oxidation product, and, after 24 hours, (*S*)-**2b** was isolated in 45% yield in highly enantioenriched form (98% ee). Gratifyingly, another protein from the kit, ATA 251, showed the opposite selectivity and could be successfully employed in the preparation of (*R*)-**2b** (46%, 99% ee). Hence, by the right choice of the biocatalyst, both enantiomers are accessible through 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) catalysed the selective amidation of (*R*)-**2b** my means of isopropyl acetate as donor to give acetamide (*R*)-**5b**. In this approach, conserving also the chiral integrity of the resolu-



Scheme 3 Oxidative and acylative kinetic resolution

tion product, both enantiomers were obtained in almost enantiomerically pure form [(*S*)-**2a**: 98% ee; *R*-enantiomer as acetamide (*R*)-**5a**: 99% ee].

In summary, an operationally convenient, flexible and scalable route towards 1-furylalkylamines has been developed. By using inexpensive furfurals and alkyl halides in combination with benzhydrylamine 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-catalysed oxidation or lipase-catalysed acetylation, both *R*- and *S*-enantiomers are accessible in excellent optical purity. Further optimisation with regard to the transformation of hydroxymethylfurfural-derived imines as well as in-depth studies on the enzymatic resolution processes is ongoing in our group.

All reactions that were carried out under an argon atmosphere were performed with anhydrous solvents under anhydrous conditions. Anhydrous THF was freshly distilled from sodium and benzophenone, anhydrous MeCN was distilled from CaH_2, 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 (including ATA 025 and ATA 251) were obtained from Strem (96-7125, Codexis ATA Screening Kit); proteins from the kit are also individually available from Codexis. 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 recrystallisation. Reactions were monitored by thin-layer chromatography (TLC) carried out on precoated silica gel plates (Macherey-Nagel, TLC Silica gel 60 F_{254}) using UV light and $KMnO_4$ solution or Hanessian's stain for visualisation. Uncorrected melting points were measured with a Büchi melting-point apparatus using open glass capillaries. ^{1}H and ^{13}C NMR spectra were recorded at r.t. with a Bruker AV-300 instrument. Chemical shifts are reported in parts per million (ppm) calibrated by using residual non-deuterated solvents as internal reference [$CHCl_3$ at δ = 7.26 ppm (^{1}H NMR) and δ = 77.00 ppm (^{13}C NMR)]. IR spectra were recorded with a Shimadzu IR Affinity-1 FTIR spectrometer; absorption bands are reported in wavenumbers (cm^{-1}). High-resolution mass spectrometry was performed with a Finnigan MAT 900 S by electrospray ionisation. For standard resolution, either an Agilent LC/MSD VL with electrospray ionisation or an Agilent 8940A GC-System with a mass detector 5975 employing helium as carrier gas was used. Gas chromatography was performed with a Hewlett Packard HP 6890 Series GC System using a Macherey-Nagel FS- Lipodex E (25 m × 0.25 mm) column, N_2, 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).

Preparation of Furfurylidene Imines; General Procedure

At r.t., benzhydrylamine (18.3 g, 100 mmol) was added to a solution of the aldehyde (100 mmol) in EtOH (400 mL) and the reaction mixture was stirred overnight. Product precipitation was observed in most cases and could be further promoted by cooling with an ice-bath or by adding a few drops of water. The solids were filtered off, washed with cold Et_2O and recrystallised from EtOH to yield analytically pure imines.

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

Yield: 24.2 g (92.6 mmol, 93%); pale-yellow crystals; mp 102 °C; R_f = 0.60 (cyclohexane–EtOAc, 3:1).

FTIR (neat, ATR): 3435 (br w), 2877 (w), 1645 (s), 1446 (m), 1273 (m), 1020 (s), 933 (s), 759 (s), 732 (s), 696 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18 (s, 1 H), 7.52 (d, *J* = 1.4 Hz, 1 H), 7.24–7.47 (m, 10 H), 6.79 (d, *J* = 3.4 Hz, 1 H), 6.46 (dd, *J* = 3.4, 1.7 Hz, 1 H), 5.57 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.9, 149.8, 145.0, 143.4, 128.5, 127.9, 127.1, 114.5, 111.7, 78.1.

GC-MS (t_R = 15.0 min): *m*/*z* (%) = 261 (32) [M^+], 167 (100), 149 (12), 128 (5), 77 (5), 51 (6).

Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.78; N, 5.36. Found: C, 82.63; H, 5.80; N, 5.33.

N-5-Methylfurfurylidene-*N*-(diphenylmethyl)amine (3b)

Yield: 25.4 g (92.3 mmol, 92%); beige crystals; mp 100 °C; R_f = 0.60 (cyclohexane–EtOAc, 3:1).

FTIR (neat, ATR): 3024 (w), 2877 (w), 1643 (s), 1525 (m), 1386 (m), 1022 (s), 941 (m), 781 (m), 736 (m), 698 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 0.7 Hz, 1 H), 7.13–7.29 (m, 10 H), 6.59 (d, *J* = 3.3 Hz, 1 H), 6.00 (dd, *J* = 3.3, 0.9 Hz, 1 H), 5.50 (s, 1 H), 2.29 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.8, 150.5, 149.8, 143.5, 128.5, 128.1, 127.1, 116.6, 108.3, 77.8, 14.1.

GC-MS (t_R = 15.5 min): *m*/*z* (%) = 275 (82) [M^+], 232 (12), 198 (13), 167 (100), 152 (38), 128 (8), 115 (8), 104 (5), 99 (10), 79 (11), 51 (11).

Anal. Calcd for $C_{19}H_{17}NO$: C, 82.87; H, 6.22; N, 5.08. Found: C, 82.90; H, 6.29; N, 5.05.

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

Yield: 1.64 g (5.37 mmol, 84%); beige solid; mp 89 °C; R_f = 0.44 (cyclohexane–EtOAc, 3:1).

FTIR (neat, ATR): 3028 (w), 2860 (w), 1633 (s), 1525 (m), 1377 (m), 1085 (s), 1018 (m), 954 (m), 786 (m), 694 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 7.31–7.33 (m, 8 H), 7.20–7.25 (m, 2 H), 6.80 (d, *J* = 3.3 Hz, 1 H), 6.40 (d, *J* = 3.3 Hz), 5.59 (s, 1 H), 4.44 (s, 2 H), 3.37 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6, 152.0, 150.1, 143.3, 128.5, 128.0, 127.2, 114.7, 111.0, 77.8, 66.7, 58.3.

GC-MS (t_R = 15.7 min): *m*/*z* (%) = 305 (15) [M^+], 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 $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.58. Found: C, 78.47; H, 6.31; N, 4.52.

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

Yield: 1.74 g (5.19 mmol, 86%); beige solid; mp 42 °C; R_f = 0.39 (cyclohexane–EtOAc, 3:1).

FTIR (neat, ATR): 3105 (w), 2860 (w), 1637 (s), 1492 (m), 1145 (s), 1026 (s), 935 (s), 921 (m), 785 (m), 696 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.15 (s, 1 H), 7.31–7.33 (m, 8 H), 7.20–7.25 (m, 2 H), 6.80 (d, *J* = 3.3 Hz, 1 H), 6.41 (d, *J* = 3.3 Hz), 5.59 (s, 1 H), 4.68 (s, 2 H), 4.58 (s, 2 H), 3.39 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.2, 152.1, 150.1, 143.3, 128.5, 128.0, 127.1, 114.7, 111.1, 95.7, 77.8, 61.2, 55.5.

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

Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.17. Found: C, 74.91; H, 6.32; N, 4.09.

N-5-(Benzyloxymethyl)furfurylidene-*N*-(diphenylmethyl)amine (3e)

Yield: 2.42 g (6.34 mmol, 91%); beige solid; mp 74 °C; R_f = 0.36 (cyclohexane–EtOAc, 3:1).

FTIR (neat, ATR): 3026 (w), 2852 (w), 1635 (s), 1492 (m), 1089 (s), 1070 (s), 948 (s), 810 (m), 736 (s), 696 (s) cm^{-1}.

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

^{13}C NMR (75 MHz, $CDCl_3$): δ = 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.

GC-MS (t_R = 19.4 min): *m*/*z* (%) = 381 (10) [M^+], 274 (2), 167 (100), 152 (16), 139 (2), 128 (2), 115 (3), 105 (3), 91 (24), 77 (13), 65 (12), 51 (13).

Anal. Calcd for $C_{26}H_{23}NO_2$: C, 81.86; H, 6.07; N, 3.67. Found: C, 81.98; H, 6.19; N, 3.65.

N-5-(Acetoxymethyl)furfurylidene-*N*-(diphenylmethyl)amine (3f)

Yield: 1.55 g (4.64 mmol, 93%); colourless crystals; mp 97 °C; R_f = 0.64 (cyclohexane–EtOAc, 3:1).

FTIR (neat, ATR): 3086 (w), 1734 (s), 1633 (m), 1226 (m), 1031 (m), 765 (m), 698 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.16 (s, 1 H), 7.23–7.35 (m, 10 H), 6.67 (d, *J* = 3.4 Hz, 1 H), 6.07 (d, *J* = 3.3 Hz, 1 H), 5.61 (s, 1 H), 5.08 (s, 2 H), 2.08 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 152.3, 152.0, 149.9, 143.2, 128.5, 128.0, 127.2, 114.9, 112.5, 77.9, 58.2, 20.9.

Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.43; H, 5.73; N, 4.20.

Preparation of Furfurylamines; General Procedure

The corresponding imine (5.0 mmol) was dissolved in anhydrous DMF (25 mL). At 0 °C, *t*-BuOK (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 H_2O (15 mL) and saturated sodium bicarbonate solution (25 mL), and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure and excess DMF was removed under high vacuum. The residue was redissolved in MeOH (25 mL) and HCl (1 M, 25 mL) was added. The solution was stirred at r.t. for 2 h, then extracted with Et_2O (3 × 50 mL). At 0 °C, the aqueous layer was brought to pH >12 by addition of aqueous sodium hydroxide solution (5 M) and extracted with Et_2O (3 × 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)

Prepared according to the general procedure using allyl bromide (907 mg, 7.5 mmol).

Yield: 460 mg (3.36 mmol, 67%); colourless liquid.

FTIR (neat, ATR): 3369 (br w), 3076 (w), 2978 (w), 1639 (w), 1147 (m), 1008 (s), 916 (br s), 883 (s), 804 (s), 731 (s) cm^{-1}.

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

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6, 141.3, 134.7, 117.8, 109.9, 104.3, 49.2, 40.9.

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

Prepared by the general procedure using imine **3a** (6.53 g, 25 mmol), *t*-BuOK (3.37 g, 30 mmol), and iodomethane (5.30 g, 37.5 mmol).

Yield: 2.58 g (23.2 mmol, 93%); colourless liquid.

FTIR (neat, ATR): 2972 (w), 1583 (br m), 1147 (m), 1006 (m), 927 (m), 873 (br m), 806 (br m), 731 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 1.6 Hz, 1 H), 6.28 (dd, *J* = 3.2, 1.6 Hz, 1 H), 6.08 (d, *J* = 3.2 Hz, 1 H), 4.06 (q, *J* = 6.7 Hz, 1 H), 1.53 (br s, 2 H), 1.41 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4, 141.3, 110.1, 103.3, 45.2, 22.2.

GC (Lipodex E): t_R = 7.7 [(*S*)-**2b**], 8.2 [(*R*)-**2b**] min.

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

Prepared according to the general procedure using bromoethane (817 mg, 7.5 mmol).

Yield: 390 mg (3.11 mmol, 62%); colourless liquid.

FTIR (neat, ATR): 2964 (w), 2875 (w), 1593 (br w), 1506 (w), 1147 (m), 1074 (w), 1006 (m), 883 (br w), 731 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.32 (dd, *J* = 1.8, 0.8 Hz, 1 H), 6.29 (dd, *J* = 3.3, 1.8 Hz, 1 H), 6.10 (d, *J* = 3.3 Hz, 1 H), 3.82 (t, *J* = 6.7 Hz, 1 H), 1.81 (ddq, *J* = 13.5, 7.3, 6.7 Hz, 1 H), 1.68 (ddq, *J* = 13.5, 7.3, 6.7 Hz, 1 H), 1.54 (br s, 2 H), 0.91 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 141.3, 110.0, 104.3, 51.4, 29.6, 10.5.

1-(2-Furyl)pentylamine (2d)

Prepared according to the general procedure using 1-bromobutane (1.03 g, 7.5 mmol).

Yield: 610 mg (3.98 mmol, 80%); colourless liquid.

FTIR (neat, ATR): 2956 (m), 2858 (m), 2360 (w), 1593 (bw), 1147 (m), 1008 (m), 912 (m), 883 (m), 729 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.27 (dd, *J* = 1.7, 0.8 Hz, 1 H), 6.24 (dd, *J* = 3.1, 1.7 Hz, 1 H), 6.05 (d, *J* = 3.1 Hz, 1 H), 3.83 (t, *J* = 6.9 Hz, 1 H), 1.61–1.80 (m, 4 H), 1.15–1.36 (m, 4 H), 0.84 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 141.1, 109.9, 104.0, 49.8, 36.2, 28.3, 22.5, 13.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_9H_{16}NO$: 154.1226; found: 154.1226.

1-(2-Furyl)-2-phenylethylamine (2e)

Prepared according to the general procedure using benzyl bromide (1.28 g, 7.5 mmol).

Yield: 680 mg (3.64 mmol, 73%); colourless liquid.

FTIR (neat, ATR): 3026 (w), 1602 (br w), 1494 (w), 1145 (w), 1008 (m), 883 (m), 731 (s), 698 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 1.8 Hz, 1 H), 7.19–7.29 (m, 3 H), 7.11–7.14 (m, 2 H), 6.27 (dd, *J* = 3.1, 1.8 Hz, 1 H), 6.07 (d, *J* = 3.1 Hz, 1 H), 4.18 (dd, *J* = 8.2, 5.3 Hz, 1 H), 3.14 (dd, *J* = 13.4, 5.3 Hz, 1 H), 2.87 (dd, *J* = 13.4, 8.2 Hz, 1 H), 1.47 (br s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.2, 141.3, 138.3, 129.3, 128.4, 126.5, 110.1, 104.8, 51.2, 43.1.

1-(2-Furyl)-3-butynylamine (2f)

Prepared according to the general procedure using propargyl bromide (892 mg, 7.5 mmol).

Yield: 488 mg (3.61 mmol, 72%); colourless liquid.

FTIR (neat, ATR): 3294 (w), 2914 (w), 1600 (br w), 1427 (w), 1143 (w), 1008 (m), 883 (m), 734 (s), 640 (br s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.33 (dd, *J* = 1.8, 0.6 Hz, 1 H), 6.30 (dd, *J* = 3.2, 1.8 Hz, 1 H), 6.21 (d, *J* = 3.2 Hz, 1 H), 4.12 (dd, *J* = 7.3, 5.2 Hz, 1 H), 2.70 (ddd, *J* = 16.6, 5.1, 2.6 Hz, 1 H), 2.56 (ddd, *J* = 16.6, 7.3, 2.6 Hz, 1 H), 2.04 (t, *J* = 2.6 Hz, 1 H), 1.74 (br s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.1, 141.5, 110.1, 104.9, 80.9, 70.7, 48.7, 26.8.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_8H_{10}NO$: 136.0757; found: 136.0756.

1-(5-Methyl-2-furyl)ethylamine (2g)

Prepared according to the general procedure using iodomethane (1.06 g, 7.5 mmol).

Yield: 440 mg (3.51 mmol, 70%); colourless liquid.

FTIR (neat, ATR): 2968 (w), 2922 (w), 1564 (w), 1219 (m), 1018 (m), 862 (br m), 781 (s), 698 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.91 (d, *J* = 2.9 Hz, 1 H), 5.81 (m, 1 H), 3.96 (q, *J* = 6.7 Hz, 1 H), 2.22 (s, 3 H), 1.62 (br s, 2 H), 1.34 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6, 150.7, 105.7, 103.8, 45.1, 22.1, 13.4.

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

Prepared according to the general procedure using bromoethane (817 mg, 7.5 mmol).

Yield: 510 mg (3.66 mmol, 73%); colourless liquid.

FTIR (neat, ATR): 2962 (w), 2875 (w), 1562 (br w), 1219 (m), 1018 (m), 960 (w), 877 (br m), 779 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.98 (d, *J* = 2.9 Hz, 1 H), 5.87 (d, *J* = 2.9 Hz, 1 H), 3.76 (t, *J* = 6.8 Hz, 1 H), 2.25 (s, 3 H), 1.81 (ddq, *J* = 13.9, 7.3, 6.8 Hz, 1 H), 1.67 (ddq, *J* = 13.9, 7.3, 6.8 Hz, 1 H), 1.47 (br s, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 150.8, 105.7, 105.0, 51.4, 29.4, 13.6, 10.7.

1-[5-(Methoxymethyl)-2-furyl]propylamine (2i)

Prepared according to the general procedure using bromoethane (817 mg, 7.5 mmol).

Yield: 40 mg (0.23 mmol, 12%); colourless liquid.

FTIR (neat, ATR): 2962 (w), 2893 (w), 1552 (w), 1190 (w), 1085 (s), 1018 (m), 941 (m), 788 (s), 700 (s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.23 (d, *J* = 3.1 Hz, 1 H), 6.06 (d, *J* = 3.1 Hz, 1 H), 4.35 (s, 2 H), 3.81 (t, *J* = 6.7 Hz, 1 H), 3.35 (s, 3 H), 1.82 (dqd, *J* = 6.7, 7.4, 13.2 Hz, 1 H), 1.68 (dqd, *J* = 6.7, 7.4, 13.2 Hz, 1 H), 1.67 (br s, 2 H), 0.92 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.9, 150.5, 110.0, 105.0, 66.6, 57.8, 51.5, 29.4, 10.6.

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), and the reaction was monitored by GC analysis. Aqueous NaOH (5 M, 15 mL) was added and the solution was extracted with EtOAc (3 × 50 mL). The solvent was removed in vacuo and the residue was redissolved in MeOH (30 mL) and $NaBH_4$ (90 mg, 2.38 mmol) was added. Upon complete reduction of acetylfuran (reaction monitored by TLC), HCl (1 M, 20 mL) was added and the solution was extracted with Et_2O (3 × 75 mL). These extracts were discarded. The aqueous layer was adjusted to pH 12 by addition of aqueous NaOH (5 M) and then extracted with Et_2O (3 × 75 mL). The combined organic extracts was dried over $MgSO_4$ and the volatiles were carefully removed in vacuo to give 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).[13] Optical purity was determined by GC analysis from the corresponding acetamide **5b** after derivatisation with acetic anhydride.

Lipase-Catalysed 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 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 HCl (1 M, 15 mL) and the aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo. Acetamide (*R*)-**5b** was obtained as a colourless solid (95 mg, 0.62 mmol, 35%, 99% ee); mp 47–49 °C; R_f = 0.22 (cyclohexane–EtOAc, 3:7). The aqueous layer was adjusted to pH 12 by addition of aqueous NaOH (5 M, 15 mL) and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and the volatiles were carefully removed in vacuo. (*S*)-**2b** was obtained as colourless liquid (80 mg, 0.72 mmol, 40%, 98% ee).[13]

Compound 5b

FTIR (neat, ATR): 3271 (br m), 2935 (w), 1641 (br s), 1504 (s), 1371 (s), 1151 (s), 1008 (s), 966 (m), 921 (m), 734 (br s) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.29 (dd, ^3J = 1.8 Hz, ^4J = 0.8 Hz, 1 H), 6.26 (dd, ^3J = 3.1 Hz, ^3J = 1.8 Hz, 1 H), 6.11–6.15 (m, 1 H), 6.08–6.27 (br s, 1 H), 5.16 (dq, ^3J = 6.9 Hz, ^3J = 6.9 Hz, 1 H), 1.93 (s, 3 H), 1.43 (d, ^3J = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.2, 155.5, 141.8, 110.2, 105.5, 42.9, 23.2, 19.6.

GC (Lipodex E): t_R = 20.1 [(*S*)-**5b**], 20.9 [(*R*)-**5b**] min.

Acknowledgment

We gratefully acknowledge financial support provided by the Fonds der Chemischen Industrie (Liebig fellowship for J.D.), the Deutsche Forschungsgemeinschaft (DE1599/4-1) and the Dr.-Otto-Röhm-Gedächtnisstiftung.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380201.

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