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ORIGINAL PAPER

2-Amino-1,3,5-triazine chemistry: hydrogen-bond networks, Takemoto thiourea catalyst analogs, and olfactory mapping of a sweet-smelling triazine

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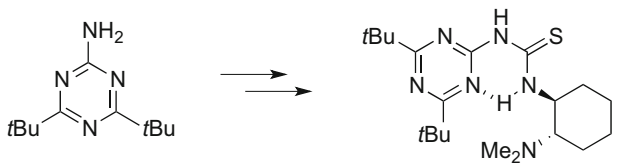
Abstract The chemistry of 4,6-dialkyl-2-amino-1,3,5-triazines with bulky alkyl substituents was investigated and their use as building blocks for preparing chiral thiourea organocatalysts explored. Reaction of ammonia with 4,6-di-*tert*-butyl-2-chloro-1,3,5-triazine gave 4,6-di-*tert*-butyl-1,3,5-triazin-2-amine which formed extended hydrogen-bond networks in the solid state according to X-ray crystallography. Selected heterocyclic amines were converted to isothiocyanates, and the latter reacted with (*S*,*S*)-2-(dimethylamino)cyclohexylamine to give enantiopure 1-hetaryl-3-[2-(dimethylamino)cyclohexyl]thioureas, with hetaryl representing either 4,6-dimethyl-1,3-diazin-2-yl, 4,6-diisopropyl-1,3,5-triazin-2-yl, or 4,6-di-*tert*-butyl-1,3,5-triazin-2-yl groups. These compounds are structural analogs of Takemotos's chiral thiourea organocatalysts (1-[3,5-bis(trifluoromethyl)phenyl]-3-[(1*S*,2*S*)-2-(dimethylamino)cyclohexyl]thiourea) with an aza-aryl instead of the 3,5-bis(trifluoromethyl)phenyl group. They feature a strong intramolecular N–H to N-1 hydrogen bond, as shown by X-ray crystallography of 1-(4,6-di-*tert*-butyl-1,3,5-triazin-2-yl)-3-[2-(dimethylamino)cyclohexyl]thiourea in the solid state and by ^{1}H NMR spectroscopy of all derivatives in $CDCl_3$ solution, which prevents them from acting as bifunctional organocatalyst. In the reaction of 4,6-di-*tert*-butyl-2-chloro-1,3,5-triazine with ammonia, 4,6-di-*tert*-butyl-2-ethoxy-1,3,5-triazine was identified as side-product displaying a mildly sweet, floral odor that is unusual for a 1,3,5-triazine. Analogs (>35) of 4,6-di-*tert*-butyl-2-ethoxy-1,3,5-triazine were prepared to define the important structural factors of the olfactophore.

Graphical abstract



Keywords Amines · Heterocycles · Hydrogen bonds · Odoriferous substances · Triazines

Introduction

Symmetric 1,3,5-triazines have been used as architectural elements in the building of designed target structures in coordination chemistry and crystal engineering [1–3], for UV-filters [4–7], molecular opto-electronics [8–10], extended organic solids [11, 12], or symmetric molecules in general [13]. The bulk availability of cyanuric chloride by trimerization of cyanogen chloride [14] and the possibility of performing gradual S_NAr substitutions of chloride at the triazine core provide synthetic opportunities [15] which facilitate the finding and structural optimization of lead structures, as exemplified in the search for triazine-based herbicides [16]. The high reactivity of halotriazines, which is nevertheless readily controlled by adapting reaction conditions, has enabled their use as carboxylic acid

Dedicated to Prof. Dr. Walter Weissensteiner on the occasion of his retirement.

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activating reagents [14, 17–22] or reactive linker units for reactive anchor-dyes in textile dyeing [23, 24].

We have recently introduced a copper-catalyzed cross-coupling of doubly or triply halogenated azacycles with tertiary alkyl Grignard reagents that gave direct access, among a variety of products, to 2-alkylated 4,6-dichloro-1,3,5-triazines and 2,4-dialkylated 6-chloro-1,3,5-triazines, and thus to bulky azacyclic building blocks with electrophilic sites for further synthetic manipulation [25]. The building blocks obtained using that methodology have led, inter alia, to new syntheses of geometrically restrained selenacalix [3] triazines [26], bulky ligands for studying organometallic coordination chemistry [27, 28], metal complexes for dye-sensitized solar cells [29–31], ligands for transition metal catalysis [32], or building blocks for medicinal chemistry [33, 34]. Compound 2,4-di-*tert*-butyl-6-chloro-1,3,5-triazine (**1**) in particular lends itself for introducing the bulky, symmetric, and electron-withdrawing 4,6-di-*tert*-butyl-2-triazinyl group, which we hoped might act as steric and electronic analog (isostere) of the 3,5-bis(trifluoromethyl)phenyl group (Scheme 1).

The latter is a structural element of hydrogen-bond donor catalysts of the Schreiner (**2**) [35] and Takemoto (**3**) [36–39] type (Scheme 1). An immediate aim of the project was to develop syntheses of analogs of Takemoto's catalyst **3** bearing heteroaryl groups like 1,3,5-triazin-2-yl or related 1,3-pyrimidin-2-yl. In the course of those studies, an additional aspect transpired—literally—when a triazine derivative displayed a faintly sweet, floral odor. We then perform a qualitative structure–activity profiling, i.e., "mapping" of its olfactophore.

Results and discussion

The family of bifunctional Takemoto catalysts **3** combines a basic tertiary amine with an *N*-arylthiourea unit. The privileged 3,5-bis(trifluoromethyl)phenyl aryl substituent has an acidifying function upon the thiourea unit and cannot be easily replaced by other substituents. We hoped that introduction of heterocyclic aza-aryl groups would produce analogs of **3** for asymmetric organocatalysis with more strongly acidic thiourea NH-bonds, while allowing for additional structural variety in the heterocyclic unit. This line of thinking came from a comparison of pK_a values of trifluoromethyl substituted anilines [40, 41] including **4** with those of several amino-azaarenes (Fig. 1) [13].

The estimated N–H acidity of **4** in aqueous solution is comparable to that of 2-aminopyridine,[1] whereas 2-aminopyrimidine and 2-amino-1,3,5-triazine with their additional ring-nitrogen are considerably more acidic. On the other hand, aza-arylamines are stronger bases than **4**, with ring nitrogen acting as site of protonation [42]. Still, the basicity is not marked, and we assumed that the presence of bulky groups in positions 4/6 would prevent the endocyclic nitrogen from acting as Brønsted base.

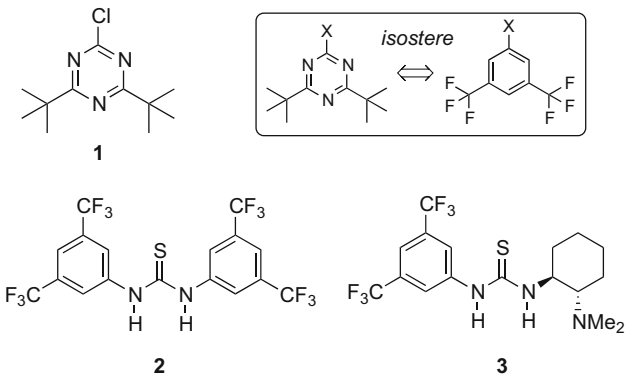
To synthesize the target thioureas **5**, we opted for a disconnection to the known (1*S*,2*S*)-2-(dimethylamino)-1-aminocyclohexane (**6**) [43] and the heterocyclic isothiocyanates **7**, which should be accessible from the heterocyclic amines **8** (Scheme 2).

Triazinylamines **8** and pyrimidylamines **9** were obtained by several methods: first, reaction of chlorotriazine **1** [25] with aqueous ammonia in ethanol gave 2-aminotriazine **8a**, accompanied by a trace of ethoxy derivative **10a** (Scheme 3a). This side-product will be commented upon in detail later. The bulky triazinylamines **8b/c** and 2-pyrimidylamine **9a** emerged from similar S_NAr reactions of chlorinated precursors [25] and the respective amines. Pyrimidylamine **9b** was prepared by condensation of the *β*-diketone with guanidine [44], while 2-aminotriazines **8d**–**8g** with less bulky substituents R were synthesized from nitriles (RCN) and guanidine according to Kabbe et al. (Scheme 3b) [45].

Aminotriazine **8a** formed large, transparent, colorless crystal blocks by slow evaporation of a solution in hexane. The X-ray crystal structure shows the importance of hydrogen-bonding patterns. Each NH_2 group acts as two-fold H-bond donor to N-5 in one, and to N-1 in another adjacent molecule (Fig. 2).

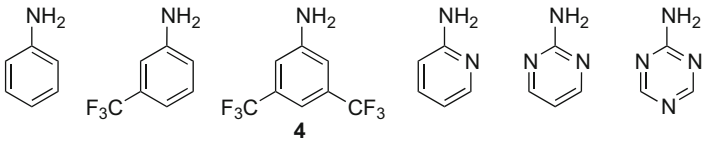
The structure can be interpreted as consisting of hydrogen-bonded dimers involving two symmetrically independent molecules A and B which are joined via two NH to N-1 hydrogen bonds [N…N′ = 305.5(2)/307.4(2) pm for A/B] in an 8-membered ring, with the planes of the aza-arene rings being tilted toward one another by 68°

Scheme 1



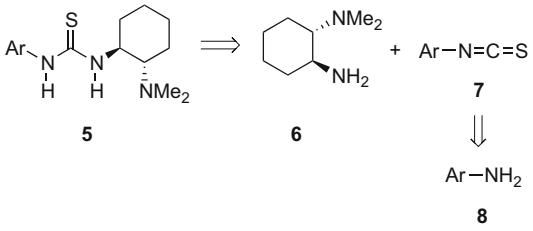
[1] The pK_a value for NH_2-ionization of **4** was derived from that of aniline by taking into account incremental substitution effects of the CF_3-group [40], or by applying a relationship given in Ref. [41].

Fig. 1 N–H acidity of some arylamines in neutral and protonated form, compared to that of aza-arylamines



			4			
pK_a (RNH_2) [NH_3 (*l*)]	21.2	18.7	15.6			
pK_a (RNH_2) [H_2O]	27.3	25.4	(22-23)	23.5	20.5	14.9
pK_a (RNH_3^+) [H_2O]	4.9	3.5	1.15	6.7	3.5	2.9

Scheme 2

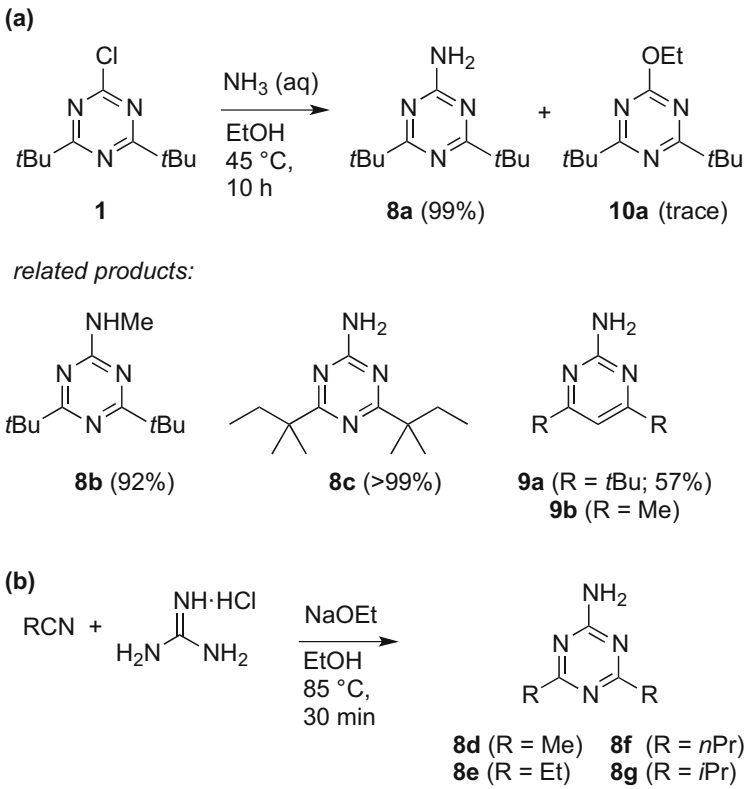


5 **6** **7** **8**

(Fig. 3). The A–B dimers are further stacked [A…A′/B…B′ stacking distance 474 pm] and connected by two weaker N-5 to H–N hydrogen bonds [325.4(2)/330.1(2) pm for A/B]—which are severely out of linearity compared to the aromatic heterocyclic core—along the *c*-axis, forming an infinite channel structure with a hydrophilic interior and a hydrophobic outside.

Heterocyclic amines including aminopyridines or aminopyrimidines have been converted to isothiocyanates

Scheme 3



[46] by reaction with thiophosgene and base [47, 48]. Reaction of **9b** with thiophosgene and sodium bicarbonate gave the known isothiocyanate **11** (Scheme 4a) [47], but the same reaction conditions failed with triazinylamines **8a** or **8g**, presumably due to the low nucleophilicity of their amino group.

Other approaches for converting amines to isothiocyanates [46], including reactions with CS_2 and DCC [49], or with thiophosgene and strong base in one pot showed little success; at least, minor amounts of product (from **8g**) were observed by GC–MS analysis in the latter case. Eventually, we developed a two-step procedure based on the Andreasch–Kaluza isothiocyanate synthesis [50–52] by stirring **8a/g** overnight with NaH and CS_2 in THF to generate a presumed dithiocarbamate, followed by addition of ethyl chloroformate and triethylamine [52], which immediately gave isothiocyanates **7a/g** in fair yields (Scheme 4b). Dolman has reported a related approach to convert amines to isothiocyanates for amines that fail to give dithiocarbamates with NEt_3 and CS_2, but using tosyl chloride as activator [53]. The heterocyclic isothiocyanates **11** and **7a/g** are stable to aqueous workup, but decompose when washed with ammonium chloride solution. Purification by quick chromatography over methanol-deactivated silica gel was possible, albeit with some losses, to give the products in moderate, unoptimized yields. Their reactivity toward amines was explored in a test reaction of **7a** with aniline to give thiourea **12** (Scheme 5a). Takemoto catalyst analogs **5** were then prepared by stirring chiral amine **6** [43] with each of **11** and **7a/g** in toluene solution (Scheme 5b).

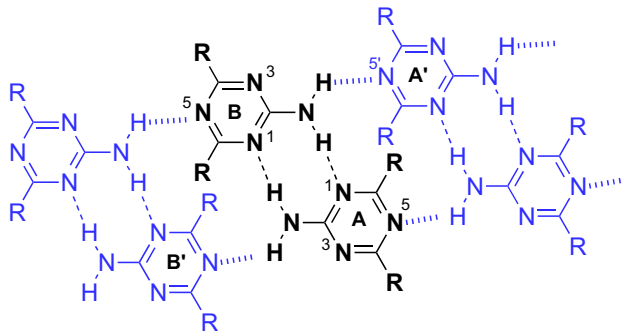


Fig. 2 Sketch of sheet-forming hydrogen-bonding patterns in the crystal structure of **8a**

The ^{1}H NMR spectra of both **5** and **12** displayed characteristic signals for NH groups, with each one signal at high and one at low frequency [**12**, 13.02 and 8.59 ppm; **5–1**, 11.48 (d, $J = 5.7$) and 8.37 ppm; **5–2**, 11.11 (d, $J = 6.3$) and 8.38 ppm; **5–3**, 11.07 (d, $J = 6.1$) and 8.37 ppm]. The presence of a vicinal coupling for the higher frequency NH signals in **5** places them at a cyclohexyl position. Given their considerable high field shift, they must be involved in a hydrogen bond, but not to the dimethylamino nitrogen, since this would be sterically challenging in *trans*-diaminocyclohexane derivatives. The hydrogen bond must be connected to a N-1/3 ring-nitrogen of the triazine or pyrimidine unit. The finding of an analogous hydrogen bond in **12**, where a basic amino group is not available, corroborates this. In **12**, the hydrogen bond is

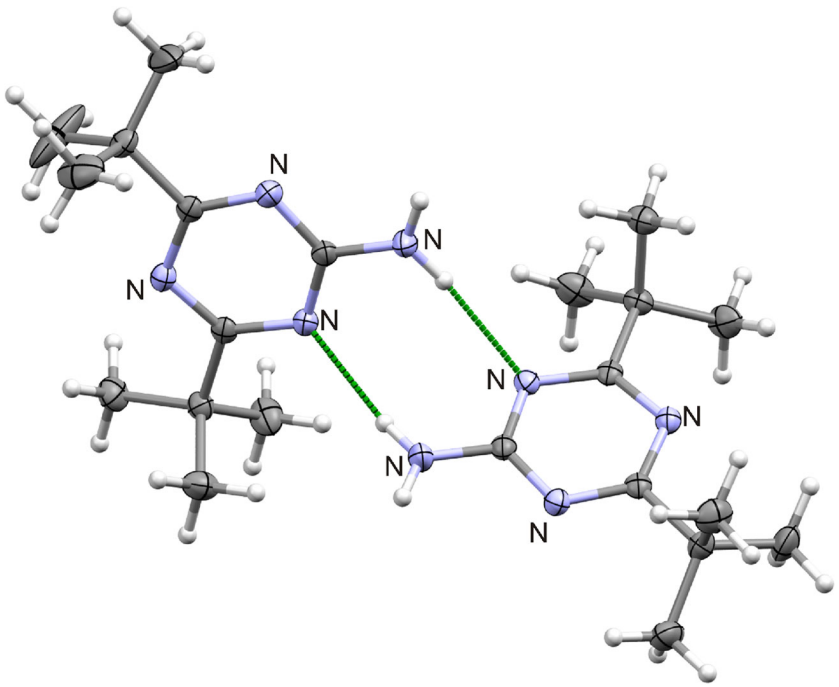
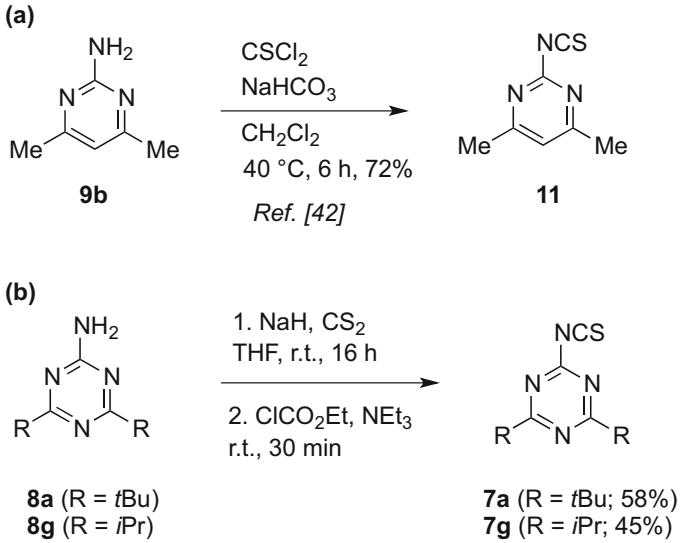
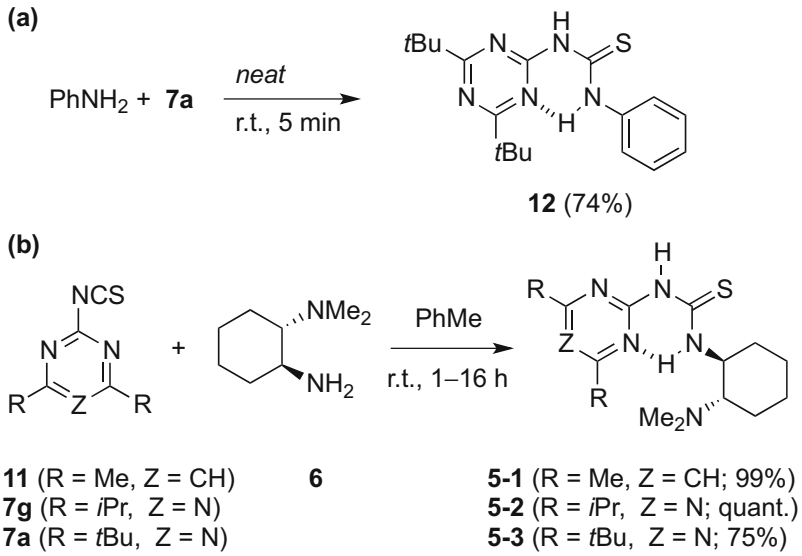


Fig. 3 X-ray molecular structure of **8a**. Characteristic hydrogen-bonded dimer formed by parallel amino-NH to azacyclic N-1/3 hydrogen bonding between two independent molecules (A/B) in the asymmetric unit

Scheme 4



Scheme 5



sufficiently strong to block rotation of the heterocyclic fragment around the C-2–NH axis, leading to separate signals for the *tert*-butyl groups and ring carbons in ^{1}H and ^{13}C NMR spectroscopy. In **5**, that rotation is faster, and the heteroaromatic groups show twofold local symmetry on the NMR timescale. The ^{13}C NMR spectra of **5** and **12** display a signal for the thiourea carbon (177.8–178.4 ppm). An X-ray structure determination for **5–3** supports the NMR assignments by showing the presence of a six-membered ring set up by an intramolecular hydrogen bond from one thiourea NH to triazine N-1/3 (Fig. 4).

The HNCS-units of two symmetrically independent molecules form antiparallel, double C=S…H–N-hydrogen bonds [S…N′ = 341.1(2)/341.4(2) pm for A/B], thereby

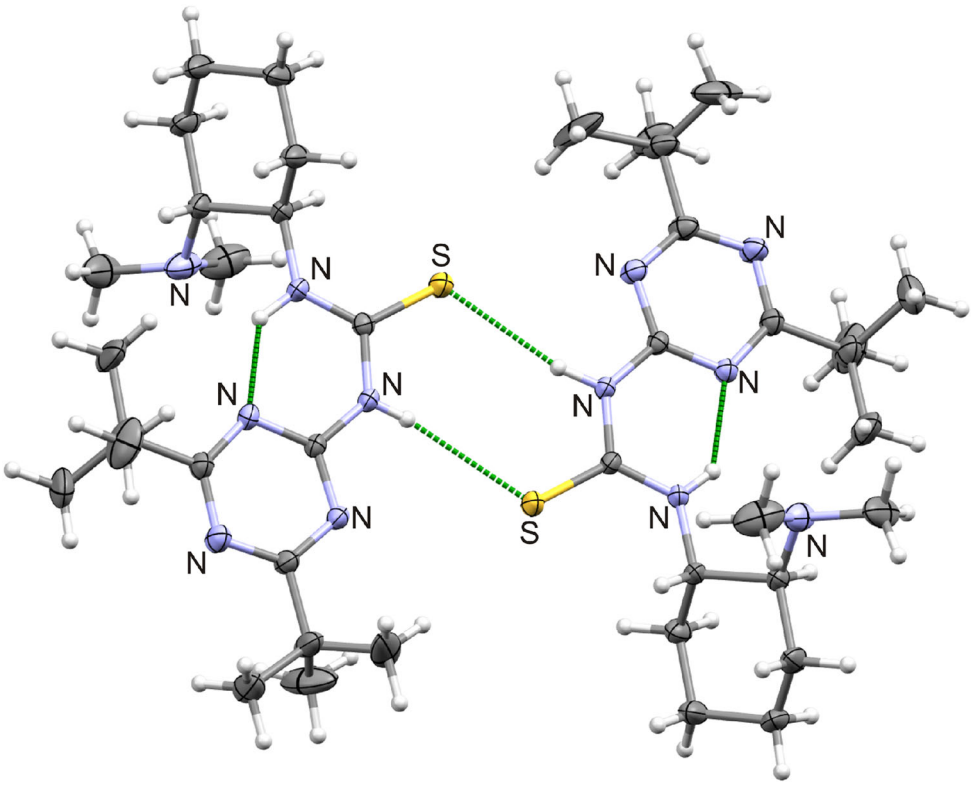


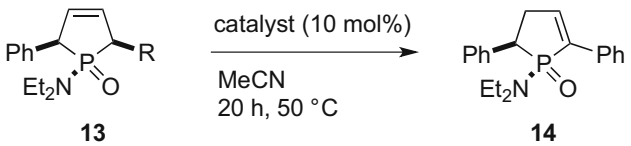
Fig. 4 X-ray molecular structure of **5–3**. A dimeric unit of two independent molecules in the asymmetric unit created by antiparallel hydrogen bonding along C=S…H–N is shown. Disordered *tert*-butyl substituents are omitted for clarity

forming hydrogen-bonded dimers. Surprisingly, the lone-pair of the basic dimethylamino unit is not involved in any hydrogen-bonding interaction or close contact. The *tert*-butyl groups are disordered. Similar intramolecular hydrogen bonds have already been found in 2-pyridylthioureas, triazinylureas, and -thioureas by either ^{1}H NMR spectroscopy or X-ray crystallography [54–57]. The spectral properties of azacyclic thioureas **5** in $CDCl_3$ differ from those of Takemoto's catalyst **3**, NH signals of which are not visible at ambient temperature in the same solvent due to chemical exchange, but can be resolved at low temperature, where the presence of two monomeric conformers and two dimeric associates is revealed [58]. Compounds **5** show a preference for the same intramolecular hydrogen-bonded structure in solution and the solid state.

We have tested the aza-aryl analogs **5** of Takemoto's catalyst (**3**) as bifunctional organocatalysts in an organocatalytic, asymmetric isomerization of *meso-trans-trans*-2,5-diphenyl-1-(diethylamino)-2,5-dihydrophosphole oxide (**13**) to the corresponding 2-phospholene oxide **14** [59] (Scheme 6).

Takemoto's catalyst **3** had induced an *ee* of 88 % at quantitative conversion in this reaction [60]. Unfortunately, neither **5–1** nor **5–3** display catalytic activity in this reaction under the above or similar conditions. Consequently, it appears that the intramolecular hydrogen bond offsets the bifunctional properties of aza-aryl analogs of Takemoto's

Scheme 6



catalyst, and that neither the lowered basicity of triazines nor the steric shielding present in **5–3** due to the *tert*-butyl groups is sufficient to preclude this interaction. The question of whether 4,6-di-*tert*-butyl-2-triazinyl can replace the 3,5-bis(trifluoromethyl)phenyl substituent in thiourea-type hydrogen-bonding catalysts therefore found a clear-cut answer that was negative.

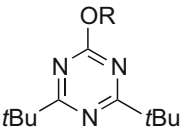
However, as often in experimental research, we made an unrelated and surprising observation in the course of the above studies: while working up the reaction mixture of 2,4-di-*tert*-butyl-6-chloro-1,3,5-triazine (**1**) with ammonia in ethanol (Scheme 3a), a sweet smell was noted, and the crude crystalline heterocyclic amine **8a** obtained emitted a sweet, floral odor. This was rather surprising, since neither triazines in general, nor any heterocyclic amine derivatives in particular would appear to be suitable candidates for sweet-smelling compounds. Yet, it turned out that purified

samples of **8a** are odorless. Inspection of the GC/MS-trace and the ^{1}H NMR data of crude **8a** indicated that ethoxy-triazine **10a** was present as impurity to the extent of 1.5 mol% in the crude product. Compound **10a** was independently synthesized from **1** and sodium ethoxide (vide infra), and indeed had olfactory properties similar to those of crude amine **8a** with the **10a** impurity. Numerous aromatic nitrogen heterocycles are known to the perfumer, but are described as having burnt, meaty (acetylpyrimidine), burnt, earthy, nutty, roasted (pyrazines), popcorn (acetylpyridine), nutty, green, fatty, vegetable or tobacco (alkylpyridines), sweaty (picoline), floral (terpenyl-substituted pyridines) or marine (4-alkadienylpyridines), roasted (pyrazoles), animalic (alkylquinolines) or leather, green woody, moss, earthy (*sec*-alkyl quinolines) notes [61, 62]. The presence of a sweet, floral odor note in a triazine motivated us to perform structure/odor relationship studies to analyze the olfactophore in **10a**, and possibly vary the olfactory profile. Structural variations included exchange or removal of ring-substituents, or the replacement of ring-nitrogen by methine (CH) units. Over 35 derivatives, 28 of them new compounds, were prepared, using various combinations of established methodology. The outlines of the syntheses will be indicated briefly, but details can be found in the supporting information. Olfactory properties of the compounds have been evaluated, though not by professionals, and are given in general terms, without claim for particular accuracy.

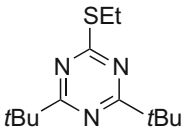
Since the sweet smell had initially been detected in an amino-triazine sample, a range of amino-azacycles (already shown Scheme 3) was obtained, but had either no discernible, or only a faint, uncharacteristic smell. A series of alkoxy-triazines were then synthesized by S_NAr reaction of **1** with sodium alkoxide to give alkoxytriazines **10a**–**10j**, or with NaSEt as nucleophile to give thioether **15** (Scheme 7).

The olfactory properties of **10a** and **10b** were similar in quality, and of moderate intensity for both. The odor of isopropoxy-analog **10f** was reminiscent of **10a**, but weaker, whereas other alkoxy analogs had either faint, unspecific odors, or none at all. Purified thioether **15** had a faint smell reminiscent of **10a**, but assumed a hydrocarbon, gas-like odor on standing, presumably due to degradation to sulfur-containing compounds. The change of *tert*-butyl to larger *tert*-amyl (**16a**) or 3-ethylpentyl (**16c**) groups gave faintly smelling or odorless compounds; only the mixed *tert*-butyl-*tert*-amyl compound **16b** had an odor reminiscent of **10a**, but with lower intensity. Isopropyl analog **16d** had a weaker, sweetish smell, with an aspect of clover (eugenol-like). Diethyl triazine **16e** had a sweetish, green, fennel-type odor with aggressive ammoniacal overtones. A similar dependency of odor properties on structure was seen with pyrimidines **17**, which were prepared by S_NAr substitution

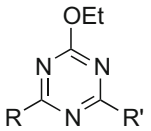
Scheme 7



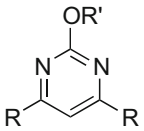
10a (R = Et)
10b (R = Me)
10c (R = *n*Pr)
10d (R = *n*Bu)
10e (R = *n*Am)
10f (R = *i*Pr)
10g (R = *i*Bu)
10h (R = *i*Am)
10i (R = *sec*-Bu)
10j (R = *t*Bu)



15



16a (R, R' = *t*Am)
16b (R, R' = *t*Bu, *t*Am)
16c (R, R' = CEt_3)
16d (R, R' = *i*Pr)
16e (R, R' = Et)

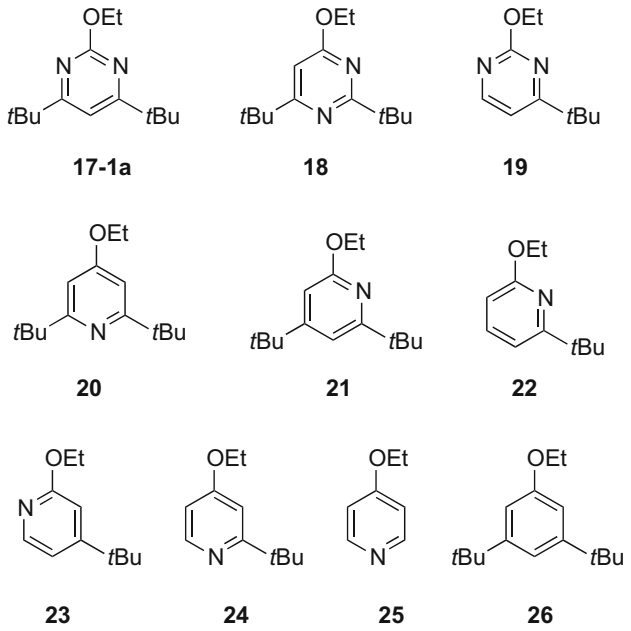


17-1a (R, R' = *t*Bu, Et)
17-2a (R, R' = *i*Pr, Et)
17-3a (R, R' = Me, Et)
17-3b (R, R' = Me, Me)
17-3c (R, R' = Me, *i*Pr)
17-3d (R, R' = Me, *n*Am)

of the chloro-precursors with sodium alkoxides. Analog **17–1a** has a similar, but slightly weaker odor compared to **10a**. Ethoxydiisopropylpyrimidine **17–2a** has a weak odor with fennel and clover aspects. The low melting solid **17–3b** had a rather intense, aggressive, ammoniacal, and camphoresque odor with sweet fennel undertones. Ethyl ether **17–3a** and isopropyl ether **17–3c** have similar, but overall milder odor properties like **17–3b**, but *n*-amyl ether **17–3d** displays only weak odor. Removal of nitrogen from **10a** to give **17–1a** retains the odor characteristics, at lower intensity. Further replacements of nitrogen with methine (CH) and de-alkylations were studied systematically; the required compounds (Scheme 8) were obtained by a combination of known methods, as detailed in the supporting information.

The regioisomeric de-aza analog **18** had only a faint smell with hydrocarbon aspect. Di-de-aza analog **20** was almost odorless, while **21** had a very faint, sweet smell with hydrocarbon tones, while arene **26** displayed a faint, sweetish smell of different character and lower intensity than **10a**. De-alkylation generally increased odor intensity relative to fully alkylated reference compounds: **19** had a mild, sweet and carrot, clover (eugenol-like)-type odor; **22** had a medium intensity, green, carrot-like odor, **23** a very weak sweetish fennel odor, **24** a medium intensity, pyridine-like, sweaty odor that was neither sweet nor agreeable. Finally, 4-ethoxypyridine had a moderate

Scheme 8



pyridine-like, ammoniacal odor. In conclusion, the olfactory "mapping" of **10a** shows that the presence of N-1 and N-3 together with a small alkoxy group (OMe, OEt) at C-2 are key elements of the olfactophore. Steric shielding of ring nitrogens by bulky groups at C-4/6 appears to reduce aggressive pyridine- and ammoniacal-type odors.

Conclusions

In this work, we have explored the use of 2-amino-1,3,5-triazines as readily available building blocks for preparing new types of chiral organocatalysts of the Takemoto type. Triazineamines were successfully converted to isothiocyanates, and the latter were found to react with amines to form the desired thiourea derivatives. However, the structure of those compounds is characterized by the presence of a strong intramolecular hydrogen bond from thiourea NH to aza-aryl N-1/3, which cancels any hydrogen-bond donor characteristics required for bifunctional organocatalysis, and therefore 4,6-di-*tert*-butyl-1,3,5-triazine-2-yl is not a suitable isosteric replacement for 3,5-bis(trifluoromethyl)-phenyl. Nevertheless, the 2-amino-1,3,5-triazine unit is a reliable hydrogen-bond donor and acceptor unit for crystal engineering, and bulky 2,6-dialkyl-1,3,5-triazine-2-amines are useful materials for such purposes. In the course of the synthesis of triazin-2-yl-amines, an alkoxy triazine with sweet odor characteristics was found, and the requirements for generating that odor were explored by structure-variation studies.

Experimental

Reagents and solvents were obtained from commercial suppliers and used without further purification. Solvents were dried by passing through a column of Al_2O_3 and then kept over 3 Å molecular sieves under an argon atmosphere. Column chromatography (CC) was performed on silica gel 60 (35–70 μm particle size) as flash chromatography with 0.2 bar positive air pressure. Thin layer chromatography was performed on glass plates coated with silica gel 60 F_{254} and visualized with UV light (254 nm). NMR spectra were recorded at the indicated frequencies at ambient temperature (19–25 °C) and referenced to tetramethyl-silane [TMS, δ (^{1}H) = 0.00 ppm] or residual solvent peaks [in $CDCl_3$: δ (^{1}H) = 7.26 ppm; in DMSO-d_6: δ (^{1}H) = 2.50 ppm]. ^{13}C NMR spectra were referenced to solvent peaks ($CDCl_3$, δ = 77.16 ppm; DMSO-d_6, δ = 39.52 ppm). All new compounds gave corresponding elemental analyses (C, H, N, typically ±0.3 %). The experimental section gives selected experimental data for the most important compounds. Additional data including experimental details and copies of ^{1}H and ^{13}C NMR spectra for all compounds prepared are provided as supporting information.

4,6-Di-tert-butyl-1,3,5-triazin-2-amine (**8a**, $C_{11}H_{20}N_4$)
To a solution of 8.66 g 2-chloro-4,6-di-*tert*-butyl-1,3,5-triazine (**1** [25]; 38.0 mmol) in 70 cm^3 EtOH, 50 cm^3 aqueous 25 % NH_3 was added and the mixture stirred at 45 °C for 7.5 h. After cooling, the volume was reduced to ca. 50 cm^3 in vacuum, and the resulting crystals were filtered off (fraction 1, 6.16 g). The filtrate was extracted with CH_2Cl_2, the extract dried over $MgSO_4$, filtered, and evaporated to dryness (fraction 2, 1.68 g). Total yield was 7.84 g (99 %). X-ray quality crystals were obtained by slow evaporation from a CH_2Cl_2/hexanes solution in an open flask. Larger crystals were washed with hexanes, crushed into smaller parts, and dried in air. *M.p.*: 117–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 18H, CH_3), 5.37 (br s, 2H, NH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.01 (CH_3), 39.17 (C), 167.05 (C), 185.15 (C) ppm; IR (KBr): $\bar{\nu}$ = 3435, 3309, 3202, 2967, 1632, 1535, 1232, 1186, 1001, 846 cm^{-1}; GC–MS (EI$^+$): *m*/*z* = 208 (M$^+$), 193.

2,4-Di-tert-butyl-6-ethoxy-1,3,5-triazine
(**10a**, $C_{13}H_{23}N_3O$)
2-Chloro-4,6-di-*tert*-butyl-1,3,5-triazine (**1** [25]; 5.00 g, 22.0 mmol) was added to a solution of 1.01 g sodium

metal (44.0 mmol) in 30 cm^3 EtOH at r.t. After stirring for 1 h, most of the EtOH was removed in vacuum, 10 cm^3 water was added, and the mixture extracted with *t*BuOMe (3 × 50 cm^3) to give a crude product (5.279 g). Purification by CC (*t*BuOMe/hexanes 1:50) gave 5.198 g (99.6 %) of slightly yellow oil, which was further purified by Kugelrohr distillation (130 °C, ca. 10 mbar) to give a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.35$ (s, 18H, CH_3), 1.44 (t, $J = 7.0$ Hz, 3H, CH_3), 4.49 (q, $J = 7.0$ Hz, 2H, CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.41$ (CH_3), 28.89 (CH_3), 39.48 (C), 63.49 (CH_2), 170.57 (C), 187.32 (C) ppm; IR (capillary): $\bar{\nu} = 2965$, 1537, 1336, 1239, 1069, 920 cm^{-1}; GC–MS (EI^+): $m/z = 237$ (M^+), 222, 208, 194.

2,4-Di-tert-butyl-6-isothiocyanato-1,3,5-triazine (**7a**, $C_{12}H_{18}N_4S$)

2-Amino-4,6-di-*tert*-butyl-1,3,5-triazine (**8a**; 2.08 g, 10 mmol) was added to a suspension of 1.28 g NaH (32 mmol, 3.2 equiv) in 30 cm^3 THF. After 30 min of stirring at r.t., 3.02 cm^3 CS_2 (50 mmol, 5 equiv.) was added at 0 °C and the mixture stirred overnight for 20 h at r.t. Ethyl chloroformate (1.43 cm^3, 15 mmol, 1.5 equiv.) was added, followed by 2.8 cm^3 Et_3N (20 mmol, 2 equiv.), and the mixture stirred at r.t. for 30 min. The reaction was quenched with the addition of 18 cm^3 2.4 M aq HCl and *t*BuOMe for extraction of the product. Washing of the organic phase with water, drying (Na_2SO_4), filtration, and evaporation gave 3.63 g of crude product. Purification by CC on 150 g of MeOH-deactivated SiO_2 (hexanes, then *t*BuOMe/hexanes 1:50) gave 1.45 g (58 %) of **7a** as slightly brownish-yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.37$ (s, 18H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.88$ (CH_3), 39.86 (C), 147.48 (C), 162.03 (C), 188.08 (C-2/4) ppm; IR (capillary): $\bar{\nu} = 2965$, 2929, 2870, 2125, 2100–1900 br, 1983, 1537, 1507, 1372, 1134, 912, 845 cm^{-1}; GC–MS (EI^+): $m/z = 250$ (M^+), 235, 208, 84.

2,4-Diisopropyl-6-isothiocyanato-1,3,5-triazine (**7g**, $C_{10}H_{14}N_4S$)

2-Amino-4,6-diisopropyl-1,3,5-triazine (**8g** [45]; 901 mg, 5.0 mmol), 640 mg NaH (16 mmol, 3.2 equiv), and 1.5 cm^3 CS_2 (25 mmol) were stirred in 20 cm^3 THF overnight. Ethyl chloroformate (0.71 cm^3, 7.5 mmol, 1.5 equiv.) and 1.4 cm^3 NEt_3 (10 mmol) were successively added, and the mixture was stirred for 30 min at r.t. The reaction was quenched with H_2O and extracted with *t*BuOMe. After drying of the organic phase (Na_2SO_4), filtration, and evaporation, the crude product was purified by CC on MeOH-deactivated SiO_2 (*t*BuOMe/hexanes 1:50) to give an oily product (499 mg, 45 %). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.32$ (d, $J = 6.9$ Hz, 12H), 3.07 (sept, $J = 6.9$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.10$ (CH_3), 37.41 (CH), 147.58 (C), 186.24 (C) ppm, one (C) not detected; IR (capillary): $\bar{\nu} = 2972$, 2932, 2875, 1983 (br 1900–2100), 1542, 1516, 1378 cm^{-1}; GC–MS (EI^+): $m/z = 222$ (M^+), 207, 194, 111, 85, 70.

1-[(1S,2S)-2-(Dimethylamino)cyclohexyl]-3-(4,6-dimethylpyrimidin-2-yl)-thiourea (**5–1**, $C_{15}H_{25}N_5S$)

(1*S*,2*S*)-2-(Dimethylamino)cyclohexylamine (**4** [43]; 1.07 g, 7.5 mmol) was added to a solution of 830 mg 2-isothiocyanato-4,6-dimethylpyrimidine (**11** [47, 48]; 5.02 mmol) in 10 cm^3 toluene and stirred for 3 h at r.t. The solvent was removed and the residue separated by CC (CH_2Cl_2/MeOH 30:1–20:1–12.5:1). Evaporation gave crude **5–1** as foam (1.598 g, quantitative), which retained some *t*BuOMe solvent. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.10$–1.47 (m, 4H), 1.66-1.76 (m, 1H), 1.80–1.94 (m, 2H), 2.29 (s, 6H, NMe_2), 2.39 (s, 6H, 2 Me), 2.56 (td, $J = 10.5$, 3.4 Hz, 1H), 2.71–2.76 (m, 1H), 4.15 (ddd, $J = 10.5$, 6.6, 4.0 Hz, 1H), 6.66 (s, 1H), 8.37 (br s, 1 NH), 11.48 (br d, $J = 5.7$ Hz, 1 NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.55$ (CH_2), 23.97 (CH_3), 24.77 (CH_2), 25.24 (CH_2), 32.00 (CH_2), 40.67 (CH_3), 56.81 (CH), 66.77 (CH), 114.27 (CH), 157.20 (C), 167.51 br (C), 178.02 (C=S) ppm; MS (CI, CH_4): $m/z = 308.3$ ($M+H^+$), 166, 124; IR (ATR): $\bar{\nu} = 3429$, 3178, 3030, 2929, 2858, 1598, 1511, 1371, 1164, 1040, 788, 706 cm^{-1}.

1-(4,6-Diisopropyl-1,3,5-triazin-2-yl)-3-[(1S,2S)-2-(dimethylamino)cyclohexyl]thiourea (**5–2**, $C_{18}H_{32}N_6S$)

(1*S*,2*S*)-2-(Dimethylamino)cyclohexylamine (**4** [43]; 594 mg, 4.18 mmol) was added to a solution of 773 mg isothiocyanate **7g** (3.48 mmol) in 5 cm^3 toluene, and the reaction mixture stirred overnight. Evaporation and purification by CC (CH_2Cl_2 and then CH_2Cl_2/MeOH 30:1–20:1) gave a foam which was crushed to powder, washed with *t*BuOMe, and dried in vacuum to give colorless solid (1300 mg, quant.), retaining some *t*BuOMe. A sample for analysis was further dried in vacuum. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.07$–1.19 (m, 1H), 1.21–1.46 (m, 16H), 1.72–1.79 (m, 1H), 1.84–1.96 (m, 2H), 2.25 (s, 6H, NMe_2), 2.55 (td, $J = 10.9$, 3.3 Hz, 1H), 2.60–2.67 (m, 1H), 1.98 (br s, 2H, *i*Pr-CH), 4.21 (m, 1H), 8.38 (s, 1 NH), 11.11 (d, $J = 6.3$ Hz, 1 NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.96$ (CH_3), 21.00 (CH_3), 21.75 (CH_2), 24.98 (CH_2), 25.34 (CH_2), 32.33 (CH_2), 37.19 br (CH_3), 40.37 (CH), 57.29 (CH), 66.87 (CH), 162.00 (C), 177.93 (C), 184.67 br (C) ppm; MS (CI, CH_4): $m/z = 393.4$ ($M + C_2H_5^+$), 365.3 ($M + H^+$); IR (ATR): $\bar{\nu} = 3419$, 3198, 2931, 2861, 1570 br, 1536 br, 1391, 1150, 840 cm^{-1}.

1-(4,6-Di-tert-butyl-1,3,5-triazin-2-yl)-3-[(1S,2S)-2-(dimethylamino)cyclohexyl]thiourea (**5–3**, $C_{20}H_{36}N_6S$)

Isothiocyanate **7a** (116 mg, 0.46 mmol) was combined with 79 mg (1*S*,2*S*)-2-(dimethylamino)cyclohexylamine (**4**

[43]; 0.56 mmol) in 1 cm^3 PhMe and stirred overnight. Evaporation and purification by CC (CH_2Cl_2–CH_2Cl_2/MeOH 30:1–20:1) gave colorless solid **5–3** (136 mg, 75 %). X-ray quality crystals were obtained by slow evaporation from a concentrated toluene solution. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08–1.50 (m, 4H), 1.33 (br s, 18H, *t*Bu), 1.72–1.99 (m, 3H), 2.24 (br s, 6H, NMe_2), 2.51–2.62 (m, 2H), 4.23–4.35 (m, 1H), 8.37 (br s, 1 NH), 11.07 (br d, J = 6.1 Hz, NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.68 (CH_2), 25.12 (CH_2), 25.42 (CH_2), 28.84 (CH_3), 32.69 (CH_2), 39.62 (C), 40.36 (CH_3), 57.33 (CH), 66.89 (CH), 161.85 (C), 178.00 (C), 187.30 br (C) ppm; MS (CI, CH_4): m/z = 393.4 ($M + H^+$); IR (ATR): = 3190, 3127, 3047, 2935, 2862, 1573, 1510, 1173, 1151, 683 cm^{-1}.

1-(4,6-Di-tert-butyl-1,3,5-triazin-2-yl)-3-phenylthiourea (**12**, $C_{18}H_{25}N_5S$)

It was obtained by reaction of 70 mm^3 distilled aniline (0.77 mmol) with 160 mg isothiocyanate **7a** (0.64 mmol) neat for 5 min. Addition of 5 cm^3 hexanes and filtration gave 132 mg of colorless solid. The filtrate was evaporated, and the residue crystallized from CH_2Cl_2/hexanes (overlayering) to give 30 mg of needles; total yield 162 mg (74 %) of **12** as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (br s, 9H, *t*Bu), 1.39 (br s, 9H, *t*Bu), 7.27 (t, J = 7.5 Hz, 1 H-Ar), 7.43 (t, J = 7.8 Hz, 2 H–Ar), 7.71 (d, J = 7.7 Hz, 2 H–Ar), 8.59 (br s, 1 NH), 13.02 (br s, 1 NH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.87 (br s, CH_3), 29.00 (br s, CH_3), 39.81 (br s, 39.81), 125.05 (CH), 126.54 (CH), 128.5 (CH), 138.20 (C), 161.67 (C), 178.40 (C), 184.78 (br s, C), 187.27 (br s, C) ppm; IR (ATR): $\bar{\nu}$ = 3184, 3071, 2963, 1581, 1516, 1322, 1175, 1153, 744, 685 cm^{-1}; MS (CI, CH_4): m/z = 372.2 ($M + C_2H_5^+$), 344.2 ($M + H^+$), 343.2 (M^+), 251, 209.

X-ray crystal structure analysis for 8a and 5–3

The single crystals of **8a** and **5–3** were used for data collection at 123.0(2) K on a four-circle Bruker Kappa APEX II CCD system equipped with a MONTEL mirror monochromator and a Mo FR591 rotating anode (λ = 0.71073 Å). Integration of the intensities and correction for Lorenz and polarization effects were performed using APEX2 suite of software [63]. The crystal structures were solved by direct methods and refined by a full-matrix least-squares method on F^2 using the program SHELXL-2014 [64] in conjunction with SHELXLE [65].

Complete crystallographic details for **8a** and **5–3** are available as Supplementary data [CCDC 1055819 (**8a**) and 1055820 (**5–3**)] and have been deposited at the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge, CB21EZ, UK; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk. Any request to the CCDC for this material should quote the full literature citation.

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