A Novel Route to Racemic and Nonracemic Products of the Ugi Reaction: Synthesis of Ugi's Labile α-Adducts from Iminoaziridines and Carboxylic Acids, and Their Transformations**

Helmut Quast* and Sven Aldenkortt

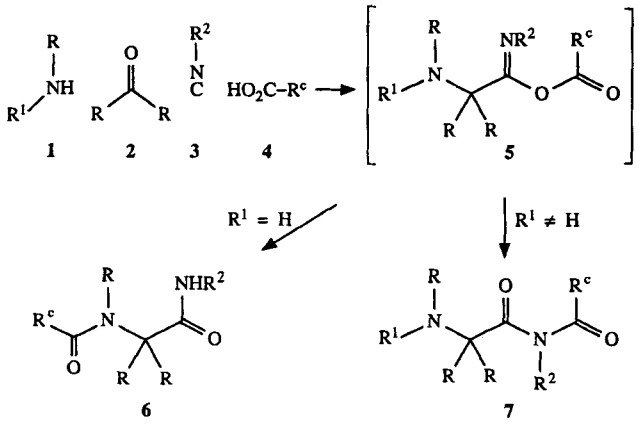
Dedicated to Professor Ivar Ugi on the occasion of his 65th birthday

Abstract: Iminoaziridines (**11**) are highly reactive synthetic equivalents for three of the four components in the Ugi four-component condensation. Thus, iminoaziridines react rapidly with carboxylic acids at temperatures as low as −20 °C to afford α-amino isoimides (**14**), which are identical to the elusive α-adducts of isocyanides in the Ugi reaction. 1,4-Migration of the acyl group ($O \rightarrow \alpha$-N) in **14** furnishes the α-acylamino amides **15**. Very little, if any, racemisation is observed when carboxylic acids react with nonracemic iminoaziridines [(*R*)-**11a,c**], which are readily available. Mumm rearrangement by $O \rightarrow N$-acyl 1,3-migration to afford α-amino imides (**16e,f**) competes if the $O \rightarrow \alpha$-N 1,4-shift is slowed down by steric hindrance. The latter acyl shift is catalysed by carboxylic acids while the former is not. The iminoaziridines (*R*)-**11a,c** react quantitatively and without racemisation with hydrazoic acid to produce the 5-aminoalkyltetrazoles (*R*)-**21a,c**.

Keywords
aziridines · imides · isoimides · rearrangements · Ugi reaction

Introduction

During the second half of this century, only a handful of reactions have been discovered that have profoundly influenced organic synthesis. A prominent member of this group is the Ugi reaction, a four-component condensation (4CC), reported for the first time in 1959[2] and thoroughly reviewed since then on several occasions.[3–11] In reference [5] it is described as follows: "Amines **1** and carbonyl compounds **2**, such as aldehydes or ketones, react with isonitriles **3** and suitable acids **4** to form unstable α-adducts **5** which are converted by spontaneous secondary reactions into stable α-amino acid derivatives **6**. Instead of amines and the carbonyl compounds, it is also possible and often advisable to use their condensation products, such as aminals, Schiff bases, and enamines" (Scheme 1). The stable α-acylamino amides **6** may be converted into true peptides by cleavage of the N–R bond. This last step completes a sequence generating a new amino acid residue from an amine **1**, an aldehyde and an isocyanide **3** (4CC peptide synthesis). Alternatively, cleavage of the α-C–N bond removes the auxiliary moiety formed from the ketone **2** and the isocyanide **3** (4CC peptide fragment condensation).[12] The importance of the Ugi condensation in α-amino acid and peptide chemistry was greatly enhanced by employing nonracemic chiral amines [e.g., (*S*)-α-phenylethanamine,[3, 13] α-aminoalkylferrocenes,[14] carbohydrate derivatives[15, 16] and methyl esters of α-amino acids[17b]] as starting materials to induce diastereoselectivity in the reaction. A very recent report describes a combinatorial synthesis using a convertible isocyanide,[18] namely, cyclohexenyl isocyanide, devised and employed by Ugi and Rosendahl more than three decades ago.[19] Not only can the enamine group in products **6** (R^2 = cyclohexenyl) be hydrolysed to afford the primary amides,[19] but also converted into a variety of functional groups.[18]



Scheme 1. The Ugi four-component condensation.

α-Acylamino *N*,*N*-dimethylamides **10**, which closely resemble the Ugi products **6**, are obtained in one step from carboxylic acids **4** and 3-dimethylamino-2*H*-azirines **8** (Scheme 2).[20] The latter have thus evolved as synthons for α,α-substituted α-amino acids in peptide synthesis.[21] In the course of our initial studies

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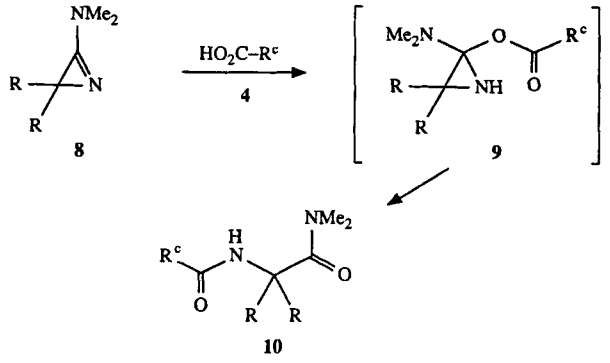
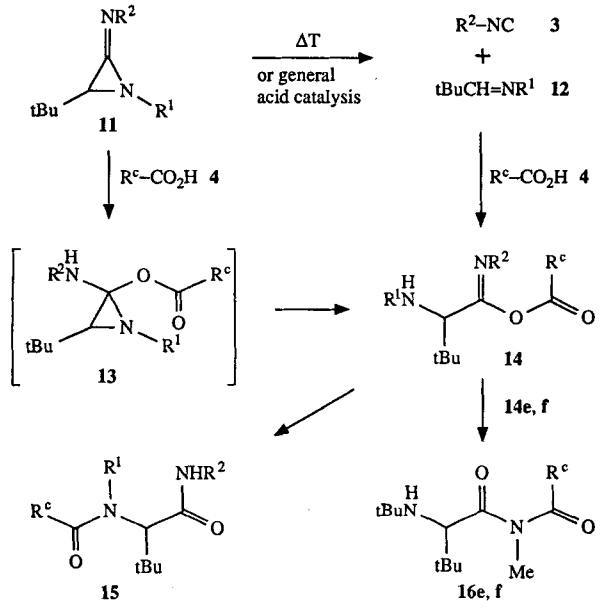


Scheme 2. α-Acylamino amides from aminoazirines and carboxylic acids.

on iminoaziridines **11**,[22] which are isomers of the 3-amino-2*H*-azirines reported around the same time,[23] we found that, surprisingly, iminoaziridines could not be titrated with 0.1 M perchloric acid in acetic acid,[24] though their structure would suggest that they are sufficiently basic.[25] This result was explained in terms of the formation of nonbasic compounds, namely, α-acetylamino amides **15** (R^c = Me), from **11** by reaction with acetic acid (Scheme 3, **11** → **13** → **14** → **15**).[26] Clearly, the α-acetylamino amides **15** are identical to the products **6** formed in the Ugi reaction of acetic acid and 2,2-dimethylpropanal (pivaldehyde).[27] We have now taken up these early observations and report here on the synthesis of racemic and nonracemic α-acylamino amides **15** from iminoaziridines **11** and on the characterisation of the first observable intermediates, the α-amino isoimides **14**, which are identical to the unstable α-adducts of the Ugi reaction. We also disclose that the *O* → *N*-acyl 1,4-migration to the α-amino group in **14** (R^1 = *t*Bu) requires catalysis by the carboxylic acid. Otherwise, an *O* → *N*-acyl 1,3-shift (Mumm rearrangement) occurs to afford α-amino imides **16**. Finally, we report on the reaction of iminoaziridines **11** with hydrazoic acid, which furnishes 5-(1-aminoalkyl)-tetrazoles **21** in quantitative yield.



	R^i
3a, 12a	Me
3b, 12b	*t*Bu

	R^c
4a	Ph
4b	CH_2*t*Bu
4c	$CH_2NHCOPh$
4d	$CH(tBu)_2$

	R^1	R^2
11a	Me	Me
11b	Me	*t*Bu
11c	*t*Bu	Me

	R^1	R^2	R^c
13a – 15a	Me	Me	Ph
13b – 15b	Me	Me	CH_2*t*Bu
13c – 15c	Me	Me	$CH_2NHCOPh$
13d – 15d	Me	*t*Bu	Ph
13e, 14e, 16e	*t*Bu	Me	$CH(tBu)_2$
13f – 16f	*t*Bu	Me	Ph

Scheme 3. Reaction of iminoaziridines **11** with carboxylic acids **4**, and the Ugi reaction of **3**, **4** and **12**.

Results

The 2-imino-1-methylaziridine **11a** reacted with carboxylic acids **4a–c** in inert solvents at 0–25 °C to afford colourless crystalline 1:1 adducts **15a–c** (Table 1, entries 1–3). Similarly, **11b** and **4a** gave **15d** (entry 4). The yields of the crude products were virtually quantitative. The structures of the α-acylamino amides **15a–d** were assigned on the basis of their IR, MS, ^{1}H NMR and ^{13}C NMR spectra (Tables 2–4), and their lack of basicity alluded to in the Introduction. Furthermore, **15a** was prepared independently by Ugi reaction from benzoic acid, methyl isocyanide and imine **12a** (Table 1, entry 9). A 1:1 mixture of the latter two reactants was conveniently obtained by thermolysis of **11a**.[28] Remarkably, hardly any racemisation occurred when the nonracemic iminoaziridine (*R*)-**11a**[28] was treated with benzoic acid (entry 1). This was established from the ^{1}H NMR spectrum of a solution of the product (*R*)-**15a** containing Pirkle's alcohol **22** as chiral shift reagent[29] (Table 3).

The 2-imino-1-*tert*-butylaziridine **11c** reacted with benzoic acid under the same conditions as described above to afford a noncrystalline 1:1 adduct in quantitative yield (Table 1, entry 6), which, surprisingly, was not identical with the crystalline main product **15f** of the Ugi reaction of methyl isocyanide, imine **12b**[25] and benzoic acid (entry 7). The NMR spectra of the noncrystalline 1:1 adduct indicated the presence of a secondary *N*-*tert*-butylamino group, of an *N*-methyl group resonating at rather low field in both ^{1}H and ^{13}C NMR spectra and showing no sign of any coupling with a vicinal proton, and of two different amide groups absorbing at relatively low field in the ^{13}C NMR spectrum. The IR spectrum was characterised by two carbonyl bands at around $\tilde{\nu}$ = 1680 and 1690 cm^{-1}, indicative of an *N*-alkyl imide moiety. The combined spectroscopic evidence confirmed that the product was the α-amino imide **16f**. Symmetrical acyclic imides with large substituents preferentially adopt the (*E*,*Z*) configuration.[30] Only one of the two possible (*E*,*Z*) configurations of the unsymmetrical imides **16** is displayed in Scheme 3. No racemisation of the imide (*R*)-**16f** was observed, when the starting material was the nonracemic iminoaziridine (*R*)-**11c**.[25]

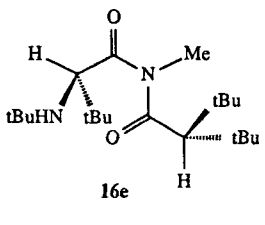
With a view to observing intermediates of the reaction of iminoaziridines and carboxylic acids, we turned to the extremely hindered di-*tert*-butylacetic acid (**4d**).[31] As expected, **4d** reacted only slowly with **11c** (Table 1, entry 5). A single intermediate product was indeed formed in quantitative yield, which slowly rearranged to afford a low-melting crystalline material. In addition, small amounts of methyl isocyanide, imine **12b** (some of which hydrolysed to 2,2-dimethylpropanal), and the acid **4d** were formed from the intermediate product. The molecular formula of the final crystalline product corresponded to a 1:1 adduct of **4d** and **11c**. Its IR spectrum resembled that of **16f**

Table 1. Conditions and results of the Ugi reaction of **3**, **4** and **12**, and the reaction of iminoaziridines **11** with carboxylic acids **4**. The enantiomeric ratios were determined by ^{1}H NMR in the presence of Pirkle's alcohol **22** (2 equiv). Entries 1–7 describe preparative experiments; entries 8–16 describe experiments that were carried out in NMR tubes.

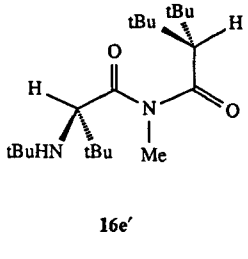
Entry	Cpd. (*R*:*S*)	R^cCO_2H (equiv)	Solvent	*T*/°C	*t*	Products [a] (*R*:*S*) [b]	Yield/%
1	(*R*)-**11a** (83:17)	**4a** (1)	Et_2O	0→25	5 h	(*R*)-**15a** (81:19)	70 [c]
2	**11a**	**4b** (1)	Et_2O	0→25	1 d	**15b**	81 [c]
3	**11a**	**4c** (1)	MeOH	20–25	2 d	**15c**	51 [c]
4	**11b**	**4a** (1)	Et_2O	0	0.5 h	**15d**	95 [c]
5	**11c**	**4d** (1)	Et_2O	20–25	5 d	**16e**, **16e′**	68
6	(*R*)-**11c** [d]	**4a** (1)	Et_2O	0→25	4 h	(*R*)-**16f** [d]	100
7	**3a**+**12b**	**4a** (1.5)	C_6H_6	20–25	2 d	**15f**, **16f**, **19** [e]	54 (**15f**)
8	**11c**	**4d** (1)	$C_6D_5CD_3$	20–25	1 h	**14e**	100
9	**3a**+**12a**	**4a** (1)	C_6D_6	20–25	3 d	**15a**	100
						15f:**16f**:**17**:**19**	**15f**:**16f**
10	(*R*)-**11c** [d]	**4a** (0.5)	$C_6D_5CD_3$	−78→0	9 h	3:96[d]:1:–	3:97
11	(*R*)-**11c** [d]	**4a** (1)	C_6D_6	20–25	1 h	14:81[f]:5:–	15:85
12	(*R*)-**11c** [d]	**4a** (3)	$C_6D_5CD_3$	−78→0	8 h	89[d]:10[d]:1:–	90:10
13	(*R*)-**11c** [d]	**4a** (5)	$C_6D_5CD_3$	−78→0	3 h	89[d]:8[d]:3:–	92:8
14	**3a**+**12b**	**4a** (0.5)	C_6D_6	20–25	15 h	22:65:2:10	25:75
15	**3a**+**12b** [g]	**4a** (1)	C_6D_6	20–25	2 d	50:33:4:13	60:40
16	**3a**+**12b** [h]	**4a** (4)	C_6D_6	20–25	14 h	64:20:5:11	76:24

[a] The conversions were quantitative, except in two cases, see footnotes [g,h]. [b] The enantiomeric ratios of products were not determined when the yield was less than 5%. [c] Yield after recrystallisation; the yield of the crude product was quantitative. [d] (*R*):(*S*) > 99:1. [e] Ratio of products: 71:16:13. [f] (*R*):(*S*) = 95:5. [g] The conversion was 93%. [h] The conversion was 88%.

indicating the presence of an imide moiety. The high-field ^{1}H (600 MHz) and ^{13}C (151 MHz) NMR spectra recorded at 20–25 °C showed signals broadened by exchange between nonequivalent sites of groups belonging to two diastereomers present in similar proportions, in addition to more or less broad signals that had already coalesced. The limit of slow exchange was reached for all signals, when the high-field NMR spectra, including a ^{13}C,^{1}H COSY spectrum, were recorded at −20 °C (Tables 3, 4). Two similar diastereomers A and B (ca. 3:2) were then observed, and assigned the α-amino imide structures **16e** and **16e′**, because, in accordance with the preferred (*E*,*Z*) configuration of acyclic imides,[30] two equilibrating diastereomers are expected for a nonsymmetrical imide. In view of the bulky groups present, it comes as no surprise that the rate of **16e**⇌**16e′** equilibration occurs within the range of the NMR timescales. Of course, we cannot distinguish on the basis of the existing spectroscopic evidence whether the slightly more stable diastereomer A is **16e** or **16e′**.



16e



16e′

The preparative experiments (entries 1–7) show that the nature of the final products of the reactions between iminoaziridines **11** and carboxylic acids **4** depends on the size of the alkyl group at the ring nitrogen atom of **11**. Formation of the two types of products, the α-acylamino amides **15** and α-amino imides **16**, can readily be explained in terms of the common intermediates **13** and **14**. The latter belong to the unstable and hence hardly known class of acyclic isoimides (= *O*-acyl isoamides = *O*-acyl imidates = imino anhydrides)[32, 33] and are identical to the elusive α-adducts of the Ugi reaction. 1,4-Transfer of the acyl to the methylamino group of the isoimides **14a–d** yields the expected Ugi products **15a–d**. If there is a *tert*-butylamino group at the 4-position as in **14e,f**, the 1,4-migration appears to be too slow to compete successfully with the Mumm rearrangement (→**16e,f**). The Mumm rearrangement of isolated[32] and elusive[33–35] isoimides to yield imides has been observed in many cases, including in the Ugi reaction of tertiary enamines.[36] It should be noted that the (intramolecular) *O* → *N*-acyl 1,3-migration occurs only if the C=N moiety of the isoimide adopts the (*E*) configuration.[35]

The interpretation of the results obtained from the iminoaziridine **11c** (Table 1, entries 5 and 6) appeared to be inconsistent with the fact that, in the Ugi reaction of methyl isocyanide, *N*-*tert*-butylimine **12b** and benzoic acid (entry 7), a shift of the benzoyl group from *O* → α-*N* did occur in the α-adduct **14f** to yield the α-benzoylamino amide **15f**. Only small amounts of the Mumm product **16f** were observed under these conditions. In order to resolve this apparent contradiction and to characterise some of the hitherto unknown α-adducts **14** (α-amino isoimides) by NMR spectroscopy, we performed a number of small-scale experiments and monitored them by ^{1}H NMR spectroscopy.

Immediately after mixing [D_6]benzene solutions containing equivalent amounts of (*R*)-**11c** and benzoic acid, the ^{1}H NMR spectrum revealed the presence of an unstable intermediate product (**14f**) besides small amounts of **16f** and traces of **15f**. The proportion of the latter two compounds increased at the expense of the intermediate product until it had disappeared (Figs. 1 and 2). No further change in the ^{1}H NMR spectrum of the mixture was observed after about three to four hours. The α-benzoylamino amide **15f** and the α-amino imide (*R*)-**16f** were formed in the ratio 15:85 (Table 1, entry 11). In addition, small equivalent amounts of methyl isocyanide and imine **12b**, which probably arose from (*R*)-**11c** by general acid-catalysed [2+1] cycloreversion,[37] and small amounts of the known α-amino amide **17**[37] were detected. This result corresponded essentially to the outcome of the preparative experiment (Table 1, entry 6) performed under somewhat different conditions.

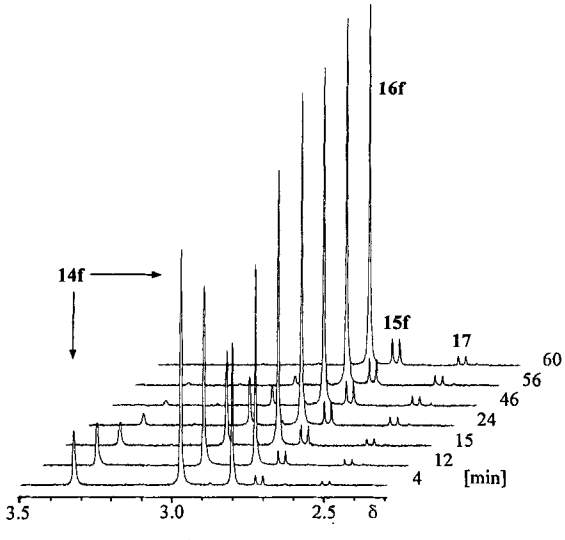


Fig. 1. *N*-Methyl signals in the ^{1}H NMR spectra recorded for a solution in [D_6]benzene of the intermediate product **14f** formed in the reaction of the iminoaziridine (*R*)-**11c** (1 equiv) and benzoic acid (1 equiv), and of the final products **15f** and **16f** (cf. Table 1, entry 11). The 1:1:1 triplet (δ = 1.81, ca. 10%) arising from small amounts of methyl isocyanide is not shown.

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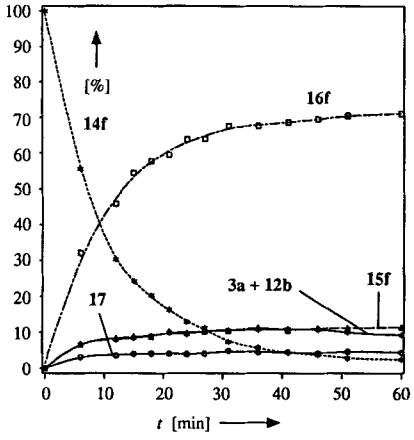


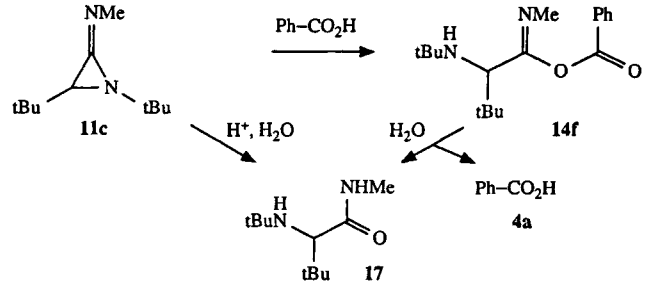
Fig. 2. Consumption (conversion vs. time) of the intermediate product **14f**, formed in the reaction of the iminoaziridine (*R*)-**11c** (1 equiv) with benzoic acid (1 equiv), and the formation of the final products **15f** and **16f**. Small amounts of methyl isocyanide (**3a**), imine **12b** and the hydrolysis product **17** result from side reactions (cf. Table 1, entry 11). The data were obtained from the *N*-methyl signals in ^{1}H NMR spectra recorded for a solution in [D$_6$]benzene (Fig. 1).

The initial step in the reaction of (*R*)-**11c** and benzoic acid could be monitored conveniently by ^{1}H NMR spectroscopy when [D$_8$]toluene solutions of the reactants were mixed at −78 °C. The intermediate product made its appearance very slowly at −40 °C, and at a convenient rate at −20 °C. No earlier intermediate could be detected. The conversion to the intermediate product went to completion within one hour at −20 °C, and it was found to be stable at this temperature.

As expected, the reaction of the iminoaziridine **11c** with di-*tert*-butylacetic acid (**4d**) was slow enough to be monitored by ^{1}H NMR and IR spectroscopy at temperatures as high as room temperature (entry 8). Formation of the intermediate product was complete after one hour. It subsequently underwent a slow Mumm rearrangement to afford an equilibrated mixture of the diastereomeric imides **16e** and **16e′**. The hypothetical product of the *O* → α-*N*-acyl 1,4-shift could not be detected, but, unexpectedly, small amounts of methyl isocyanide, imine **12b** and di-*tert*-butylacetic acid were observed, which increased when the solution of the intermediate product was briefly heated at 70 °C.

The α-amino isoimide structures **14e,f** were assigned to the intermediate products on the basis of IR, ^{1}H NMR and ^{13}C NMR spectra (Tables 2–4). Unstable isoimides of this type, whose (*Z*) → (*E*) diastereomerisation preceding the Mumm rearrangement is not retarded by special groups (-NRAr, -OR) at the nitrogen atom,[32] have hitherto been studied only by IR[33a] and UV spectroscopy.[33b] The ^{1}H and ^{13}C NMR spectra of **14e,f** are characterised by *N*-methyl signals at relatively low field. The carbon spectra exhibit absorptions of C=N (δ = 157) and carbonyl groups (δ = 170, **14e**; 162, **14f**). Comparison of the IR frequencies found for **14e** in the range of the carbonyl and C=N bands ($\tilde{\nu}$ = 1747 and 1694 cm^{-1}) with those of *N*-aryl-*O*-benzoyl isobenzamides ($\tilde{\nu}$ = 1737 and 1680 cm^{-1})[33a] leaves no doubt of the α-amino isoimide structure for the intermediate products.

While exclusively *O* → *N*-acyl 1,3-migration occurred in the highly encumbered α-amino isoimide **14e**, the fate of the α-amino isoimide **14f** at higher temperatures (above 0 °C) surprisingly depended on the amount of benzoic acid present (Table 1, entries 10–13). Treatment of the iminoaziridine (*R*)-**11c** with only 0.5 equivalents of benzoic acid at low temperature led almost exclusively to Mumm rearrangement of the intermediate product **14f** (entry 10). The process occurred very slowly below 0 °C and at a convenient rate at +10 °C. Only 3% α-benzoylamino amide **15f** and 96% Mumm product **16f** were detected after three hours. One equivalent of benzoic acid gave rise to **15f** and **16f** in a ratio of 15:85 (entry 11). An excess of benzoic acid (entries 12 and 13) dramatically increased the rate of the *O* → *N*-acyl 1,4-migration, which could now be monitored conveniently at 0 °C. With five equivalents of acid (entry 13), consumption of the intermediate product **14f** was complete in one and a half hours, and the ratio of (*R*)-**15f**:(*R*)-**16f** was 92:8. This result indicates that only the 1,4-transfer of the acyl to the α-amino group is accelerated by the excess of benzoic acid, and not the Mumm rearrangement. Remarkably, both reactions occurred without any racemisation. Formation of small amounts of the α-amino amide **17** may be rationalised in terms of hydrolysis of the iminoaziridine **11c**, the α-amino isoimide **14f**, or both.



Scheme 4. Formation of the hydrolysis product **17**.

The surprising results obtained with the α-amino isoimide **14f**, which is equivalent to an α-adduct of the Ugi reaction but generated in a different way, prompted us to study the particular Ugi reaction in which **14f** is the expected intermediate (Table 1, entries 14–16). The experimental conditions chosen closely resembled those in the experiments with the iminoaziridine **11c** described in the preceding paragraph. Mixtures of equivalent amounts of methyl isocyanide and the imine **12b** were obtained by thermolysing solutions of **11c** in [D$_6$]benzene. Benzoic acid was added, and the course of the Ugi reaction monitored by ^{1}H NMR spectroscopy (Fig. 3). Initially, α-adduct **14f** was detected; this was followed by a slow rise in the concentrations of the stable products. One equivalent of benzoic acid gave the α-benzoylamino amide **15f** and the α-amino imide **16f** as major products in the proportion of 60:40 (entry 15). In addition,

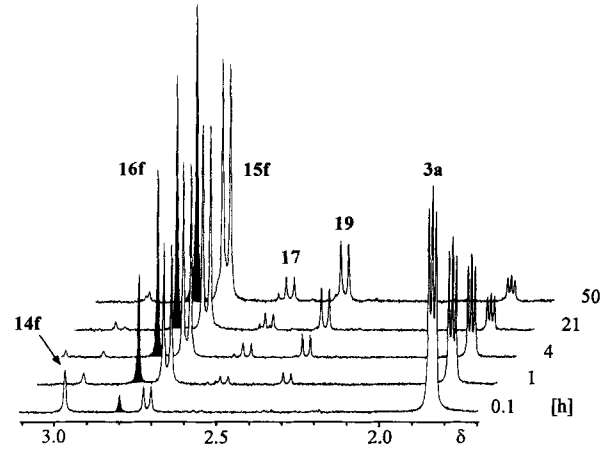
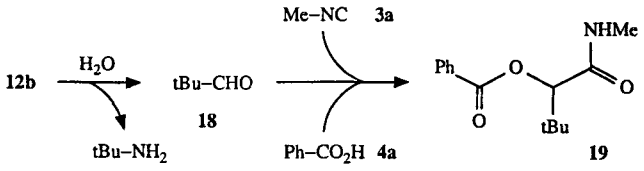


Fig. 3. *N*-Methyl signals in ^{1}H NMR spectra recorded during the course of the Ugi reaction of methyl isocyanide (**3a**), imine **12b** and benzoic acid (1 equiv). Besides the major products **15f** (50%) and **16f** (33%), formed from the α-adduct **14f**, the hydrolysis product **17** and the Passerini product **19** are formed in side reactions (cf. Table 1, entry 15).

small amounts of **17** were formed by hydrolysis of **14f**; the product **19**, formed in a Passerini reaction, was also identified by comparison with an authentic sample prepared from methyl isocyanide (**3a**), 2,2-dimethylpropanal (**18**) and benzoic acid (**4a**) (Scheme 5). Some of the imine **12b** had clearly been



Scheme 5. Formation of the Passerini product **19**.

hydrolysed by traces of moisture to afford **18**. Use of less than one equivalent of benzoic acid (0.5 equiv) changed the ratio of the major products **15f**:**16f** to 25:75 (Fig. 4, top; Table 1, entry 14), while an excess of benzoic acid (4 equiv) reversed this ratio to 76:24 (Fig. 4, bottom; Table 1, entry 16).

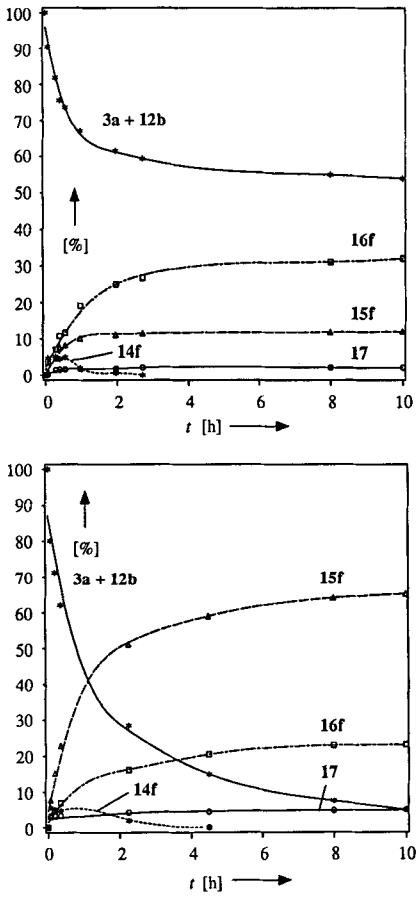
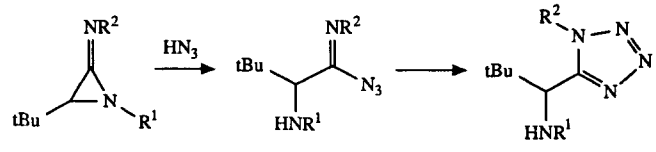


Fig. 4. The Ugi reaction of methyl isocyanide (**3a**), imine **12b** and benzoic acid (0.5 equiv, top; 4 equiv, bottom) showing the disappearance (conversion vs. time) of the α-adduct **14f** and the formation of the final products **15f** and **16f**. Small amounts of the hydrolysis product **17** and the Passerini product **19** (not included) are formed in side reactions. The data were obtained as those of Figure 2 (cf. Table 1, entries 14 and 16).

Finally, from the large number of weakly acidic compounds—besides carboxylic acids—that have so far been used in the Ugi four-component condensation,[3–11] we chose hydrazoic acid as a further example for the reaction with iminoaziridines **11**. Treatment of **11** with a solution of hydrazoic acid in diethyl ether afforded nice crystals of the 1:1 adducts in virtually quantitative yield (Scheme 6). The 5-(α-aminoalkyl)tetrazole



	R^1	R^2
(*R*)-**11a**, (*R*)-**20a**, (*R*)-**21a**	Me	Me
11b, **20b**, **21b**	tBu	Me
(*R*)-**11c**, (*R*)-**20c**, (*R*)-**21c**	Me	tBu

Scheme 6. Reaction of **11** with hydrazoic acid in diethyl ether.

structures **21** were assigned to these products on the basis of the spectroscopic data (Tables 2–4). Very little, if any, racemisation occurred when the nonracemic iminoaziridines (*R*)-**11a** and (*R*)-**11c** were employed as starting materials. This was evident from ^{1}H NMR spectra recorded from solutions of **21** in the presence of Pirkle's alcohol **22**.[29] Similar tetrazole derivatives were obtained by Ugi et al.[3–6] and by Opitz and Merz.[38]

Discussion

Despite the impact of the Ugi four-component condensation, its crucial intermediates, the α-adducts of the isocyanides, have as yet remained elusive. This can be traced back to the fact that their formation is rate-limiting under the conditions of the Ugi reaction while their conversion by $O \rightarrow \alpha$-*N*-acyl 1,4-migration is fast. The reaction of iminoaziridines **11** with carboxylic acids **4** (Scheme 3) not only opens up a novel access to the products **15** of the Ugi reaction, but also allows for the first time the spectroscopic characterisation of α-adducts because their formation from **4** and **11** is already fast at low temperatures. These α-adducts do indeed possess the anticipated[2–6] α-amino isoimide structure **14**. The conversion vs. time diagrams (Figs. 2 and 4) and stereochemical evidence confirm that the isoimides **14** truly result from a direct attack of the carboxylic acid at the iminoaziridine **11** (or of the carboxylate ion at the iminoaziridinium ion **11**·H$^+$), and not from a general acid-catalysed [2+1] cycloreversion of **11** to give isocyanide **3** and imine **12** followed by Ugi reaction with the carboxylic acid. Very little, if any, racemisation is observed in the final products (*R*)-**15f** and (*R*)-**16f** obtained from (*R*)-**11c** and benzoic acid.

Acyclic isoimides undergo a $O \rightarrow N$-acyl 1,3-shift to afford imides (Mumm rearrangement),[32–35] which are strongly favoured for energetic reasons. Ugi and Steinbrückner obtained the product of this rearrangement from piperidino isobutene, cyclohexyl isocyanide and benzoic acid, because a $O \rightarrow \alpha$-*N*-acyl 1,4-transfer is precluded in the corresponding α-adduct.[36] We have now found that both 1,3- and 1,4-migrations of the acyl group may become competitive if the latter is retarded by a bulky group at the α-amino group as in **14f**. This structural feature allowed a study of external factors that influence the outcome of the competition 1,3- vs. 1,4-migration in **14f**. The results demonstrate that the latter is catalysed by benzoic acid while the former is not.

In the α-amino isoimide **14e** obtained from **11c** and di-*tert*-butylacetic acid, both the α-amino group and the *O*-acyl moiety are highly hindered. As expected, only a slow Mumm rearrangement affording the imides **16e**, **16e'** was observed. This is yet another demonstration of the long-known fact that this rear-

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rangement is not significantly influenced by steric effects.[34a] Apparently, the opposite is true for the $O \rightarrow \alpha$-*N*-acyl 1,4-migration of the Ugi reaction. We note in passing that small amounts of methyl isocyanide, the imine **12b** and di-*tert*-butylacetic acid from **14e** are formed by reversion of the α-addition of an imine and a carboxylic acid at an isocyanide.

Formation of the 5-(α-aminoalkyl)tetrazoles **21** (Scheme 6) is interpreted in terms of the addition of hydrazoic acid across the C=N double bond of the iminoaziridines **11** followed by rapid ring opening to afford the imidoyl azides **20**, which are identical to the corresponding α-adducts formed by reaction of hydrazoic acid and the imines **12** with the isocyanides **3**. Cyclisation of **20** yields the final products. Remarkably, hardly any racemisation occurred in this sequence when nonracemic iminoaziridines (*R*)-**11a** and (*R*)-**11c** were used as starting materials. Analogous 5-(α-aminoalkyl)tetrazoles obtained from nonracemic dipeptides in the reaction of phosphorous pentachloride and hydrazoic acid was completely racemic. Racemisation of the intermediate imidoyl azides were invoked to rationalise this result.[39a] Structures of type **21** are interesting subunits of 1,5-disubstituted tetrazole dipeptide analogues, which are conformational mimics of the *cis* amide bond.[39]

Concluding Remarks

The results disclosed in this article demonstrate that iminoaziridines are highly reactive and, if required, nonracemic chiral synthetic equivalents for three of the four components of the Ugi four-component condensation, namely, the primary amine, the carbonyl compound, and the isocyanide. In cases where the Ugi reaction is plagued by steric hindrance[40] or other retarding factors, the highly reactive iminoaziridines may be the reagents of choice. Nonracemic chiral iminoaziridines are readily available,[25, 28] and very little, if any, racemisation occurs in their reactions with two important classes of weak acids (carboxylic acids and hydrazoic acid) that have been used in the Ugi four-component condensation. Retention of the configuration of the iminoaziridine precursors was demonstrated[37] and is anticipated in other cases. Finally, we note that the high reactivity of iminoaziridines reverses the relative rates: formation of α-amino isoimides in the novel route is very fast and their transformation to the final products the rate-limiting step. Thus, we have been able to characterise and study the intermediate α-adducts of the Ugi reaction for the first time.

Experimental Procedure

General: Instrumentation, solvents and reagents: ref. [37]. Conditions and results: Table 1. Melting points, IR and MS (70 eV): Table 2. ^{1}H NMR: Table 3. ^{13}C NMR: Table 4. High-field ^{1}H and ^{13}C NMR: Bruker DMX 600. The assignments are based on DEPT spectra and ^{13}C,^{1}H COSY spectra (**15a–c**, **16f**). Ratios of enantiomers were determined from 5 integrations of signals in 200 MHz ^{1}H NMR spectra recorded in the presence of **22** (2 equiv) [29].

The iminoaziridines (*R*)-**11a** [28], (*R*)-**11b** and **11c** [25] were prepared as reported recently. Solutions of equivalent amounts of **3a** and **12** were obtained as described [25] by heating degassed [D_6]benzene solutions of **11a** (110 °C, 5 h) and **11c** (130 °C, 10 h) in flame-sealed NMR sample tubes. **4d** was prepared according to the published procedure [31] and sublimed three times at 95 °C/10^{-2} Torr; m.p. 73–74 °C (ref. [31]: 74 °C); IR (CCl_4): $\tilde{\nu}$ = 1745 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ = 1.13 (*t*Bu), 2.18 (CH); (C_6D_6): δ = 1.08 (*t*Bu), 2.20 (CH); ^{13}C NMR ($CDCl_3$): δ = 30.7, 34.5 (*t*Bu), 64.6 (CH), 180.8 (C=O); (C_6D_6): δ = 30.8, 34.6 (*t*Bu), 64.6 (CH), 181.1 (C=O). **3a** [41] and solutions of HN_3 in diethyl ether [42] were prepared according to published procedures. **4c** and **22** (*R*:*S* = 99:1) were obtained from Aldrich, **18** from Riedel–de Haën. The petroleum ether (PE) had a boiling range of 30–50 °C.

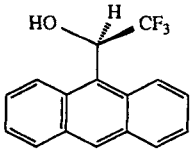

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Table 2. Melting points, IR and MS data.

Cpd. *R*:*S*	M. p. [°C]	IR (KBr) [cm^{-1}] NH	Amide I	II	MS (70 eV, EI) *m/z* (%) M^+	Fragments
(*R*)-**15a** 81:19	126–128	3300	1665 1615	1545	262 (1)	205 (3), 204 (12), 175 (2), 105 (42), 77 (10), 42 (3)
15b	108–110	3350	1675 1630	1540	256 (1)	225 (1), 210 (2), 198 (7), 169 (1), 100 (31), 57 (6), 42 (1)
15c	159–168	3320	1670 1640	1555		
15d	175–176	3310	1670 1610	1540	304 (1)	205 (3), 204 (16), 105 (42), 77 (9), 57 (2), 42 (3)
15f	158–159	3410	1675 1620	1490	304 (0.1)	247 (2), 246 (8), 190 (19), 105 (34), 77 (7), 57 (2)
19	165 (subl.)	3300	1655 1715 (ester)	1545		
(*R*)-**21a** 80:20	93–94	3360				
21b	67–68	3320				
(*R*)-**21c** >99:<1	123–125	3320				
			C=X			
14e			1747	1694 [a]		
16e, **16e'**[b]	46	3400 (br.) 3470 3280	1696 1692	1666 1683 [a]	–	339 (0.2), 297 (2), 155 (1), 142 (25), 86 (19), 71 (4), 57 (12), 41 (3)
(*R*)-**16f** >99:<1	oil	3280 3330 (br.)	1686 [a] 1687	1679 [c]	–	289 (0.3), 247 (6), 191 (3), 142 (13), 105 (12), 86 (20), 57 (4), 41 (3)

[a] Recorded from a solution in tetrachloromethane. [b] Mixture of equilibrating diastereomers. [c] Neat liquid.

(*R*)-2-(*N*-Benzoyl-*N*-methylamino)-*N*,3,3-trimethylbutanamide [(*R*)-**15a**]: Under N_2, a solution of **4a** (122 mg, 1.0 mmol) in diethyl ether (4 mL) was added dropwise to a stirred solution of (*R*)-**11a** (*R*:*S* = 83:17, 140 mg, 1.0 mmol) in diethyl ether (20 mL) cooled to 0 °C. The solution was allowed to warm to 20–25 °C over 1.5 h and was stirred at this temperature for 3.5 h. Distillation of the solvent under vacuum yielded a colourless oil (264 mg, quant.), which afforded colourless crystals (184 mg, 70%, *R*:*S* = 81:19) on crystallisation from PE/ethyl acetate. $C_{15}H_{22}N_2O_2$ (262.4): calcd C 68.67, H 8.45, N 10.68; found C 68.35, H 8.59, N 10.57.

2-[*N*-Methyl-*N*-(3,3-dimethyl)butanoylamino]-*N*,3,3-trimethylbutanamide (15b): According to the procedure given for (*R*)-**15a**, pale yellow crystals (256 mg, quant.), m.p. 102–106 °C, were obtained from **4b** and **11a** after 1 d. Recrystallisation from PE afforded colourless crystals (207 mg, 81%). $C_{14}H_{28}N_2O_2$ (256.4): calcd C 65.59, H 11.01, N 10.93; found C 64.97, H 11.29, N 10.60.

2-[*N*-(Benzoylaminoacetyl)-*N*-methylamino]-*N*,3,3-trimethylbutanamide (15c): A solution of **4c** (179 mg, 1.0 mmol) and **11a** (140 mg, 1.0 mmol) in dry methanol (20 mL) was stirred for 2 d at 20–25 °C under N_2. Distillation of the solvent under vacuum yielded a pale yellow oil (320 mg, quant.), which afforded colourless crystals (163 mg, 51%) on crystallisation from PE/ethyl acetate (10 mL, 10:3) at −21 °C. $C_{17}H_{25}N_3O_3$ (319.4): calcd C 63.93, H 7.89, N 13.16; found C 63.71, H 7.91, N 12.94.

2-(*N*-Benzoyl-*N*-methylamino)-*N*-*tert*-butyl-3,3-dimethylbutanamide (15d): According to the procedure given for (*R*)-**15a**, colourless crystals (292 mg, 96%), m.p. 174–175 °C, were obtained from **4a** (122 mg, 1.0 mmol) and **11b** (182 mg, 1.0 mmol) after 0.5 h. Recrystallisation from PE/ethyl acetate (20 mL, 3:1) yielded colourless crystals (289 mg, 95%). $C_{18}H_{28}N_2O_2$ (304.4): calcd C 71.02, H 9.27, N 9.20; found C 71.28, H 9.29, N 9.11.

2-(*N*-*tert*-Butyl-*N*-benzoylamino)-*N*,3,3-trimethylbutanamide (15f): A solution of **3a** and **12b** (1:1) in benzene was prepared by heating a degassed solution of **11c** (365 mg, 2.0 mmol) in dry benzene (5 mL) in a sealed, thick-walled glass tube at

Table 3. Chemical shifts (δ) in ^{1}H NMR spectra (200 MHz). Spectra of nonracemic compounds were also recorded in the presence of Pirkle's alcohol (**22**, 2 equiv). The averages of the chemical shifts of the enantiomers $[\delta(R)+\delta(S)]/2$ and (in italics) the differences of resonance frequencies $\nu(R)-\nu(S)$ [Hz], taken from these spectra, are listed. Similar values of chemical shifts (in italics) may be exchanged.

Cpd.	*t*Bu	—CH—	NMe (R^1)	NR^2	$J_{NH,Me}$	NH [a]	R^c	[b]
(*R*)-**15a**	1.17	5.00	3.09	2.72	*4.8*	6.6	7.42 (m)	C
	1.07	4.83	2.99	2.60				C
	−21.5	*−19.7*	*9.8*	*−7.2*				
15b	1.069	4.99	3.15	2.75	*4.8*	6.2 1.9	[c]	C
15c	1.09	4.87	3.22	2.78	*4.8*	7.3 1.9	[d] 7.40 – 7.52 7.79 – 7.87	C
15d	1.18	4.89	3.07	1.35		6.0	7.42 (m)	C
(*R*)-**21a**	1.00	3.60	2.20	4.12		1.8		C
	0.92	3.50	2.06	4.02				C
	−2.4	*−2.4*	*4.8*	*0.9*				
21b	1.04	3.91	2.21	1.80		1.7		C
	*t*Bu	—CH—	N*t*Bu					
14e	1.10	3.16 [a]	1.20	3.07		2.2	1.15 (2 *t*Bu) 2.22 (CH)	B
(*R*)-**14f** [e]	1.13	3.34	1.23	2.97		[f]	[f]	B
	1.13	3.46	1.28	2.89		[f]	[f]	T
15f	1.21	3.87	1.24	2.86	*4.8*	9.0	7.34 – 7.54	C
	1.08	3.76	1.13	2.74				C
	–	*8.4*	–	–				
16e, 16e' [g]								
A	0.93	5.02	1.11	3.326		2.2	0.996 (*t*Bu) 1.077 (*t*Bu) 2.87 (CH)	C
B	0.96	4.44	1.074	3.332		2.2	0.996 (*t*Bu) 1.146 (*t*Bu) 3.52 (CH)	C
(*R*)-**16f**	0.95	4.48	1.08	3.15		2.1	7.46 – 7.61	C
	1.04	4.75	1.19	2.69				B
	3.3	–	–	*4.7*				
19	1.07	5.19		2.36	*4.8*	5.5	7.01 – 7.14 8.10 – 8.15	B
	1.13	5.09		2.82	*4.8*	5.9	7.45 – 7.67 8.07 – 8.12	C
(*R*)-**21c**	0.90	3.74	0.95	4.14		1.6		C
	0.85	3.72	0.91	4.09				C
	2.0	–	–	–				

[a] Broad signal. [b] Solvent: B = [D$_6$]benzene, C = [D]trichloromethane, T = [D$_8$]toluene. [c] δ = 1.069 (*t*Bu), 2.21, 2.38 (AB, $^2J_{AB}$ = 14.4 Hz, CH_2). [d] δ = 4.34, 4.25, 1.7 (ABX, ^2J = 18.0 Hz, $^3J_{CH,NH}$ = 4.2, 4.0 Hz, CH_2NH). [e] Spectrum recorded at −20 °C. [f] Hidden under the signal of the solvent. [g] 600 MHz spectrum recorded at −20 °C from a solution of an equilibrated mixture of diastereomers A and B (3:2).

Table 4. Chemical shifts (δ) in ^{13}C NMR spectra recorded from solutions of some derivatives of 3,3-dimethylbutanoic acid. Similar values (in italics) from carbon atoms that bear the same number of protons may be exchanged.

Cpd.	Me_3C	—CH—	—NMe (R^1)		NR^2	C=X	CH_x R^c	quat.C [a]
(*R*)-**15a**	27.9	35.3	62.7	36.6	25.8	170.2 173.4	126.8 136.4 128.5 129.8 (Ph)	C
15b	27.6	35.0	61.6	34.4	25.8	170.6 173.7	29.9 31.5 (*t*Bu) 45.0 (CH_2)	C
15c	27.7	35.5	63.1	32.5	26.0	167.2 169.4 170.0	127.0 133.9 128.5 131.7 (Ph) 42.0 (CH_2)	C
15d	27.9	35.4	63.3	36.4	28.7 51.2	169.0 173.5	126.8 136.5 128.5 129.7 (Ph)	C
(*R*)-**21a**	26.6	35.9	65.1	35.4	34.2	155.9		C
21b	27.1	36.0	64.1	35.6	36.0 62.2	157.1		C
	Me_3C	—CH—	—$NCMe_3$					
14e	27.5	36.2	*64.25*	50.8 30.5	35.8	157.1 169.8	*64.54* (CH) 31.1 34.8 (2 *t*Bu)	B
(*R*)-**14f** [b]	27.2	35.9	63.2	50.9 30.1	35.1	156.8 161.7	128.8 136.9 130.3 133.8 (Ph)	T
(*R*)-**15f**	30.2	36.4	74.3	60.1 31.1	26.0	174.8 176.4	127.7 140.8 128.2 130.5 (Ph)	C
16e, 16e' [c]								
A	26.42	35.90	63.3	50.01 30.73	34.3	177.2 183.4	60.2 (CH) 29.69 36.35 30.68 36.52 (*t*Bu)	C
B	26.42	35.90	61.4	50.10 31.05	32.8	179.3 180.3	61.2 (CH) 29.74 36.35 30.71 36.26 (*t*Bu)	C
(*R*)-**16f**	26.9	35.3	61.4	50.8 30.0	36.0	173.8 181.4	128.3 135.5 128.7 131.5 (Ph)	B
19	26.5	34.5	81.7	– –	25.6	165.5 168.5	128.7 130.4 129.9 133.3 (Ph)	B
(*R*)-**21c**	26.5	36.3	56.1	50.7 29.3	34.5	158.2		C

[a] Solvent: B = [D$_6$]benzene, C = [D]trichloromethane, T = [D$_8$]toluene. [b] Spectrum recorded at −50 °C. [c] 151 MHz Spectrum recorded at −20 °C from a solution of an equilibrated mixture of diastereomers A and B (3:2).

130 °C for 10 h [25]. After addition of **4a** (366 mg, 3.0 mmol), the mixture was kept at 20–25 °C for 2 d with exclusion of air. Dichloromethane (30 mL) was added followed by extraction with saturated aqueous $NaHCO_3$ (2 × 30 mL) and water (2 × 20 mL). Drying of the organic layer with K_2CO_3 and distillation of the solvent under vacuum yielded a pale yellow oil (542 mg) consisting of **15f**, **16f** and **19** (71:16:13, ^{1}H NMR). Recrystallisation from PE/ethyl acetate (10:1, 10 mL) at −20 °C yielded colourless crystals (329 mg, 54%). $C_{18}H_{28}N_2O_2$ (304.4): calcd C 71.02, H 9.27, N 9.20; found C 70.87, H 9.36, N 9.07.

2-(*N*-*tert*-Butylamino)-*N*-(2-*tert*-butyl-3,3-dimethylbutanoyl)-*N*,3,3-trimethylbutanamide (16e): A solution of **4d** (172 mg, 1.0 mmol) in diethyl ether (5 ml) was added to a stirred solution of **11b** (182 mg, 1.0 mmol) in diethyl ether (10 mL) under N_2. The solution was stirred at 20–25 °C for 5 d, while the conversion was monitored by IR spectroscopy. The solution was extracted with saturated aqueous $NaHCO_3$ (2 × 20 mL) and water (2 × 20 mL). Drying of the organic layer with Na_2SO_4 and distillation of the solvent under vacuum yielded colourless crystals (241 mg, 68%). $C_{21}H_{42}N_2O_2$ (354.6): calcd C 71.14, H 11.94, N 7.90; found C 71.05, H 12.22, N 7.84.

(*R*)-2-(*N*-*tert*-Butylamino)-*N*-benzoyl-*N*,3,3-trimethylbutanamide [(*R*)-16f]: According to the procedure given for (*R*)-**15a**, a colourless oil ($R:S$ = >99:<1, 304 mg, quant.) was obtained from **4a** and (*R*)-**11c** ($R:S$ = 99:1) after 4 h. The product was pure (^{1}H NMR). $C_{18}H_{28}N_2O_2$ (304.4): calcd C 71.02, H 9.27, N 9.20; found C 71.01, H 9.50, N 9.15.

2-(*O*-Benzoyloxy)-*N*,3,3-trimethylbutanamide (19): Methyl isocyanide (**3a**) (123 mg, 3.0 mmol) was added under N_2 to a stirred solution of **4a** (366 mg, 3.0 mmol) and **18** (258 mg, 3.0 mmol) in diethyl ether (10 mL) cooled to 0 °C. The mixture was allowed to warm to 20–25 °C over 1.5 h and stirred at this temperature for 10 h. The solution was extracted with saturated aqueous $NaHCO_3$ (2 × 20 mL) and water (2 × 20 mL) and dried with Na_2SO_4. Distillation of the solvent under vacuum yielded a colourless solid (696 mg, 93%). Recrystallisation from cyclohexane (3 mL) afforded colourless needles (479 mg, 64%). $C_{14}H_{19}NO_3$ (249.3): calcd C 67.45, H 7.68, N 5.62; found C 67.38, H 7.70, N 5.58.

(*R*)-1-Methyl-5-[1-(*N*-methyl)amino-2,2-dimethylpropyl]-1*H*-tetrazole [(*R*)-21a]: A solution of HN_3 in diethyl ether (10 mL, 0.2 M, 2.0 mmol) was added dropwise under N_2 to a stirred solution of (*R*)-**11a** ($R:S$ = 83:17, 140 mg, 1.0 mmol) cooled to 0 °C. The solution was allowed to warm to 20–25 °C over 1.5 h, following which the solvent was distilled under vacuum to afford colourless crystals (184 mg, quant.), m.p. 90–93 °C. Recrystallisation from PE/ethyl acetate (2:1) yielded colourless crystals ($R:S$ = 80:20, 154 mg, 84%). $C_8H_{17}N_5$ (183.2): calcd C 52.43, H 9.35, N 38.22; found C 52.39, H 9.35, N 38.35.

1-*tert*-Butyl-5-[1-(*N*-methyl)amino-2,2-dimethylpropyl]-1*H*-tetrazole (21b): According to the procedure described for (*R*)-**21a**, colourless crystals (226 mg, quant.), m.p. 64–68 °C, were obtained from **11b** and HN_3. Recrystallisation from diethyl ether afforded colourless prisms (203 mg, 90%). $C_{11}H_{23}N_5$ (225.3): calcd C 58.63, H 10.29, N 31.08; found C 58.39, H 10.54, N 30.89.

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(*R*)-5-[1-(*N*-*tert*-Butyl)amino-2,2-dimethylpropyl]-1-methyl-1*H*-tetrazole [(*R*)-21c]: According to the procedure described for (*R*)-**21a**, colourless crystals (226 mg, quant.) were obtained from (*R*)-**11c** (*R*:*S* = 99:1) and HN_3. Recrystallisation from PE/ethyl acetate afforded colourless needles (*R*:*S* = 99:1, 203 mg, 90%). $C_{11}H_{23}N_5$ (225.3): calcd C 58.63, H 10.29, N 31.08; found C 58.44, H 10.58, N 30.74.

Small-scale experiments were performed with **11c**, (*R*)-**11c** or **3a** + **12** in NMR sample tubes, which were dried at 200–300 °C and filled with Ar, and dry deuterated solvents (0.5 mL). The conversions were monitored by ^{1}H NMR spectroscopy (200 MHz), and the ratios of the products were calculated from integrations of *N*-methyl signals. In low-temperature experiments carried out in [D_8]toluene as solvent, the temperature of the samples (−78 °C at the onset) was allowed to rise in steps of 10°. After complete conversion, the ratios of enantiomers were determined from ^{1}H NMR spectra recorded after addition of **22** (2 equiv). Ratios of reactants, conditions, and results: Table 1 (entries 8–16).

a) (*R*)-**11c** (a μmol) and **4a** (b μmol) in [D_6]benzene: a = 96, b = 100 (entry 11) (Figs. 1, 2); in [D_8]toluene: a = 134, b = 67 (entry 10); a = 50, b = 151 (entry 12); a = 34, b = 168 (entry 13).

b) **3a** (a μmol) + **12b** (a μmol) and **4a** (b μmol) in [D_6]benzene: a = 138, b = 68 (entry 14) (Fig. 4, top); a = 108, b = 110 (entry 15) (Fig. 3); a = 38, b = 150 (entry 16) (Fig. 4, bottom).

c) **3a** (98 μmol) + **12a** (98 μmol) and **4a** (108 μmol) in [D_6]benzene (entry 9).

d) **11c** (6 mg, 33 μmol) and **4d** (6 mg, 35 μmol) in [D_8]toluene (entry 8).

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