Aromatic Nitro Groups and Their Reactions with Chelated Ester Enolates

Daniel Stolz, Uli Kazmaier,* Rigobert Pick

Institut für Organische Chemie, Universität des Saarlandes, 66123 Saarbrücken, Germany
Fax +49(681)3022409; E-mail: u.kazmaier@mx.uni-saarland.de

Received 1 May 2006

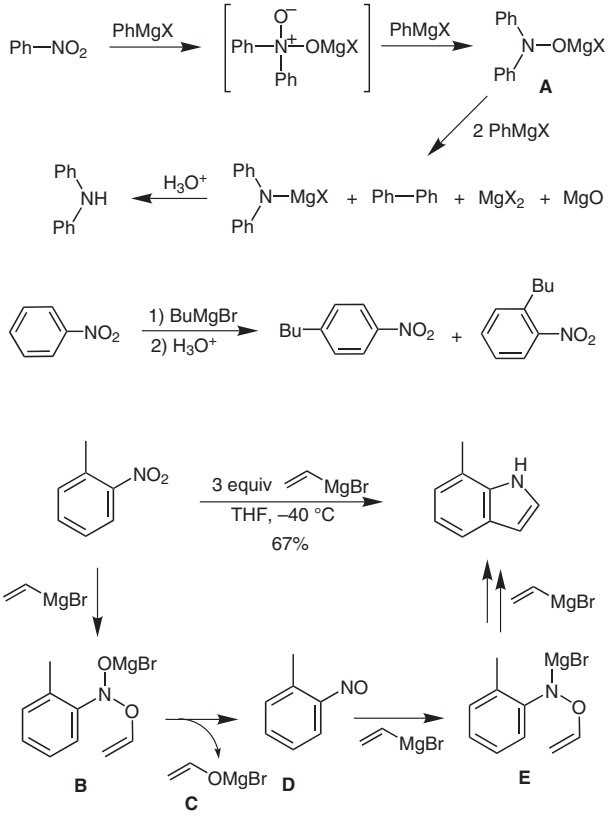
Abstract: Chelated amino acid ester enolates react with aromatic nitro compounds in a 1,3-addition mode at the nitro group giving amino acids bearing an aryl(hydroxy)amino side chain. Best results were obtained with trifluoroacetyl-protected glycinates. Two equivalents of enolate are necessary for complete conversion, because one equivalent is oxidized during the reaction.

Key words: amino acids, chelates, enolates, nitroarenes, nitrosoarenes

Nitro compounds play an important role as key intermediates in organic synthesis. Besides the very popular nitro aldol reaction,[1] of major interest is the conversion of the nitro group into other functionalities. For example, nitro compounds can easily be reduced either to amines[2] or to nitroso, hydroxyamino, and hydrazino derivatives, depending on the pH and the reducing agent.[3] Dehydration of nitroalkanes allows the in situ generation of nitrile oxides, reactive intermediates which undergo rapid 1,3-dipolar cycloaddition.[4] Very recently Carreira's[5] and our own group[6] reported independently a reductive conversion of nitro groups into nitriles.

Less investigated, but not of less interest, are additions of C-nucleophiles to the nitro group.[7] In 1927 Gilman and McCracken,[8] and a little later Kursanov and Solodkov[9] investigated the reaction of nitrobenzene with an excess of phenylmagnesium chloride and obtained diphenylamine via the hydroxylamine derivative **A**, which was reduced in situ by excess Grignard reagent (Scheme 1). Other Grignard reagents such as benzyl- and allylmagnesium halides also attack the nitro group at nitrogen (1,2-addition),[10] and the intermediates formed can be converted into different products depending on the reaction conditions used.[11] Interestingly, alkyl Grignard reagents show different reaction behavior; they preferentially undergo conjugate addition at the aromatic ring system (Scheme 1).[12]

In 1989 Bartoli et al. reported an efficient synthesis of 7-substituted indoles by addition of vinylmagnesium bromide to substituted nitrobenzenes.[13] The first step is nucleophilic attack of the Grignard reagent on the oxygen (and not on the nitrogen) of the nitro group. The resulting labile O-alkylated intermediate **B** then undergoes elimination of enolate **C,** giving an aromatic nitroso compound **D**.[14] This is attacked a second time by the Grignard reagent and the *O*-vinylhydroxylamine derivative **E** formed

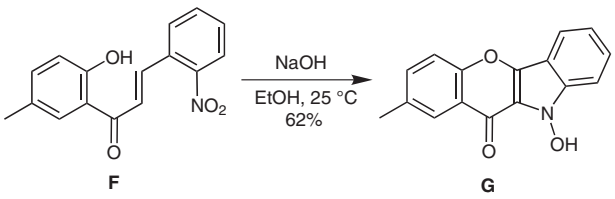


Scheme 1

undergoes a [3,3]-sigmatropic rearrangement to give the indole (Scheme 1).

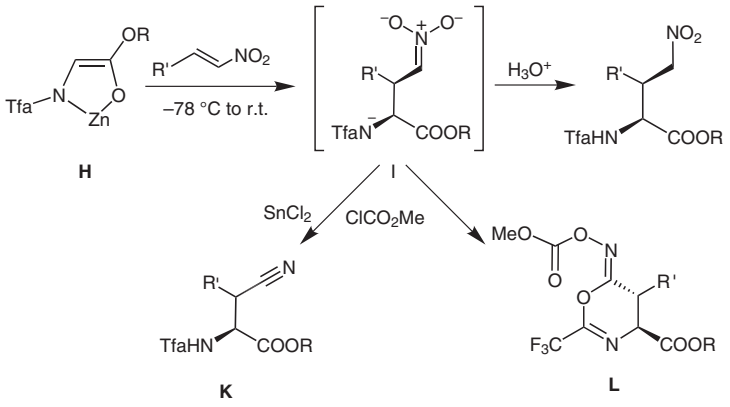
In principle, nitro groups can also be attacked by enolates, as indicated by the conversion of chalcone **F** into benzopyranone **G** (Scheme 2).[15] But, to the best of our knowledge, no other examples of this type of addition have been reported in the literature.

For several years our group has been investigating the reactions of chelated amino acid ester enolates as nucleophiles in various types of reactions.[16] Based on their high reactivity, these enolates react under very mild reaction



Scheme 2

SYNTHESIS 2006, No. 19, pp 3341–3347
Advanced online publication: 04.09.2006
DOI: 10.1055/s-2006-950228; Art ID: C04706SS



Scheme 3

conditions to give a wide range of unnatural amino acids. Very recently, we reported the highly stereoselective 1,4-addition of these enolates **H** towards nitroalkenes (Scheme 3).[17] Interestingly, the nitronates **I**, formed as intermediates, could be trapped not only by hydrogen chloride but also by acyl halides giving nitriles **K**[6] or different heterocycles such as **L**[18] depending on the reaction conditions and protecting groups used.

Therefore, we have focused our interest on the reactions of aromatic nitro compounds (Figure 1), because we were interested to see if these substrates also react in a conjugate fashion via nucleophilic attack of the enolate **H** on the aromatic ring (a), or if reaction occurs directly on the nitro group (b).[19]

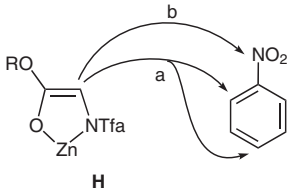
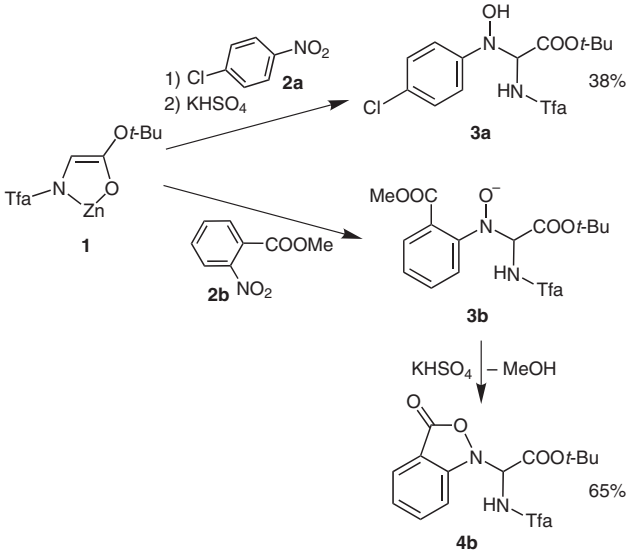


Figure 1 Nucleophilic attack of chelated enolates on nitroarenes.

Based on our previous good results obtained with trifluoroacetyl-protected *tert*-butyl glycinate,[16] we used enolate **1** as the nucleophile in the reaction with 1-chloro-4-nitrobenzene (**2a**). Indeed, a reaction was observed, however, it was not at the aromatic ring system but at the nitro group, and the *N*-arylhydroxylamine **3a** was obtained in very moderate yield (<20%). In addition, the yield varied strongly from reaction to reaction, hence, we attempted to optimize the reaction conditions. During these investigations we found, that increasing the amount of nucleophile to 2.5 equivalents gave the expected product in a very clean reaction, but still only 38% yield (Scheme 4). This was quite surprising, because all the starting material was consumed. In contrast, methyl 2-nitrobenzoate (**2b**) gave a much higher yield of addition product. In this case, the hydroxylamine derivative **3b** was not obtained, the product was the lactonization product **4b**, which was not unexpected. We assumed that the cyclized product **4b** is more stable compared to the primary addition products **3a** (or **3b**, respectively). With respect to the structure of **3a**, the N-hydroxylated aminal structure may be sensitive towards hydrolysis, especially under acidic conditions. Therefore we also changed the workup protocol.

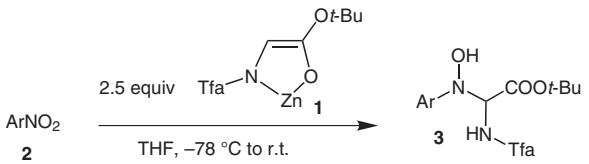
Frequently, we used 1 M potassium hydrogen sulfate solution to keep the organic layer neutral to avoid deprotection of the *tert*-butyl ester and to suppress acid-catalyzed elimination of water from the addition product; obviously, these conditions were not sufficiently mild. However, when a buffer solution (pH ~6) was used instead, the expected product **3a** was obtained in near quantitative yield (Table, entry 1). To prove the generality of this reaction, we subjected several other nitroarenes to these optimized conditions (entries 2–8).

The yield obviously depends on the electronic nature of the aromatic ring system. With electron-withdrawing substituents the yields were generally very high and they decrease slightly with decreasing electron-withdrawing properties, as illustrated in the series of halogen-substituted derivatives (Table 1, entries 1–3). Several other functionalities such as cyano or ester groups are tolerated as well (entries 4 and 5), because obviously the attack on the



Scheme 4

Table 1 Addition of Chelated Enolates to Various Nitroarenes

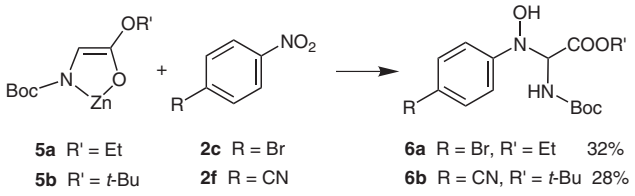


Entry	Substrate	Ar	Product	Yield[a] (%)
1	**2a**	4-ClC_6H_4	**3a**[19]	95
2	**2c**	4-BrC_6H_4	**3c**[19]	88
3	**2d**	4-IC_6H_4	**3d**	74
4	**2e**	4-$MeO_2CC_6H_4$	**3e**[19]	85
5	**2f**	4-NCC_6H_4	**3f**[19]	85
6	**2g**	5-quinolyl	**3g**	60[b]
7	**2h**	Ph	**3h**	81
8	**2i**	2-Cl-5-$MeOC_6H_3$	**3i**	77

[a] Workup conditions: NH_4OAc/AcOH buffer (pH 6).
[b] Starting material (31%) recovered.

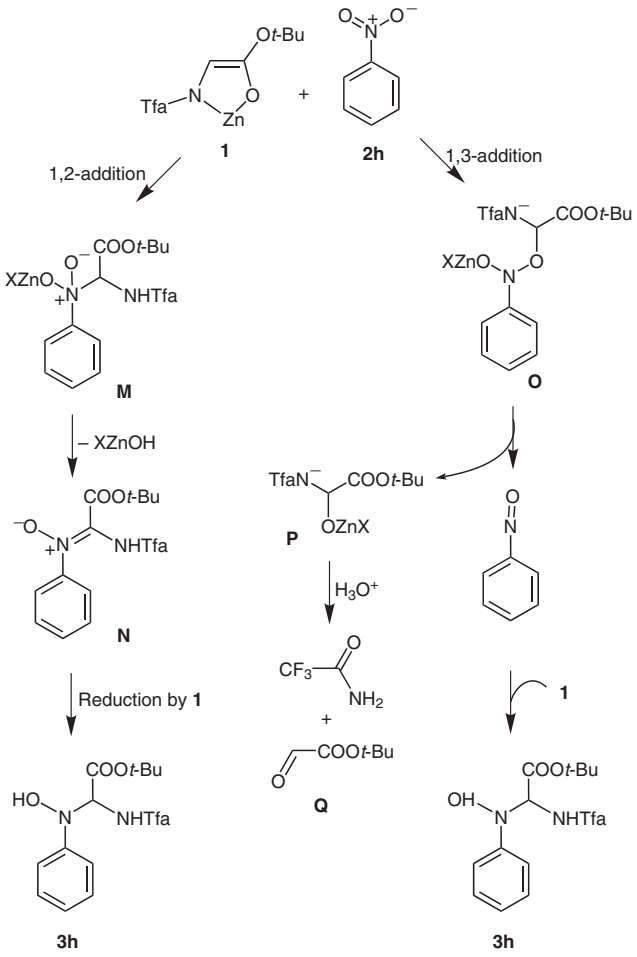
nitro group is much faster than the attack on these, also well-activated, functionalities. Even with nitrobenzene the yield was good (entry 7), but no reaction was observed with 4-nitroanisole and other 'electron-rich' nitro derivatives, as well as pyridine *N*-oxides. Introduction of one additional electron-withdrawing group, as in **2i**, resulted again in a good yield of product **3i** (entry 8).

To show the influence of the attacking nucleophile, we also varied the substitution pattern on the glycinate (Scheme 5). This showed that in this reaction the trifluoroacetyl protecting group is superior, because with carbamates such as **5** the yields dropped dramatically, and this decrease was nearly independent of the ester used.



Scheme 5

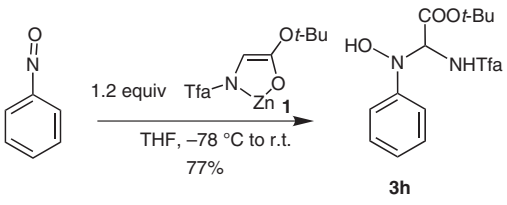
Interestingly, good yields were only obtained if at least two equivalents of the enolate were used. This indicates that in this case one equivalent may act as the nucleophile and the second equivalent may act as the reducing agent, comparable to the Grignard additions shown in Scheme 1. In the respect that the nucleophilic attack on the nitro group can occur either on nitrogen (1,2-addition) or on oxygen (1,3-addition), one can in principle propose two mechanistic scenarios (Scheme 6). If the attack occurs directly at the nitrogen of **2h** (1,2-addition), an intermediate **M** should be formed which can eliminate zinc hydroxide



Scheme 6

giving nitrone **N**. Such a mechanism was proposed by Bartoli for the benzyl and allyl Grignard addition,[10,11] but we were not able to detect any nitrone intermediate. On the other hand, if the enolate attacks in a 1,3-fashion on the oxygen of **2h**, one might expect an intermediate **O**, which eliminates deprotonated α-hydroxyglycine **P** giving nitrosobenzene, which can also be attacked by the second equivalent of enolate with formation of the expected product **3h**.

To gain evidence for the 1,3-addition, we investigated the reaction of nitrosobenzene with enolate **1** under the same reaction conditions as the corresponding nitro compound **2h** (Scheme 7), although only a slight excess of the enolate **1** (1.2 equiv) was used. Indeed, the reaction gave the same product **3h** and the yield was very close to that ob-

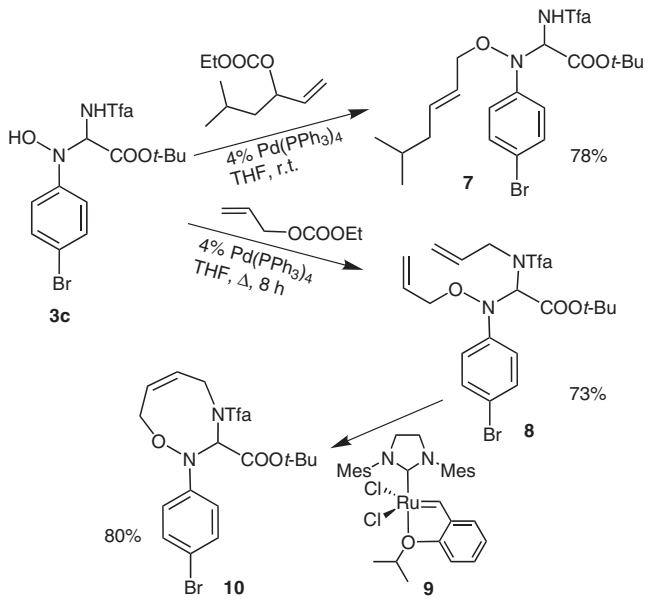


Scheme 7

tained starting from the nitro compound **2h** (Table 1, entry 7).

We also attempted to detect the corresponding oxidation products. Looking closely at intermediate **P**, one might expect that this hemiaminal intermediate will either decompose directly in solution, or, at the very least, during acidic workup. Therefore, we took sample probes during the reaction, quenched them with 1 M potassium hydrogen sulfate solution and analyzed them by GC/MS and NMR. After 1 minute at –78 °C the glyoxylate **Q** could already be unambiguously detected, what clearly indicates that nucleophilic attack on the nitro group is a very rapid process and that the reaction proceeds via this second 1,3-addition pathway.

Of course, we were also interested to see if it is possible to further modify the hydroxylamine derivatives **3**. First we attempted to trap the deprotonated intermediates directly with alkylation agents such as methyl iodide or benzyl bromide, but no alkylation was observed under these conditions. Therefore, we investigated the palladium-catalyzed allylic alkylation (Scheme 8). During our studies on the application of this important reaction to the synthesis of amino acids,[20] we observed that slightly acidified alcohols can be allylated under nearly neutral conditions with allylic carbonates.[21] Using these allylic substrates, the alcoholate is formed in situ during π-allyl complex formation, and this base then deprotonates the acidified alcohol functionality, generating the required nucleophile. One might expect that this protocol should also operate with the hydroxylamine derivatives **3** and **6**. Indeed, the O-allylation of **3c** worked very well at room temperature giving monoallylated product **7**. In principle, further palladium-catalyzed transformations should be possible at the aryl halide moiety. Interestingly, no N-allylation was observed under these mild reaction conditions. But under more drastic conditions and with an excess of allylation agent (3 equiv) both acidic positions can be allylated.[22] Product **8** thus obtained was subsequently subjected to ring-closing metathesis using the Hoveyda–Blechert catalyst **9**, providing cyclic derivative **10**.



Scheme 8

In conclusion, we have shown that chelated enolates are versatile nucleophiles for direct addition to aromatic nitro groups. The first step of the reaction is a reduction of the nitro group by the enolate to the corresponding nitroso compound, which is attacked by a second equivalent of the enolate. Therefore, in principle, the reaction products **3** can be obtained from either aromatic nitro or nitroso derivatives, but in general nitro compounds are more easily available.

All reactions were carried out in oven-dried glassware (100 °C) under argon. All solvents were dried before use. THF was distilled from $LiAlH_4$. The products were purified by flash chromatography on silica gel (32–63 μm). Mixtures of EtOAc and hexanes were generally used as eluents. TLC: commercially precoated Polygram SIL-G/UV_{254} plates (Macherey–Nagel). Visualization was accomplished with UV light and $KMnO_4$ soln. Melting points were determined on a Büchi melting point apparatus and are uncorrected. ^1H and ^{13}C NMR were obtained on a Bruker DRX-500 spectrometer. HRMS were recorded on a Finnigan MAT 90 (CI) mass spectrometer. Elemental analysis was carried out at the department of chemistry, University of Saarbrücken.

Additions of Chelated Enolates to Nitroarenes; General Procedure

The base used for enolate formation was prepared directly before use. In a Schlenk flask HMDS (428 mg, 2.65 mmol) was dissolved in THF (2 mL) under N_2. 1.6 M *n*-BuLi (1.64 mL, 2.63 mmol) was added dropwise at –20 °C and the mixture was allowed to stir at r.t. for 10 min. The mixture was cooled to –78 °C and a soln of $ZnCl_2$ (187 mg, 1.38 mmol, dried previously in vacuo with a hot-air gun) was added with the amino acid derivative (1.25 mmol) in THF (3 mL). The suspension was stirred at –78 °C for further 30 min to form the chelated ester enolate. The nitroarene (0.5 mmol) was then added in THF (1 mL). The soln was allowed to warm to r.t. overnight and then diluted with Et_2O (10 mL) and hydrolyzed in an ice bath with NH_4OAc/AcOH buffer (pH 6, 10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 ×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (silica, hexane–EtOAc).

***tert*-Butyl [(4-Chlorophenyl)(hydroxy)amino][(trifluoroacetyl)amino]acetate (3a)**

Starting from **2a** (79 mg, 0.5 mmol), **3a** was obtained as a colorless solid; yield: 175 mg (95%); mp 101 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.40 [s, 9 H, OC(CH_3)$_3$], 5.68 (d, *J* = 7.9 Hz, 1 H, NC*H*CO), 5.90 (s, 1 H, NO*H*), 7.14 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.23 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.56 (d, *J* = 7.6 Hz, 1 H, N*H*CO).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.8 [OC(CH_3)$_3$], 72.6 (NCHCO), 84.8 [O*C*(CH_3)$_3$], 115.6 (q, $J_{C,F}$ = 286.1 Hz, CO*C*F_3), 118.2 (Ar*C*), 128.7 (Ar*C*), 128.8 (Ar*C*), 147.4 (Ar*C*), 157.3 (q, $J_{C,F}$ = 37.2 Hz, *C*OCF_3), 164.7 (*C*O).

HMRS (CI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{16}ClF_3N_2O_4$: 368.0751; found: 368.0746.

Anal. Calcd for $C_{14}H_{16}ClF_3N_2O_4$ (368.77): C, 45.59; H, 4.38; N, 7.59. Found: C, 45.28; H, 4.30; N, 7.57.

***tert*-Butyl [(4-Bromophenyl)(hydroxy)amino][(trifluoroacetyl)amino]acetate (3c)**

Starting from **2c** (51 mg, 0.25 mmol), **3c** was obtained as a colorless solid; yield: 91 mg (88%); mp 98 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39 [s, 9 H, OC(CH_3)$_3$], 5.68 (d, *J* = 8.0 Hz, 1 H, NC*H*CO), 6.16 (br s, 1 H, NO*H*), 7.06 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 7.35 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 7.56 (d, *J* = 7.0 Hz, 1 H, N*H*CO).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.8 [OC(*C*H$_3$)$_3$], 72.5 (N*C*HCO), 84.9 [O*C*(CH$_3$)$_3$], 115.5 (q, $J_{C,F}$ = 286 Hz, CO*C*F$_3$), 116.1 (Ar*C*), 118.5 (Ar*C*), 131.7 (Ar*C*), 147.9 (Ar*C*), 157.3 (q, $J_{C,F}$ = 38.1 Hz, *C*OCF$_3$), 164.7 (*C*O).

HMRS (CI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{16}BrF_3N_2O_4$: 412.02; found: 412.0247.

Anal. Calcd for $C_{14}H_{16}BrF_3N_2O_4$ (413.19): C, 40.69; H, 3.90; N, 6.78. Found: C, 40.82; H, 3.80; N, 6.76.

***tert*-Butyl [(Hydroxy)(4-iodophenyl)amino][(trifluoroacetyl)amino]acetate (3d)**

Starting from **2d** (125 mg, 0.5 mmol), **3d** was obtained as a yellow solid; yield: 171 mg (74%); mp 115 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 [s, 9 H, OC(CH_3)$_3$], 5.68 (d, *J* = 7.5 Hz, 1 H, NC*H*CO), 6.45 (br s, 1 H, NO*H*), 6.91 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 7.50 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 7.59 (d, *J* = 7.5 Hz, 1 H, N*H*CO).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.9 [OC(*C*H$_3$)$_3$], 72.4 (N*C*HCO), 84.8 [O*C*(CH$_3$)$_3$], 86.5 (Ar*C*), 116.6 (q, $J_{C,F}$ = 285.6 Hz, CO*C*F$_3$), 118.8 (Ar*C*), 137.6 (Ar*C*), 148.7 (Ar*C*), 157.3 (q, $J_{C,F}$ = 38.0 Hz, *C*OCF$_3$), 164.7 (*C*O).

HMRS (CI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{16}F_3IN_2O_4$: 460.0107; found: 460.0072.

Anal. Calcd for $C_{14}H_{16}F_3IN_2O_4$ (460.22): C, 36.53; H, 3.51; N, 6.09. Found: C, 35.89; H, 3.43; N, 6.12.

***tert*-Butyl {(Hydroxy)[4-(methoxycarbonyl)phenyl]amino}[(trifluoroacetyl)amino]acetate (3e)**

Starting from **2e** (18 mg, 99.4 μmol), **3e** was obtained as a colorless solid; yield: 33 mg (85%); mp 114 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 [s, 9 H, OC(CH_3)$_3$], 3.86 (s, 3 H, OCH_3), 5.84 (d, *J* = 7.6 Hz, 1 H, NC*H*CO), 6.30 (br s, 1 H, NO*H*), 7.25 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 7.67 (d, *J* = 7.6 Hz, 1 H, N*H*CO), 7.94 (d, *J* = 8.5 Hz, 2 H, Ar*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.8 [OC(*C*H$_3$)$_3$], 51.9 (O*C*H$_3$), 72.0 (N*C*HCO), 84.8 [O*C*(CH$_3$)$_3$], 115.5 (q, $J_{C,F}$ = 286.1 Hz, CO*C*F$_3$), 115.5 (Ar*C*), 124.4 (Ar*C*), 130.7 (Ar*C*), 153.0 (Ar*C*), 157.1 (*C*OCF$_3$), 164.5 (CH*C*O), 166.9 (*C*O$_2$CH$_3$).

HMRS (CI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{19}F_3N_2O_6$: 392.1195; found: 392.1201.

Anal. Calcd for $C_{16}H_{19}F_3N_2O_6$ (392.37): C, 48.98; H, 4.89; N, 7.14. Found: C, 49.17; H, 4.87; N, 7.10.

***tert*-Butyl [(4-Cyanophenyl)(hydroxy)amino][(trifluoroacetyl)amino]acetate (3f)**

Starting from **2f** (104 mg, 0.70 mmol), **3f** was obtained as a colorless solid; yield: 215 mg (85%); mp 151 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 [s, 9 H, OC(CH_3)$_3$], 5.80 (d, *J* = 7.5 Hz, 1 H, NC*H*CO), 6.32 (s, 1 H, NO*H*), 7.31 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 7.56 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 7.67 (d, *J* = 7.0 Hz, 1 H, N*H*CO).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.8 [OC(*C*H$_3$)$_3$], 71.8 (N*C*HCO), 85.1 [O*C*(CH$_3$)$_3$], 105.4 (Ar*C*), 116.2 (Ar*C*), 116.6 (CO*C*F$_3$), 119.0 (Ar*C*), 133.1 (Ar*C*), 152.9 (*C*N), 157.4 (q, $J_{C,F}$ = 39.9 Hz, *C*OCF$_3$), 164.1 (*C*O).

HMRS (CI): *m*/*z* [M]$^+$ calcd for $C_{15}H_{16}F_3N_3O_4$: 359.1093; found: 359.1082.

Anal. Calcd for $C_{15}H_{16}F_3N_3O_4$ (359.34): C, 50.14; H, 4.50; N, 11.69. Found: C, 50.18; H, 4.55; N, 11.53.

***tert*-Butyl [(Hydroxy)(5-quinolyl)amino][(trifluoroacetyl)amino]acetate (3g)**

Starting from **2g** (87 mg, 0.50 mmol), **3g** was obtained as a yellow salt; yield: 116 mg (60%); mp 122 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29 [s, 9 H, OC(CH_3)$_3$], 5.96 (d, *J* = 8.0 Hz, 1 H, NC*H*CO), 7.30 (dd, *J* = 4.0, 8.5 Hz, 1 H, Ar*H*), 7.61 (d, *J* = 2.0 Hz, 1 H, Ar*H*), 7.67 (dd, *J* = 2.0, 9.5 Hz, 1 H, Ar*H*), 7.73 (d, *J* = 7.5 Hz, 1 H, N*H*CO), 7.96 (d, *J* = 9.5 Hz, 1 H, Ar*H*), 8.05 (d, *J* = 8.5 Hz, 1 H, Ar*H*), 8.63 (d, *J* = 4.0 Hz, 1 H, Ar*H*), 9.85 (br s, 1 H, N*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.8 [OC(*C*H$_3$)$_3$], 72.0 (N*C*HCO), 84.3 [O*C*(CH$_3$)$_3$], 111.7 (Ar*C*), 115.4 (q, $J_{C,F}$ = 286 Hz, CO*C*F$_3$), 121.5 (Ar*C*), 121.6 (Ar*C*), 128.8 (Ar*C*), 129.0 (Ar*C*), 136.3 (Ar*C*), 143.9 (Ar*C*), 147.9 (Ar*C*), 148.1 (Ar*C*), 157.2 (q, $J_{C,F}$ = 37.8 Hz, *C*OCF$_3$), 164.9 (*C*O).

HMRS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{19}F_3N_3O_4$: 386.1283; found: 386.1315.

***tert*-Butyl [(Hydroxy)(phenyl)amino][(trifluoroacetyl)amino]acetate (3h)**

Starting from **2h** (62 mg, 0.50 mmol), **3h** was obtained as a colorless liquid; yield: 135 mg (81%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 [s, 9 H, OC(CH_3)$_3$], 5.76 (d, *J* = 8.0 Hz, 1 H, NC*H*CO), 6.28 (br s, 1 H, NO*H*), 6.99 (dd, *J* = 7.5 Hz, 1 H, Ar*H*), 7.17 (d, *J* = 7.5 Hz, 2 H, Ar*H*), 7.24 (dd, *J* = 7.5 Hz, 2 H, Ar*H*), 7.59 (d, *J* = 7.5 Hz, 1 H, N*H*CO).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.7 [OC(*C*H$_3$)$_3$], 72.6 (N*C*HCO), 84.5 [O*C*(CH$_3$)$_3$], 116.6 (q, $J_{C,F}$ = 286 Hz, CO*C*F$_3$), 116.8 (Ar*C*), 123.4 (Ar*C*), 128.7 (Ar*C*), 148.6 (Ar*C*), 157.2 (q, $J_{C,F}$ = 37.9 Hz, *C*OCF$_3$), 165.1 (*C*O).

HMRS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}F_3N_2O_4$: 335.1174; found: 335.1165.

***tert*-Butyl [(2-Chloro-5-methoxyphenyl)(hydroxy)amino][(trifluoroacetyl)amino]acetate (3i)**

Starting from **2i** (94 mg, 0.50 mmol), **3i** was obtained as a colorless solid; yield: 153 mg (77%); mp 97 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.46 [s, 9 H, OC(CH_3)$_3$], 3.71 (s, 3 H, OCH_3), 5.96 (d, *J* = 9.5 Hz, 1 H, NC*H*CO), 6.43 (dd, *J* = 3.0, 8.5 Hz, 1 H, Ar*H*), 6.91 (d, *J* = 8.5 Hz, 1 H, Ar*H*), 7.03 (d, *J* = 3.0 Hz, 1 H, Ar*H*), 7.37 (d, *J* = 9.5 Hz, 1 H, N*H*CO), 7.44 (s, 1 H, NO*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.7 [OC(*C*H$_3$)$_3$], 55.4 (O*C*H$_3$), 69.7 (N*C*HCO), 84.6 [O*C*(CH$_3$)$_3$], 106.9 (Ar*C*), 112.3 (Ar*C*), 115.5 (q, $J_{C,F}$ = 286 Hz, CO*C*F$_3$), 115.6 (Ar*C*), 130.1 (Ar*C*), 144.9 (Ar*C*), 156.8 (q, $J_{C,F}$ = 37.8 Hz, *C*OCF$_3$), 158.5 (Ar*C*), 165.3 (*C*O).

HMRS (CI): *m*/*z* [M – C_4H_8]$^+$ calcd for $C_{11}H_{10}ClF_3N_2O_5$: 342.0186; found: 342.0238.

***tert*-Butyl (3-Oxo-1,2-dihydro-2,1-benzisoxazol-1-yl)[(trifluoroacetyl)amino]acetate (4b)**

Starting from **2b** (91 mg, 0.50 mmol), **4b** was obtained as a yellow solid; yield: 118 mg (65%); mp 126 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29 [s, 9 H, OC(CH_3)$_3$], 6.08 (d, *J* = 7.9 Hz, 1 H, NC*H*CO), 7.33 (dd, *J* = 7.6 Hz, 1 H, Ar*H*), 7.41 (d,

J = 7.9 Hz, 1 H, Ar*H*), 7.66 (d, J = 7.6 Hz, 1 H, Ar*H*), 7.73 (dd, J = 7.7 Hz, 1 H, Ar*H*), 7.83 (d, J = 7.9 Hz, 1 H, N*H*CO).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.5 [OC(*C*H_3)$_3$], 68.3 (N*C*H-CO), 85.9 [O*C*(CH$_3$)$_3$], 112.5 (Ar*C*), 113.5 (Ar*C*), 115.3 (q, $J_{C,F}$ = 285 Hz, CO*C*F$_3$), 125.4 (Ar*C*), 125.7 (Ar*C*), 135.7 (Ar*C*), 154.7 (Ar*C*), 157.3 (q, $J_{C,F}$ = 39.1 Hz, *C*OCF$_3$), 162.1 (*C*O$_2$N), 166.9 (CH*C*O).

HMRS (CI): *m*/*z* [M]$^+$ calcd for $C_{15}H_{15}F_3N_2O_5$: 360.0933; found: 360.0899.

Anal. Calcd for $C_{15}H_{15}F_3N_2O_5$ (360.32): C, 49.99; H, 4.20; N, 7.78. Found: C, 49.75; H, 4.18; N, 7.83.

Ethyl [(4-Bromophenyl)(hydroxy)amino][(*tert*-butoxycarbonyl)amino]acetate (6a)

Starting from **2c** (101 mg, 0.50 mmol), **6a** was obtained as a pale yellow oil; yield: 63 mg (32%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.14 (t, J = 7.0 Hz, 3 H, CH$_2$C*H*$_3$), 1.33 [s, 9 H, OC(C*H*$_3$)$_3$], 4.13 (q, J = 7.0 Hz, 2 H, C*H*$_2$CH$_3$), 5.59 (d, J = 8.0 Hz, 1 H, N*H*CO), 5.91 (d, J = 8.5 Hz, 1 H, NC*H*CO), 6.82 (br s, 1 H, NO*H*), 7.04 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.29 (d, J = 8.5 Hz, 2 H, Ar*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH$_2$*C*H$_3$), 28.2 [OC(*C*H$_3$)$_3$], 62.1 (*C*H$_2$CH$_3$), 73.4 (N*C*HCO), 80.6 [O*C*(CH$_3$)$_3$], 115.4 (Ar*C*), 118.8 (Ar*C*), 131.4 (Ar*C*), 148.4 (Ar*C*), 155.7 (N*C*O$_2$), 167.4 (CH*C*O).

***tert*-Butyl [(*tert*-Butyloxycarbonyl)amino][(4-cyanophenyl)(hydroxy)amino]acetate (6b)**

Starting from **2f** (74 mg, 0.50 mmol), **6b** was obtained as a tough yellow oil; yield: 50 mg (28%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29 [s, 9 H, CHCO$_2$(C*H*$_3$)$_3$], 1.42 [s, 9 H, NHCO$_2$(C*H*$_3$)$_3$], 5.61 (br s, 1 H, N*H*CO), 6.03 (br s, 1 H, NC*H*CO), 6.37 (br s, 1 H, NO*H*), 7.28 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.53 (d, J = 8.5 Hz, 2 H, Ar*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.8 [CCO$_2$C(*C*H$_3$)$_3$], 28.2 [NCO$_2$C(*C*H$_3$)$_3$], 73.5 (N*C*HCO), 81.1 [NCO$_2$*C*(CH$_3$)$_3$], 83.8 [CCO$_2$*C*(CH$_3$)$_3$], 106.4 (Ar*C*), 116.8 (Ar*C*), 119.2 (Ar*C*), 133.6 (Ar*C*), 152.5 (*C*N), 155.7 (N*C*O$_2$), 167.7 (CH*C*O).

***tert*-Butyl {(4-Bromophenyl)[(*E*)-5-methylhex-2-enyloxy]amino}[(trifluoroacetyl)amino]acetate (7)**

To a stirred soln of **3c** (50 mg, 121 μmol) in anhyd THF (1.5 mL) was added Pd(PPh$_3$)$_4$ (5.6 mg, 4 mol%) and ethyl 1-vinyl-3-methylbutyl carbonate (23 mg, 121 μmol) at r.t. After 30 min the red soln was diluted with Et$_2$O (10 mL) and hydrolyzed with 1 M KHSO$_4$ (10 mL). The layers were separated, the aqueous layer was extracted with Et$_2$O (2 ×) and the combined organic layers were dried (Na$_2$SO$_4$). The solvent was evaporated and the crude product was purified by flash chromatography (silica, hexane–EtOAc) to give **7** as a pale yellow oil; yield: 48 mg (78%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (d, J = 2.5 Hz, 3 H, C*H*$_3$), 0.84 (d, J = 2.5 Hz, 3 H, C*H*$_3$), 1.39 [s, 9 H, OC(C*H*$_3$)$_3$], 1.57 [m, 1 H, C*H*(CH$_3$)$_2$], 1.88 (dd, J = 7.0 Hz, 2 H, C*H*$_2$CH=CH), 4.16 (m, 2 H, CH=CHC*H*$_2$O), 5.46 (m, J = 7.0, 15.0 Hz, 1 H, CH$_2$C*H*=CH), 5.57 (d, J = 7.5 Hz, 1 H, NC*H*CO), 5.65 (m, J = 7.0, 15.0 Hz, 1 H, CH=C*H*CH$_2$O), 7.08 (d, J = 8.5 Hz, 2 H, Ar*H*), 7.40 (d, J = 9.0 Hz, 2 H, Ar*H*), 7.54 (br s, 1 H, N*H*CO).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1 (*C*H$_3$), 22.2 (*C*H$_3$), 27.9 [OC(*C*H$_3$)$_3$], 28.1 [*C*H(CH$_3$)$_2$], 41.5 (*C*H$_2$CH=CH), 72.7 (N*C*HCO), 75.6 (CH=CH*C*H$_2$O), 84.3 [O*C*(CH$_3$)$_3$], 114.4 (Ar*C*), 116.4 (q, $J_{C,F}$ = 286 Hz, CO*C*F$_3$), 119.3 (Ar*C*), 124.8 (CH$_2$*C*H=CH), 131.8 (Ar*C*), 136.3 (CH=*C*HCH$_2$O), 147.1 (Ar*C*), 156.9 (q, $J_{C,F}$ = 37.8 Hz, *C*OCF$_3$), 164.4 (*C*O).

HMRS (CI): *m*/*z* [M]$^+$ calcd for $C_{21}H_{28}BrF_3N_2O_4$: 508.1185; found: 508.1164.

Anal. Calcd for $C_{21}H_{28}BrF_3N_2O_4$ (509.36): C, 49.52; H, 5.54; N, 5.50. Found: C, 49.74; H, 5.82; N, 4.92.

***tert*-Butyl [(Allyl)(trifluoroacetyl)amino][(allyloxy)(4-bromophenyl)amino]acetate (8)**

To a stirred soln of **3c** (300 mg, 0.73 mmol) in anhyd THF (3 mL) was added Pd(PPh$_3$)$_4$ (33.6 mg, 4 mol%) and allyl ethyl carbonate (285 mg, 2.19 mmol) in THF (3 mL); the mixture was refluxed for 8 h. Subsequently, the solvent was evaporated and the crude product was directly purified by flash chromatography (silica, hexane) to give **8** as a yellow oil; yield: 261 mg (73%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.44 [s, 9 H, OC(C*H*$_3$)$_3$], 4.04–4.44 (m, 4 H, CH$_2$=CHC*H*$_2$), 5.10–5.28 (m, 4 H, C*H*$_2$=CH), 5.49 (br s, 0.35 H, NC*H*CO), 5.73–5.83 (m, 2 H, CH$_2$=C*H*), 6.12 (br s, 0.65 H, NC*H*CO), 6.95 (m, 2 H, Ar*H*), 7.40 (m, 2 H, Ar*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.8 [OC(*C*H$_3$)$_3$], 48.7 (CH*C*H$_2$N), 75.1 (CH*C*H$_2$O), 76.3 (N*C*HCO), 83.7 [O*C*(CH$_3$)$_3$], 116.0 (q, $J_{C,F}$ = 287 Hz, CO*C*F$_3$), 116.3 (Ar*C*), 117.9 (*C*H$_2$=CHCH$_2$O), 118.9 (*C*H$_2$=CHCH$_2$N), 122.2 (Ar*C*), 131.9 (Ar*C*), 132.0 (*C*HCH$_2$N), 133.2 (*C*HCH$_2$O), 146.2 (Ar*C*), 163.6 (*C*O).

HRMS (CI): *m*/*z* [M]$^+$ calcd for $C_{20}H_{24}BrF_3N_2O_4$: 492.0872; found: 492.0849.

***tert*-Butyl (*Z*)-2-(4-Bromophenyl)-4-(trifluoroacetyl)-3,4,5,8-tetrahydro-2*H*-1,2,4-oxadiazocin-3-carboxylate (10)**

To a stirred soln of **8** (126 mg, 0.26 mmol) in anhyd CH_2Cl_2 (4 mL) was added a soln of Hoveyda–Blechert catalyst **9** (16 mg, 10 mol%) in anhyd CH_2Cl_2 (2 mL) at r.t. and the mixture was stirred overnight. The solvent was evaporated in vacuo and the crude product was purified by flash chromatography (silica, hexane–EtOAc) to give **9** as a wax-like colorless solid; yield: 95 mg (80%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 [s, 9 H, OC(C*H*$_3$)$_3$], 4.18 (dd, J = 8.0, 16.0 Hz, 1 H, CHC*H*$_2$N), 4.25 (d, J = 17.5 Hz, 1 H, CHC*H*$_2$O), 4.55 (d, J = 17.5 Hz, 1 H, CHC*H*$_2$O), 4.61 (dd, J = 8.0, 16.0 Hz, 1 H, CHC*H*$_2$N), 5.60 (m, J = 11.0 Hz, 1 H, OCH$_2$=C*H*), 5.86 (m, J = 8.0, 11.0 Hz, 1 H, NCH$_2$=C*H*), 6.40 (s, 1 H, NC*H*CO), 6.97 (d, J = 9.0 Hz, 2 H, Ar*H*), 7.42 (d, J = 9.0 Hz, 2 H, Ar*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.8 [OC(*C*H$_3$)$_3$], 41.2 (CH*C*H$_2$N), 71.3 (CH*C*H$_2$O), 74.7 (N*C*HCO), 83.8 [O*C*(CH$_3$)$_3$], 115.3 (Ar*C*), 115.8 (CO*C*F$_3$), 117.7 (Ar*C*), 123.5 (*C*HCH$_2$N), 130.9 (*C*HCH$_2$O), 132.0 (Ar*C*), 147.2 (Ar*C*), 157.7 (q, $J_{C,F}$ = 36.6 Hz, *C*OCF$_3$), 164.0 (*C*O).

MS (CI): *m*/*z* (%) = 465 (15), 409 (19), 363 (100), 279 (23).

Acknowledgment

Financial support by the Deutsche Forschungsgemeinschaft as well as the Fonds der Chemischen Industrie is gratefully acknowledged.

References

(1) (a) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833. (b) Ono, N. *The Nitro Group in Organic Synthesis*; VCH: New York, **2001**. (c) Marcelli, T.; Van der Haas, R. N. S.; Van Maarseveen, J. H.; Hiemstra, H. *Synlett* **2005**, 2817. (d) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643.

(2) (a) Purushothama Chary, K.; Raja Ram, S.; Iyengar, D. S. *Synlett* **2000**, 683. (b) Shojiro, M.; Makiko, O.; Toshimichi, M.; Takashi, H.; Haruki, N. *Tetrahedron Lett.* **2003**, *44*, 3717.

(3) (a) Rosso, J. A.; Bertolotti, S. G.; Braun, A. M.; Martire, D. O.; Gonzalez, M. C. *J. Phys. Org. Chem.* **2001**, *14*, 300. (b) Feng, S.-H.; Zhang, S.-J.; Yu, H.-Q.; Li, Q.-R. *Chem. Lett.* **2003**, *32*, 718.
(4) (a) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339. (b) Torssell, K. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, **1988**.
(5) Czekelius, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 612; *Angew. Chem.*, **2005**, *117*, 618.
(6) Mendler, B.; Kazmaier, U. *Org. Lett.* **2005**, *7*, 1715.
(7) (a) Kharash, H. S.; Reimnuth, O. *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall: New York, **1954**, 384. (b) Buck, P. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 120. (c) Nützel, K. In *Houben-Weyl*, Vol. 13/2a; Müller, E., Ed.; Thieme: Stuttgart, **1973**, 47.
(8) Gilman, H.; McCracken, R. *J. Am. Chem. Soc.* **1927**, *49*, 1052.
(9) Kursanov, D. N.; Solodkov, P. A. *Zh. Obshch. Khim., Ser. A* **1935**, *5*, 1487; *Chem. Abstr.*, **1936**, *30*, 2181.
(10) (a) Barboni, L.; Bartoli, G.; Marcantoni, E.; Petrini, M.; Dalpozzo, R. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2133. (b) Bartoli, G.; Palmieri, G.; Petrini, M.; Bosco, M.; Dalpozzo, R. *Gazz. Chim. Ital.* **1990**, *120*, 247. (c) Bartoli, G.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 5834.
(11) (a) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E. *Tetrahedron Lett.* **1988**, *29*, 2251. (b) Bartoli, G.; Marcantoni, E.; Petrini, M.; Dalpozzo, R. *J. Org. Chem.* **1990**, *55*, 4456.
(12) (a) Severin, T.; Schinitz, R. *Chem. Ber.* **1963**, *96*, 3081. (b) Bartoli, G.; Medici, A.; Rosini, G.; Tavernari, D. *Synthesis* **1978**, 436. (c) Bartoli, G.; Bosco, M. *Synthesis* **1980**, 616. (d) Bartoli, G.; Bosco, M.; Ciminale, F. *J. Org. Chem.* **1982**, *47*, 5229. (e) Bartoli, G. *Acc. Chem. Res.* **1984**, *17*, 109.
(13) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129.
(14) Bosco, M.; Dalpozzo, R.; Bartoli, G.; Palmieri, G.; Petrini, M. *J. Chem. Soc., Perkin Trans. 2* **1991**, 657.
(15) Dean, F. M.; Patampongse, C.; Podimuang, V. *J. Chem. Soc., Perkin Trans. 1* **1974**, 583.
(16) Reviews, see: (a) Kazmaier, U. *Amino Acids* **1996**, *11*, 283. (b) Kazmaier, U. *Liebigs Ann./Recl.* **1997**, 285. (c) Kazmaier, U. *Recent Res. Dev. Org. Chem.* **1998**, *2*, 351. (d) Kazmaier, U.; Maier, S.; Zumpe, F. L. *Synlett* **2000**, 1523.
(17) Mendler, B.; Kazmaier, U. *Synthesis* **2005**, 2239.
(18) Mendler, B.; Kazmaier, U.; Huch, V.; Veith, M. *Org. Lett.* **2005**, *7*, 2643.
(19) Stolz D., Pick R., Kazmaier U. *Synlett,* **2006**, 1616.
(20) (a) Kazmaier, U.; Zumpe, F. L. *Angew. Chem. Int. Ed.* **1999**, *38*, 1468; *Angew. Chem.* **1999**, *111*, 1572. (b) Kazmaier, U.; Zumpe, F. L. *Angew. Chem. Int. Ed.* **2000**, *39*, 802; *Angew. Chem.* **2000**, *112*, 805. (c) Kazmaier, U.; Lindner, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3303, *Angew. Chem.*, **2005**, *117*, 3368. (d) Bauer, M.; Kazmaier, U. *Recent Res. Dev. Org. Chem.* **2005**, *9*, 49.
(21) Zumpe, F. L.; Kazmaier, U. *Synthesis* **1999**, 1785.
(22) Zumpe, F. L.; Kazmaier, U. *Synlett* **1998**, 1199.