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The Boronic Mannich Reaction in a Solid-Phase Approach

Nathalie Schlienger,[a] Martin R. Bryce[b] and Thomas K. Hansen[a,*]

[a]*Medicinal Chemistry Research IV, Novo Nordisk A/S, Novo Nordisk Park, 2760 Maaloev, Denmark*
[b]*Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, UK*

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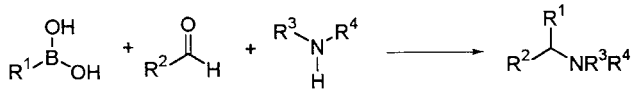
Abstract—We report herein the use of the multi-component boronic Mannich reaction (BMR) in a solid-phase approach, in which an aryl boronic acid is combined with an aldehyde and a secondary amine. We describe several examples, in which each of the three components is alternately anchored onto Wang polystyrene, giving in most cases (but not all) the expected products in high yields and purities. We also suggest, based on ^{11}B NMR studies, that the intermediate formation of a tetracoordinated boron species could represent the prerequisite for success of the BMR. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Combinatorial organic synthesis has developed over the last decade into an important tool for the generation of libraries of pharmacologically attractive molecules. Compared to traditional synthesis approaches, which involve the separate synthesis of each individual compound, combinatorial strategies produce large numbers of compounds based on a common core structure with a minimum of time and effort. Many combinatorial libraries are currently constructed using solid-phase chemistry and accordingly, the number of studies devoted to the development of new methods for synthesis on a solid support is growing continuously.[1] The majority of libraries that have been synthesized to date make use of a linear strategy, consisting of functional group manipulations in a sequential fashion starting with a support-bound functionality. An alternative strategy for the preparation of chemical libraries involves the use of multi-component condensation reactions (MCC),[2,3] in which three or more reactants are brought together in a single event to produce a final product containing features of all reactants. Compared to the linear strategy, this method therefore allows savings in time and effort since the product is formed in a single step. Unfortunately, only a few reactions can be conducted in this way. The Ugi four-component reaction, which has proven well suited for the preparation of structurally diverse libraries, is the only extensively studied MCC used in a combinatorial fashion, both in solution[4] and solid-phase synthesis.[5]

Petasis et al. have recently introduced a solution-phase protocol[6–8] for the synthesis of α-amino acids in one step by a three-component boronic Mannich reaction (BMR) based on simply mixing an aryl or alkenyl boronic acid, an amine and an aldehyde at room temperature.



We have applied this reaction to the solution-phase syntheses of 2-ketopiperazine[9] and 2-keto-1,4-diazepine[10] derivatives and recently to the preparation of pyridine derivatives.[11] As part of our research directed to the implementation of MCCs for automated generation of combinatorial libraries, we decided to investigate the potential use of the BMR in parallel synthesis on insoluble supports.[12] We anticipated that the experimental simplicity of the BMR as well as the mild reaction conditions would be well suited for the solid-phase synthesis of structurally diverse libraries of small molecules. In addition, a solid-phase approach is interesting since the reactions can be driven to completion by using excess reagents, which are subsequently removed by simple filtration. The work-up is therefore easy and can be automated, leaving the resulting anchored compound ready for the subsequent reaction steps. We investigated the solid-phase version of the BMR with either the boronic acid, the aldehyde, or the amine bound to cross-linked polystyrene.

Results and Discussion

Boronic Mannich reaction using resin-bound amines

In order to examine the feasibility of this approach we first used piperazine bound to Wang-resin **1**[13] via a

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* Corresponding author. Fax: +45-44663450; e-mail: tkha@novo.dk

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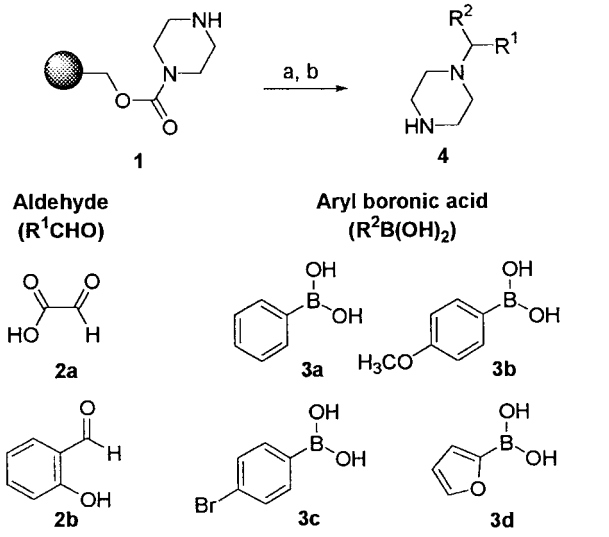


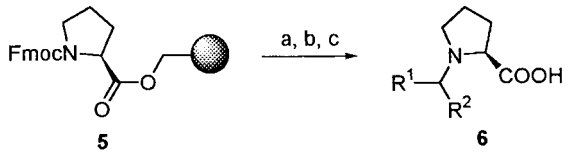
Scheme 1. Solid-phase synthesis of piperazines **4** from support-bound piperazine **1**. Reaction conditions: (a) **2** (26 equiv., 1 M), **3** (26 equiv., 1 M), DMF/1,2-dichloroethane (2:3), 50°C, 2 days; (b) TFA/CH_2Cl_2 1:1, rt, 0.5 h.

carbamate-linker as the amine component of the BMR (Scheme 1). Resin **1** was prepared as described in the literature by treatment of Wang resin sequentially with *p*-nitrophenyl chloroformate and then with piperazine. On the basis of previous results in solution, we selected glyoxylic acid (**2a**) and salicylaldehyde (**2b**) as the aldehyde components for elucidating the optimized reaction conditions for the BMR on solid phase. We chose several commercially available aryl boronic acids (**3a–d**), bearing electron withdrawing and donating substituents. A wide range of reaction conditions were tested, in which reagent concentrations, temperature and solvents were varied. We found that the reactions gave the highest yields when carried out at 50°C over 1–2 days in 1 M solution of both aldehyde and aryl boronic acid. As solvent, we used with success either a mixture of DMF/1,2-dichloroethane (2:3) or alternatively, a mixture of 2,2,2-trifluoroethanol/dioxane/DMF (5:1:4). In particular, we noticed that the reactions involving **2b** proved to be quite sensitive to the choice of solvent, e.g. the solvent mixtures containing up to 30% methanol or ethanol (solvents most frequently used for BMRs in solution synthesis) prevented the formation of the BMR products derived from **2b** and only unreacted piperazine was recovered after cleavage. In contrast, the reactions with

Table 1. Yields[14] and purities of crude products **4** (see Scheme 1) resulting from BMR with amine **1**

Product	Aldehyde	Boronic acid	Yield[a] (%)	Purity[b] (%)
4a	**2a**	**3a**	81	>95
4b	**2a**	**3b**	42	>95
4c	**2a**	**3c**	78	>95
4d	**2a**	**3d**	24	70
4e	**2b**	**3a**	63	85
4f	**2b**	**3b**	0	–
4g	**2b**	**3c**	63	88
4h	**2b**	**3d**	0	–

[a] Determined by ^{1}H NMR using DMSO-d_5 as the internal standard, based on the theoretical loading of Wang resin (1.04 mmol/g).
[b] Determined by evaporative light scattering (ELS).[15]



Scheme 2. Solid-phase synthesis of proline derivatives **6** from support-bound Fmoc-L-proline **5**. Reaction conditions: (a) 20% piperidine, DMF; (b) **2** (14 equiv., 1 M), **3** (14 equiv., 1 M), DMF/1,2-dichloroethane (2:3), 50°C, 2 days; (c) TFA/CH_2Cl_2 1:1, rt, 0.5 h.

glyoxylic acid **2a** as the aldehyde led to high yields of the desired products in a wide variety of solvents, including solvent mixtures containing methanol or ethanol. The purity and yield of several compounds resulting from reactions using resin-bound piperazine **1** are summarized in Table 1.

The results shown in Table 1 demonstrate that the BMR performed on solid-phase with amine **1** and glyoxylic acid leads in all cases to the desired product in synthetically useful yields and remarkable purities. One of the impurities observed by ^{1}H NMR in the crude reaction mixture after cleavage was piperazine trifluoroacetate salt, either resulting from incomplete reaction or from cross-linking of the piperazine during the preparation of **1** (determined[16] to be typically around 10%). The salt could be easily removed by triturating the crude mixture with a small amount of methanol and subsequent filtration. The comparison of the yields of the BMR starting either with aldehyde **2a** or **2b** reveals that the reaction generally proceeds in better yields with glyoxylic acid. The less reactive salicylaldehyde led under the same reaction conditions to products in satisfactory yields and reasonably high purities, except for the reaction involving the electron-rich boronic acid derivatives **3b** and **3d**. Whether this is due to the lower stability of these two boronic acid derivatives at the reaction temperature (50°C) compared to e.g. **3a**, or to a possible destabilization of an activated intermediate due to the enhanced electron density has not yet be established.

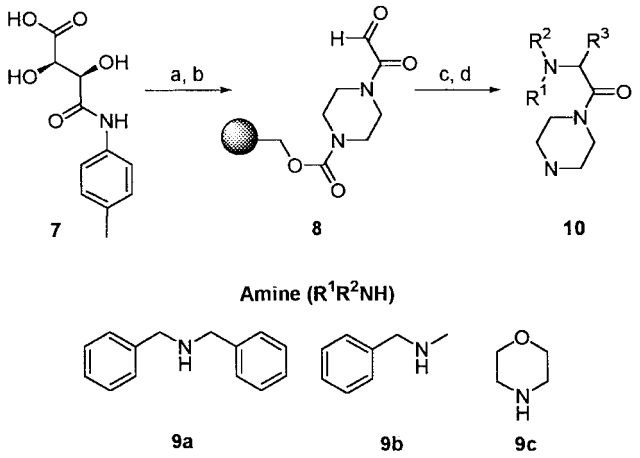
In order to establish the structure of the products **4**, compounds **4a** and **4e** were purified by recrystallization and fully characterized by ^{1}H and ^{13}C NMR, LCMS and elemental analysis. All other compounds were characterized by ^{1}H NMR, LCMS, HRMS and HPLC.

We further investigated whether this concept could be

Table 2. Yields[14] and purities of crude products **6** (see Scheme 2) resulting from BMR with resin-bound proline **5**

Product	Aldehyde	Boronic acid	De (%)	Yield[a] (%)	Purity[b] (%)
6a	**2a**	**3a**	76	82	>95
6b	**2a**	**3b**	40	90	>95
6c	**2a**	**3c**	46	86	92
6d	**2a**	**3d**	8	78	90
6e	**2b**	**3a**	88	82	>95
6f	**2b**	**3b**	74	41	84
6g	**2b**	**3c**	95	81	95
6h	**2b**	**3d**	–	0	–

[a] Determined by ^{1}H NMR using DMSO-d_5 as the internal standard, based on the theoretical loading of the Fmoc-Proline Wang resin **5** (0.84 mmol/g).
[b] Determined by ELS.[15]

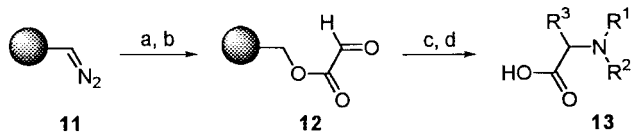


Scheme 3. Solid-phase synthesis of derivatives **10**. Reaction conditions: (a) resin **1**, *N*,*N*′-diisopropylcarbodiimide, 1-hydroxybenzotriazole, NEt_3, DMF; (b) NBu_4IO_4, DCE; (c) **9** (2.5 equiv., 0.33 M), **3** (8 equiv., 1 M), DMF/1,2-dichloroethane (2:3), 50°C, 20 h; (d) TFA/CH_2Cl_2 1:1, rt, 0.5 h.

extended to the use of resin-bound amino acids as the amine of the BMR (Scheme 2). To illustrate this approach, the reaction of resin-bound L-proline **5** under the same reaction conditions as above provided the expected compounds in similarly high yields and purities (Table 2). The reaction proceeded with strongly varying degrees of diastereoselectivity as determined by ^{1}H NMR, but the selectivity appeared to be higher in BMRs with salicylaldehyde than with glyoxylic acid. As observed earlier, the use of salicylaldehyde as the aldehyde led, in general, to lower yields than the corresponding reaction with glyoxylic acid. The main impurity detected by ^{1}H NMR in the crude products was unreacted proline.

We also attempted to perform the BMR with support-bound primary amines (1,3-diaminopropane, phenylalanine) under the same reaction conditions. Surprisingly, none of the reactions with aldehydes **2a** or **2b** and aryl boronic acids **3a**–**d** led to significant yields of the expected compounds. In most cases a mixture of products was obtained, which could not be further identified, but which did not contain the derivatives resulting from two successive BMRs on the primary amine.

We have suggested previously[11] that the choice of aldehydes, which can be used in the BMR in solution chemistry, seems to be limited to aldehydes bearing a heteroatom or a functional group, such as a hydroxyl function, in the α-position (or in special cases in the β-position as the examples with salicylaldehyde show). To extend these investigations we decided to study the reactivity of a wide range of aldehydes in the BMR using a solid-phase approach. The reactions were performed with structurally



Scheme 4. Solid-phase synthesis of derivatives **13**. Reaction conditions: (a) **7**, DMF; (b) NBu_4IO_4, DCE; (c) **9** (2.5 equiv., 0.33 M), **3** (8 equiv., 1 M), DMF/1,2-dichloroethane (2:3), 50°C, 20 h; (d) TFA/CH_2Cl_2 1:1, rt, 0.5 h.

different aldehydes, including alkyl, aryl and heterocyclic aldehydes, under the same reaction conditions as described in Scheme 1, and the crude product mixtures were analyzed by LCMS. From eleven differently substituted benzaldehydes,[17] bearing various electron withdrawing or donating substituents, only salicylaldehyde (**2b**) reacted in the expected way. Furthermore, the desired BMR products could be detected only in reactions using α-hydroxyaldehydes (e.g. glyceraldehyde) or with a few aldehydes bearing an α-heteroatom, such as phenylglyoxal or ethyl glyoxalate. The scope of aldehydes suitable for this reaction could not be increased by addition of various catalysts (e.g. acid or base catalysts, Lewis acid catalysts such as lanthanide triflates).

Boronic Mannich reaction using resin-bound glyoxylic acid as the aldehyde

Following the promising results described in Tables 1 and 2 employing glyoxylic acid as the aldehyde and the observation that the use of ethyl glyoxalate led to the BMR product, we investigated the behavior in the BMR of glyoxylic acid, linked through an ester or an amide-bond to the solid support. Both the resin-bound glyoxylic acid residues **8** and **12** (Schemes 3 and 4) were prepared as reported by us previously[18] using a strategy based on oxidative cleavage of a resin-bound tartaric acid derivative. Resin **8** was obtained by coupling tartaric acid derivative **7** to the piperazine Wang resin **1**[13] via an intermediate active ester. The oxidative cleavage of the diol was then carried out using tetrabutylammonium periodate in 1,2-dichloroethane, leading to the desired functionalized resin **8**. The preparation of glyoxalate resin **12** made use of a polymeric phenyldiazomethane **11**[19] to achieve the coupling of the tartranilic acid **7** with the polymeric support, thereby avoiding the undesired acylation of the hydroxyl groups. Oxidative cleavage with tetrabutylammonium periodate, as above, gave the expected resin **12**.

Both **8** and **12** were then subjected to BMRs with 2-furyl boronic acid (**3d**) and the three different secondary amines **9a**–**c** shown in Scheme 3. The same reaction conditions as described above were applied, with the difference being that the amine concentration was reduced for this series, since higher concentrations of amine lowered the yields.

The analyses by LCMS and by ^{1}H NMR of the crude cleavage products revealed that the expected compounds **10a**,**b** and **13a**,**b** were obtained in moderate yields but, nevertheless, in most cases in reasonable purities (Table 3) according to detection by evaporative light scattering (ELS). ^{1}H NMR spectra of the crude product mixture revealed also in all cases a by-product, which showed a sharp singlet around δ 4.0 ppm, but which could not be isolated, and we propose that these by-products might be the corresponding aminals $(R^1R^2N)_2CHCOX$. As far as compounds **10c** and **13c** are concerned, their formation was confirmed by LCMS and HRMS.[20] It remains to be noted, that no BMR products were detected in the product mixtures when phenyl boronic acid **3a** or its derivatives **3b** or **3c** were used. These examples illustrate how the outcome of the BMR can be modulated by the appropriate choice of reactants, in this case the use of more reactive boronic acids such as 2-furylboronic acid.

Table 3. Yields[14] and purities of crude products **10** and **13** (see Schemes 3 and 4) resulting from BMR with 2-furyl boronic acid (**3d**)

Product	Aldehyde	Amine	Yield[a] (%)	Purity[b] (%)
10a	**8**	**9a**	37	77
10b	**8**	**9b**	17	90
10c	**8**	**9c**	27	nd[c]
13a	**12**	**9a**	21	70
13b	**12**	**9b**	17	59
13c	**12**	**9c**	15	nd[c]

[a] Determined by ^{1}H NMR using DMSO-d_5 as the internal standard, based on the theoretical loading of Wang resin (1.04 mmol/g) for derivatives **10** and of Wang aldehyde resin (2.45 mmol/g) for derivatives **13.**
[b] Determined by ELS.[15]
[c] Not determined. See comments in Ref. 20.

Table 4. Yields[14] and purities of crude **15** (see Scheme 5) resulting from BMR with resin-bound phenylboronic acid **14**

Product	Aldehyde	Amine	Yield[a] (%)	Purity[b] (%)
15a	**2a**	**9a**	20	>95
15b	**2a**	**9b**	14	73
15c	**2a**	**9c**	26	>95
15d	**2b**	**9a**	20	>95
15e	**2b**	**9b**	20	>95
15f	**2b**	**9c**	29	>95

[a] Determined by ^{1}H NMR using DMSO-d_5 as the internal standard, based on the theoretical loading of Wang aldehyde resin (2.45 mmol/g).
[b] Determined by ELS.[15]

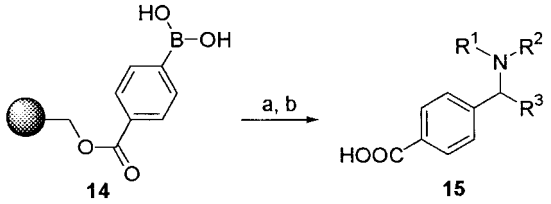
Boronic Mannich reaction using resin-bound 4-carboxyphenyl boronic acid

As an alternative to the use of resin-bound amines or aldehydes, we studied whether resin-bound boronic acids such as **14** (Scheme 5) could also be used in the BMR. The functionalized resin **14** was synthesized according to a literature procedure,[19] by coupling the commercially available 4-carboxyphenyl boronic acid with the diazo linker **11**. The resulting resin-bound boronic acid was then treated with amines **9** and aldehydes **2a** and **2b** (Scheme 5). The results, obtained under the same reaction conditions as described for the synthesis of derivatives **15**, are summarized in Table 4.

The expected products were obtained in moderate yields but high purities and were characterized by ^{1}H NMR, LCMS, HRMS and HPLC. In addition to these results we investigated the reaction of various primary amines with **14**, but no BMR products could be obtained.

Mechanistic considerations

An intriguing feature of the BMRs is the requirement of a vicinal functionality on the aldehyde. A possible explanation for this observation could be that the formation of an intermediate tetracoordinated boronate complex is required for an efficient reaction. The strong interaction between a trivalent boron atom and a carboxylic acid is a well known reaction and we assume that this might be the reason for the superiority of glyoxylic acid as the aldehyde component in the BMR. Preliminary results using ^{11}B NMR in solution synthesis strongly suggest the rapid formation of a tetracoordinated complex upon combination of glyoxylic acid with phenylboronic acid, even before any amine is added.

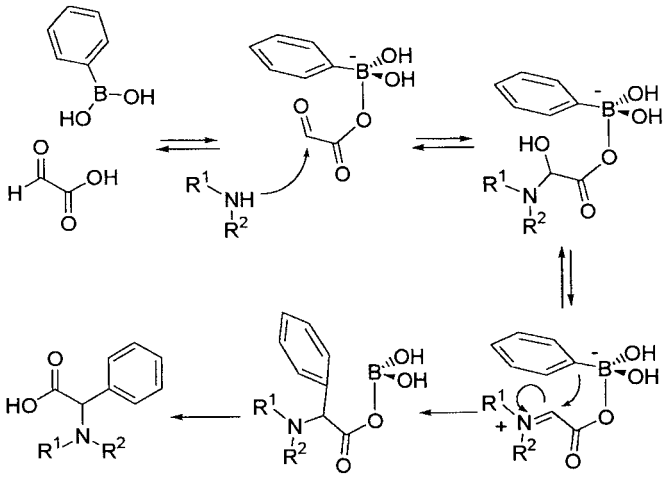


Scheme 5. Solid-phase synthesis of derivatives **15** from resin-bound boronic acid derivative **14**. Reaction conditions: (a) **9** (2.5 equiv., 0.33 M), **2** (8 equiv., 1 M), DMF/1,2-dichloroethane (2:3), 50°C, 20 h; (b) TFA/CH_2Cl_2 1:1, rt, 0.5 h.

We observed a strong upfield shift from 33.5 ppm for phenylboronic acid to 14.2 ppm for the complex, which is consistent with the formation of a tetracoordinated boronate species.[21] Dramatic changes were also observed in ^{13}C NMR studies, where the signals of glyoxylic acid monohydrate (δ 171.6, 86.3 ppm) disappear, with simultaneous appearance of new resonance signals at 130.9 and 126.0 ppm, when mixed with phenyl boronic acid. A suggestion for a mechanism of the BMR involving glyoxylic acid as the aldehyde component is shown in Scheme 6. In contrast, examining a mixture of salicylaldehyde and phenylboronic acid, no shift in ^{11}B NMR signals can initially be observed. However, upon addition of the third component, e.g. morpholine, the immediate formation of a tetracoordinated species with a chemical shift of 7.4 ppm can be noted.[22] It remains unclear at this moment, whether this complex is formed by coordination of the boron atom with the hydroxyl group of the aldehyde or with the corresponding carbinolamine, aminal or iminium ion (the three possible species resulting from interaction of the amine with the aldehyde). However, taking into account the results of BMRs with resin-bound amines **1** or **5**, it seems very unlikely, under the applied reaction conditions (i.e. high aldehyde concentration), that a significant amount of aminal is formed in the reaction mixture and hence this intermediate might not be involved. Nevertheless, it cannot be excluded that different reaction pathways could be implicated, depending on the structure of the components involved.

Conclusion

We have shown herein that the three-component boronic Mannich reaction, which has so far only been described as a solution synthesis, can also be a useful protocol in solid-phase synthesis. By the appropriate choice of different reagents, we have shown that structurally diverse compounds can be obtained in high purities using either of the three types of starting components linked to an insoluble support. The results presented herein indicate however that the success of the reaction depends on both the structure and electronic properties of each of the different components. As a particular feature of the BMR it appears that the structure of the aldehyde very strongly determines the success or failure of the reaction. In this respect, the most reactive aldehydes so far described all bear a hydroxyl function in the α- or -β-position.[6,8] We suppose that coordination events between the neighboring



Scheme 6. Hypothetical mechanism of the BMR involving glyoxylic acid as the aldehyde.

heteroatom and the boron thus forming a tetra-coordinated intermediate[23] might play an essential role in the mechanism of the BMR.

Experimental

General methods

Unless otherwise stated, ^{1}H NMR spectra were recorded at 400 MHz, whereas ^{11}B NMR spectra were measured at 160 MHz with proton decoupling at ambient temperature. Chemical shifts are given in δ-values [ppm] relative to TMS, whereas ^{11}B NMR shifts are reported relative to boron trifluoride etherate complex as the external reference. Coupling constants, *J*, are reported in Hertz.

Materials and solvents were of the highest grade available from commercial sources and used without further purification. Polystyrene (1% cross-linked) with Wang linker was purchased from Bachem (loading 1.04 mmol/g) and was used for the synthesis of **1**[13] and **8**[18]. Fmoc–Proline Wang resin (0.84 mmol/g) was purchased from Novabiochem. Resins **12**[18] and **14**[19] were prepared as previously described starting from Wang aldehyde polystyrene resin (theoretical loading 2.45 mmol/g) supplied by Novabiochem. Yields were calculated on the basis of these theoretical loadings. The purity of the compounds was determined by evaporative light scattering (ELS)[24] during an LCMS experiment. All syntheses were conducted in fritted polypropylene reactors.

HPLC Methods. The RP-HPLC analysis was performed using UV detection at 214, 254, 276, and 301 nm on a Vydac 218TP54 4.6 mm×250 mm 5 μm C-18 silica column (The Separations Group, Hesperia), which was eluted at 1 mL/min at 42°C. Three different elution conditions were used. *Method A*: The column was equilibrated with 5% acetonitrile in a buffer consisting of 0.1 M ammonium sulfate, which was adjusted to pH 2.5 with 4 M sulfuric acid. After injection the sample was eluted by a gradient of 5–60% acetonitrile in the same buffer during 50 min. *Method B*: The column was equilibrated with 5% acetonitrile/0.1% TFA/water and eluted by a gradient of 5% acetonitrile/0.1% TFA/water to 60% acetonitrile/0.1% TFA/water during 50 min. *Method C*: The column was equilibrated with 5% acetonitrile in a buffer consisting of 0.02 M sodium heptanesulphonate and 0.05 M ammonium dihydrogenphosphate, which was adjusted to pH 6.0 with ammonia solution. After injection the sample was eluted by a gradient of 5–60% acetonitrile in the same buffer during 50 min.

Typical procedure for the synthesis of compounds 4: Phenylpiperazin-1-ylacetic acid trifluoroacetate (4a). A solution of phenylboronic acid (244 mg, 4.0 mmol) and glyoxylic acid monohydrate (184 mg, 4.0 mmol) in DMF (0.8 mL) was added to a suspension of resin **1**[13] (150 mg, 0.15 mmol) in 1,2-dichloroethane (1.2 mL). The resulting mixture was shaken at 50°C for 2 days and filtered, and the resin was washed with DMF, dichloromethane and methanol. Dichloromethane (2.0 mL) and TFA (2.0 mL) were added, and the mixture was shaken for 30 min at rt. Filtration and concentration of the filtrate yielded crude **4a** from which unreacted piperazine was filtered off by trituration of the residue with methanol. Crystallization of the residue in ethyl acetate and *n*-heptane gave **4a** (25 mg, 75%) as a colorless solid. LCMS *m/z* 221 $[M+H]^+$. IR (KBr) ν 1703, 1679, 1615, 1581, 1455, 1378, 1210, 1128, 1081 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 2.60 (m, 4H), 3.07 (m, 4H), 4.18 (s, 1H), 7.33–7.38 (m, 5H), 8.6 (bs, 2H), 12.7 (bs, 1H). HPLC t_R=7.6 min (method C). HRMS calcd for $C_{12}H_{16}N_2O_2$: 220.1212; found 220.1214. Anal. Calcd for $C_{12}H_{16}N_2O_2$ CF_3COOH: C, 50.30; H, 5.13; N, 8.38; Found: C, 50.13; H, 5.20; N, 8.20.

(4-Methoxyphenyl)piperazin-1-ylacetic acid trifluoroacetate (4b). LCMS *m/z* 251 $[M+H]^+$. ^{1}H NMR (DMSO-d_6) δ 2.81 (m, 4H), 3.18 (m, 4H), 3.77 (s, 3H), 4.50 (s, 1H), 6.99 (d, 2H, *J*=8.6 Hz), 7.35 (d, 2H, *J*=8.6 Hz), 8.8 (bs, 2H). HPLC t_R=8.6 min (method C). HRMS calcd for $C_{13}H_{18}N_2O_3$: 250.1317; found 250.1318.

(4-Bromophenyl)piperazin-1-ylacetic acid trifluoroacetate (4c). LCMS *m/z* 299 $[M+H]^+$. ^{1}H NMR (DMSO-d_6) δ 2.68 (m, 4H), 3.11 (m, 4H), 4.34 (s, 1H), 7.36 (d, 2H, *J*=8.3 Hz), 7.61 (d, 2H, *J*=8.3 Hz), 8.7 (bs, 2H). HPLC t_R=13.2 min (method C). HRMS calcd for $C_{12}H_{15}BrN_2O_2$: 298.0317; found 298.0317.

(2-Furyl)piperazin-1-ylacetic acid trifluoroacetate (4d). The preparation of **4d** was performed as described for **4a** with exception of the reaction time, which was reduced to 20 h. LCMS *m/z* 211 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 2.69–2.74 (m, 2H), 2.87–2.91 (m, 2H), 3.13 (m, 4H), 4.73 (s, 1H), 6.46–6.50 (m, 2H), 7.70 (s, 1H), 8.7 (bs, 2H), 9.4 (bs, 1H). HPLC t_R=4.6 min (method C). HRMS calcd for $C_{10}H_{14}N_2O_3$: 210.1004; found 210.1007.

2-(Phenylpiperazin-1-ylmethyl)phenol trifluoroacetate (4e). A colorless solid was obtained in 61% yield after purification of the residue by silica gel column chromatography (eluting with 0–5% methanol in dichlormethane). LCMS *m/z* 269 $[M+H]^+$. IR (KBr) ν 1676, 1613, 1594, 1489, 1461, 1424, 1408, 1319, 1249, 1209, 1172, 1126 cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.71–2.86 (m, 4H), 3.23 (m, 4H), 5.14 (s, 1H), 6.78–6.84 (m, 2H), 7.05–7.09 (m, 1H), 7.25 (m, 1H), 7.32–7.51 (m, 5H), 9.0 (bs, 2H), 9.4 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 42.6, 47.6, 66.7, 115.1, 118.8, 126.4, 126.5, 127.3, 127.4, 128.0, 140.9, 154.5. HPLC t_R=21.3 min (method A). HPLC t_R=20.6 min (method B). HRMS calcd for $C_{17}H_{20}N_2O$: 268.1576; found 268.1577. Anal. Calcd for $C_{17}H_{20}N_2O$ CF_3COOH $0.5H_2O$: C, 58.31; H, 5.67; N, 7.16; Found: C, 58.50; H, 5.42; N, 6.98.

2-[(4-Bromophenyl)piperazine-1-ylmethyl]phenol trifluoroacetate (4g). LCMS *m/z* 347 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 2.72–2.90 (m, 4H), 3.27 (m, 4H), 5.20 (s, 1H), 6.82–6.89 (m, 2H), 7.12 (m, 1H), 7.41 (d, 1H, *J*=7.6 Hz), 7.49 (d, 2H, *J*=8.3 Hz), 7.56 (d, 2H, *J*=8.3 Hz), 9.0 (bs, 2H), 9.4 (bs, 1H). HPLC t_R=26.3 min (method A). HPLC t_R=26.2 min (method B). HRMS calcd for $C_{17}H_{19}BrN_2O$: 346.0681; found 346.0682.

Typical procedure for the synthesis of compounds 6: *N*-(carboxyphenylmethyl)-L-proline trifluoroacetate (6a). Fmoc-L-proline Wang resin (346 mg, 0.29 mmol) was deprotected by treatment with 20% piperidine in DMF (5 mL) for 15 min. The resin was filtered and washed with DMF, 10% acetic acid in dichloromethane, dichloromethane and methanol. The BMR is then performed as described for compound **4a**, with glyoxylic acid monohydrate (368 mg, 4.0 mmol) and phenylboronic acid (487 mg, 4.0 mmol) in a mixture of DMF (1.6 mL) and 1,2-dichloroethane (2.4 mL). Cleavage as described for **4** led to product **6a**. The desired compound (52 mg, 72%) was obtained as a diastereomeric mixture (88:12) after recrystallization from ethyl acetate/*n*-heptane. LCMS *m/z* 250 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 1.78–2.15 (m, 3.12H), 2.22–2.32 (m, 0.88H), 2.97–3.10 (m, 1H), 3.17–3.23 (m, 1H), 3.93 (m, 0.88H), 4.08 (m, 0.12H), 5.02 (s, 0.12H), 5.11 (s, 0.88H), 7.42–7.50 (m, 5H). HPLC t_R=8.6 min (method A). HPLC t_R=9.1 min (method B). HRMS calcd for $C_{13}H_{15}NO_4$: 249.1001; found 249.1000. Anal. calcd for $C_{13}H_{15}NO_4$ 0.9 CF_3COOH: C, 50.52; H, 4.55; N, 4.01; found: C, 50.37; H, 4.67; N, 3.86.

***N*-[Carboxy(4-methoxyphenyl)methyl]-L-proline trifluoroacetate (6b).** Diastereomeric mixture (7:3). LCMS *m/z* 280 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 1.83–2.09 (m, 3.3H), 2.34–2.42 (m, 0.7H), 3.11–3.15 (m, 0.7H), 3.29–3.39 (m, 1H), 3.63–3.68 (m, 0.3H), 3.79 (s, 3H), 4.22 (m, 0.7H), 4.38 (m, 0.3H), 5.27 (s, 0.3H), 5.34 (s, 0.7H), 7.02 (d, 2H, *J*=8.7 Hz), 7.47 (d, 2H, *J*=8.7 Hz), 9.2 (bs, 1H). HPLC t_R=10.0 min (method A). HPLC t_R=10.8 min (method B). HRMS calcd for $C_{14}H_{17}NO_5$: 279.1107; found 279.1105.

***N*-[(4-Bromophenyl)carboxymethyl]-L-proline trifluoroacetate (6c).** Diastereomeric mixture (77:23). LCMS *m/z* 328 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 1.80–2.02 (m, 3H), 2.11–2.27 (m, 0.23H), 2.30–2.35 (m, 0.77H), 2.98–3.14 (m, 1H), 3.20–3.34 (m, 1H), 4.07–4.15 (m, 1H), 5.09 (s, 0.23H), 5.21 (s, 0.77H), 7.47 (d, 2H, *J*=8.3 Hz), 7.67 (d, 2H, *J*=8.3 Hz). HPLC t_R=13.2 min (method A). HPLC t_R=14.3 min (method B). HRMS calcd for $C_{13}H_{14}BrNO_4$: 327.0106; found 327.0104.

***N*-(Carboxy-2-furylmethyl)-L-proline trifluoroacetate (6d).** Diastereomeric mixture (54:46) LCMS *m/z* 240 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 1.75–2.30 (m, 4H), 3.10–3.35 (m, 1H), 3.52–3.68 (m, 1H), 4.16–4.20 (m, 0.54H), 4.46–4.49 (m, 0.46H), 5.55 (s, 0.46H), 5.61 (s, 0.54H), 6.57, 6.58 (2d, 1H, *J*=2.0 Hz), 6.82 (d, 0.54H, *J*=3.3 Hz), 6.92 (d, 0.46H, *J*=3.3 Hz), 7.86, 7.82 (2d, 1H, *J*=0.8 Hz). HPLC t_R=7.2 min (method C). HRMS calcd for $C_{11}H_{13}NO_5$: 239.0794; found 239.0795.

***N*-[(2-Hydroxyphenyl)phenylmethyl]-L-proline trifluoroacetate (6e).** Diastereomeric mixture (94:6) LCMS *m/z* 298 $[M+H]^+$. ^1H NMR (DMSO-d_6) δ 1.85–2.10 (m, 4H), 3.18–3.25 (m, 1H), 3.40–3.52 (m, 1H), 4.17–4.21 (m, 1H), 5.85 (s, 0.06H), 6.01 (s, 0.94H), 6.81–6.95 (m, 2H), 7.16–7.19 (m, 1H), 7.32–7.44 (m, 3H), 7.51 (d, 1H, *J*=7.7 Hz), 7.71 (d, 2H, *J*=7.4 Hz). HPLC t_R=20.6 min (method A). HPLC t_R=20.9 min (method B). HRMS calcd for $C_{18}H_{19}NO_3$: 297.1365; found 297.1365.

***N*-[(2-Hydroxyphenyl)(4-methoxyphenyl)methyl]-L-proline trifluoroacetate (6f).** LCMS *m/z* 328 $[M+H]^+$. ^1H NMR (DMSO-d_6) only major diastereomer described (87%) δ 1.86–2.30 (m, 4H), 3.17–3.28 (m, 1H), 3.46–3.57 (m, 1H), 3.75 (s, 3H), 4.22 (m, 0.7H), 4.16–4.20 (m, 1H), 5.97 (s, 1H), 6.83–6.98 (m, 4H), 7.16–7.20 (m, 1H), 7.50–7.66 (m, 3H), 9.7 (bs, 1H). HPLC t_R=21.6 min (method A). HPLC t_R=21.8 min (method B). HRMS calcd for $C_{19}H_{21}NO_4$: 327.1471; found 327.1471.

***N*-[(4-Bromophenyl)(2-hydroxyphenyl)methyl]-L-proline trifluoroacetate (6g).** LCMS *m/z* 376 $[M+H]^+$. ^1H NMR (DMSO-d_6) only major diastereomer described (97%) δ 1.92–1.97 (m, 1H), 2.05–2.11 (m, 2H), 2.53–2.57 (m, 1H), 3.20–3.26 (m, 1H), 3.50–3.54 (m, 1H), 4.17–4.21 (m, 1H), 6.02 (s, 1H), 6.83–6.92 (m, 2H), 7.20 (m, 1H), 7.50 (d, 1H, *J*=7.6 Hz), 7.63 (d, 2H, *J*=8.5 Hz), 7.69 (d, 2H, *J*=8.5 Hz). HPLC t_R=26.4 min (method A). HPLC t_R=26.7 min (method B). HRMS calcd for $C_{18}H_{18}BrNO_3$: 375.0470; found 375.0471.

Typical procedure for the synthesis of compounds 10 and 13: (Benzylmethylamino)fur-2-ylacetic acid trifluoroacetate (13b). Resin **12**[18] (280 mg, ca. 0.52 mmol) was suspended in 1,2-dichloroethane (2.4 mL) and a solution of 2-furyl boronic acid (448 mg, 4.0 mmol) in DMF (1.6 mL) is added. After addition of *N*-benzylmethylamine

(167 μL, 1.3 mmol), the mixture was shaken for 20 h at 50°C. The resin was filtered, washed as previously described in the preparation of compound **4a** and the product cleaved off the solid support by treatment with TFA/dichloromethane (1:1, 3 mL) during 30 min. Filtration, evaporation of the solvents and purification of the crude product on a C_{18}-Sepak-cartridge, eluting with 0–30% acetonitrile in water containing 0.5% TFA, followed by recrystallization from dichloromethane and *n*-heptane gave **13b** (24 mg, 13%) as a colorless solid. LCMS *m/z* 246 $[M+H]^+$. ^1H NMR (CD_3OD) δ 2.57 (m, 3H), 4.08 (m, 1H), 4.45–4.49 (m, 1H), 4.89 (s, 1H), 6.54 (m, 1H), 6.74 (m, 1H), 7.46–7.59 (m, 5H), 7.66 (m, 1H). HPLC t_R=13.8 min (method A). HPLC t_R=13.6 min (method C). HRMS calcd for $C_{14}H_{15}NO_3$: 245.1052; found 245.1051. Anal. calcd for $C_{14}H_{15}NO_3$ 0.4 CF_3COOH 2 H_2O: C, 54.38; H, 5.98; N, 4.28; found: C, 54.11; H, 5.98; N, 4.44.

2-Dibenzylamino-2-fur-2-yl-1-piperazin-1-ylethanone trifluoroacetate (10a). LCMS *m/z* 390 $[M+H]^+$. ^1H NMR (CD_3OD) δ 2.80–2.95 (m, 2H), 3.16 (m, 2H), 3.30–3.45 (m, 2H), 3.73–3.84 (m, 4H), 4.10 (d, 2H, *J*=13.6 Hz), 5.15 (s, 1H), 6.53 (m, 1H), 6.64 (d, 1H, *J*=3.2 Hz), 7.28–7.34 (m, 10H), 7.66 (d, 1H, *J*=1.4 Hz). HPLC t_R=32.3 min (method A). HPLC t_R=39.5 min (method C). HRMS calcd for $C_{24}H_{27}N_3O_2$: 389.2103; found 389.2102.

2-(Benzylmethylamino)-2-fur-2-yl-1-piperazin-1-ylethanone trifluoroacetate (10b). LCMS *m/z* 314 $[M+H]^+$. ^1H NMR (CD_3OD) δ 2.58 (m, 3H), 2.70–2.76 (m, 1H), 3.15–3.26 (m, 3H), 3.36–3.41 (m, 1H), 3.63–3.67 (m, 1H), 3.82–3.95 (m, 2H), 4.20–4.34 (m, 2H), 5.99 (s, 1H), 6.63 (d, 1H, *J*=1.7 Hz), 6.90 (s, 1H), 7.45–7.56 (m, 5H), 7.76 (m, 1H). HPLC t_R=10.3 min (method A). HPLC t_R=13.2 min (method C). HRMS calcd for $C_{18}H_{23}N_3O_2$: 313.1790; found 313.1790.

2-Fur-2-yl-2-morpholin-4-yl-1-piperazin-1-ylethanone trifluoroacetate (10c). Seemingly unstable compound. LCMS *m/z* 280 $[M+H]^+$. HRMS calcd for $C_{14}H_{21}N_3O_3$: 279.1583; found 279.1583.

Dibenzylamino-fur-2-ylacetic acid trifluoroacetate (13a). LCMS *m/z* 322 $[M+H]^+$. ^1H NMR (CD_3OD) δ 3.89 (d, 2H, *J*=13.5 Hz), 4.31 (d, 2H, *J*=13.5 Hz), 4.96 (s, 1H), 6.52 (d, 1H, *J*=1.3 Hz), 6.65 (d, 1H, *J*=3.0 Hz), 7.33–7.47 (m, 10H), 7.64 (s, 1H). HPLC t_R=29.5 min (method A). HPLC t_R=29.5 min (method C). HRMS calcd for $C_{20}H_{19}NO_3$: 321.1365; found 321.1366.

Fur-2-ylmorpholin-4-ylacetic acid trifluoroacetate (13c). Seemingly unstable compound. LCMS *m/z* 212 $[M+H]^+$. HRMS calcd for $C_{10}H_{13}NO_4$: 211.0845; found 211.0843.

Typical procedure for the synthesis of compounds 15: 4-(Carboxymorpholin-4-yl-methyl)benzoic acid trifluoroacetate (15c). To a suspension of resin **14**[19] (320 mg, ca. 0.56 mmol) in 1,2-dichloroethane (2.4 mL) a solution of glyoxylic acid monohydrate (368 mg, 4.0 mmol) in DMF (1.6 mL) was added. After addition of morpholine (113 μL, 1.3 mmol), the mixture was shaken for 20 h at 50°C. The resin was filtered, washed and treated with TFA/dichloromethane as previously described in the preparation of compound **4**. For analytical purposes, the crude product was further purified by filtration on a C_{18}-Sepak cartridge, eluting with 0–20% acetonitrile in water containing 0.5% TFA to give **15c** (42 mg, 20%) as a colorless solid. LCMS *m/z* 266 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 2.90 (m, 2H), 3.15–3.30 (m, 2H), 3.75–3.81 (m, 4H), 5.22 (s, 1H), 7.65 (d, 2H, *J*=8.2 Hz), 8.07 (d, 2H, *J*=8.2 Hz). HPLC t_R=4.1 min (method A). HRMS calcd for $C_{13}H_{15}NO_5$: 265.0950; found 265.0951. Anal. calcd for $C_{13}H_{15}NO_5$ CF_3COOH 1.2 H_2O: C, 44.94; H, 4.63; N, 3.49; found: C, 44.65; H, 4.98; N, 3.89.

4-(Carboxydibenzylaminomethyl)benzoic acid trifluoroacetate (15a). LCMS *m/z* 376 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 3.62 (d, 2H, *J*=14.1 Hz), 3.78 (d, 2H, *J*=14.1 Hz), 4.47 (s, 1H), 7.23–7.35 (m, 10H), 7.49 (d, 2H, *J*=8.2 Hz), 7.98 (d, 2H, *J*=8.2 Hz). HPLC t_R=31.1 min (method A). HPLC t_R=30.1 min (method B). HRMS calcd for $C_{23}H_{21}NO_4$: 375.1471; found 375.1471.

4-[(Benzylmethylamino)carboxymethyl]benzoic acid trifluoroacetate (15b). LCMS *m/z* 300 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 2.44 (s, 3H), 4.28 (m, 2H), 5.34 (s, 1H), 7.41–7.57 (m, 5H), 7.72 (d, 2H, *J*=8.2 Hz), 8.16 (d, 2H, *J*=8.2 Hz). HPLC t_R=13.4 min (method A). HPLC t_R=13.9 min (method B). HRMS calcd for $C_{17}H_{17}NO_4$: 299.1158; found 299.1157.

4-[Dibenzylamino(2-hydroxyphenyl)methyl]benzoic acid trifluoroacetate (15d). LCMS *m/z* 424 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 3.68–3.78 (m, 4H), 5.44 (s, 1H), 6.81–6.88 (m, 2H), 7.12 (m, 1H), 7.25–7.34 (m, 10H), 7.48 (m, 1H), 7.64 (d, 2H, *J*=8.1 Hz), 7.91 (d, 2H, *J*=8.2 Hz). 9.8 (bs, 1H). HPLC t_R=48.8 min (method A). HPLC t_R=34.5 min (method B). HRMS calcd for $C_{28}H_{25}NO_3$: 423.1834; found 423.1833.

4-[(Benzylmethylamino)(2-hydroxyphenyl)methyl]benzoic acid trifluoroacetate (15e). LCMS *m/z* 348 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 2.57 (s, 3H), 4.14–4.38 (m, 2H), 5.82 (s, 1H), 6.88–7.00 (m, 2H), 7.25 (m, 1H), 7.43–7.53 (m, 5H), 7.61–7.67 (m, 1H), 7.83 (d, 2H, *J*=8.2 Hz), 8.01 (d, 2H, *J*=8.2 Hz). 10.3 (bs, 1H). HPLC t_R=24.6 min (method A). HPLC t_R=24.0 min (method B). HRMS calcd for $C_{22}H_{21}NO_3$: 347.1521; found 347.1520.

4-[(2-Hydroxyphenyl)morpholin-4-ylmethyl]benzoic acid trifluoroacetate (15f). LCMS *m/z* 314 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 2.99–3.08 (m, 2H), 3.24 (m, 2H), 3.76–3.93 (m, 4H), 5.85 (s, 1H), 6.89–6.95 (m, 2H), 7.22 (m, 1H), 7.59 (d, 1H, *J*=7.3 Hz), 7.77 (d, 2H, *J*=8.1 Hz), 8.00 (d, 2H, *J*=8.1 Hz). 10.3 (bs, 1H). HPLC t_R=16.9 min (method A). HPLC t_R=16.6 min (method B). HRMS calcd for $C_{18}H_{19}NO_4$: 313.1314; found 313.1312.

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15. ELS is now established as the detection method that generally reflects actual purity best, in particular when the compounds lack good UV-active chromophores. The HPLC purity (214 nm) was found in general to be in the same range as the ELS reading.
16. The amount of cross-linked piperazine was calculated indirectly after treating resin **1** under classical coupling conditions with the symmetrical anhydride (formed in situ) of phenoxyacetic acid. This reaction is high-yielding and following cleavage of the products the relative amount of free piperazine was determined by ^{1}H NMR and considered to reflect well the degree of cross-linking occurring during the preparation of resin **1**[13].
17. 4-diethylamino-, 4-methoxy, 4-chloro-, 4-fluoro-, 4-nitro-, 4-cyano-, 2-hydroxy- (**2b**), 2-trifluoromethyl-, 2-nitro-, 2,4-dinitrobenzaldehydes and benzaldehyde.
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20. We were unable to determine the purities unambiguously, since the high polarity (combined with low UV absorbance) made analytical chromatographic separation of the crude product mixtures of **10c** and **13c** difficult. ^{1}H NMR analysis showed a mixture of several compounds, which could not be separated and apparently led to the decomposition of the products during the purification procedures.
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