Communications

Multicomponent Reactions

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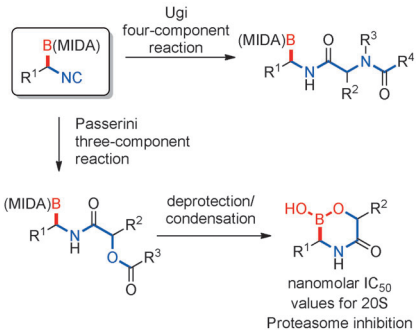
α-Boryl Isocyanides Enable Facile Preparation of Bioactive Boropeptides



Entry to Bioactive Boropeptides: MIDA-containing α-boryl isocyanides are isolable molecules which allow one-step access to boroalkyl-functionalized heterocycles as well as biologically active boropeptides through a multicomponent approach. Among these derivatives are 6-boromorpholinones, novel borocycles with nanomolar IC_{50} values for 20S proteasome inhibition. MIDA = *N*-methyliminodiacetyl.

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DOI: 10.1002/anie.201302818

α-Boryl Isocyanides Enable Facile Preparation of Bioactive Boropeptides**

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Boronic acids and their derivatives have found utility as synthetic building blocks,[1] chemosensors,[2] and as biologically active targets of synthesis.[3] Both the biological activity and chemical reactivity of boronic acids stem from boron's Lewis acidity. While useful in a broad range of applications, boron's propensity to undergo reactions with Lewis bases becomes problematic for functional-group compatibility during synthesis. Reagents that streamline installation of a carbon–boron bond in stereochemically complex, heteroatom-rich environments, are expected to find application not only as starting materials but also as late-stage precursors to the endpoints of synthesis. In regards to the latter, the borylamide motif (Figure 1), found in the structures of biologically active boropeptides, is of particular significance.[3g]

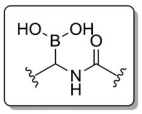


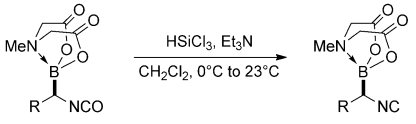
Figure 1. The borylamide motif.

Our recent efforts have been focused on the development of amphoteric molecules for the synthesis of bioactive peptides and peptidomimetics.[4] In our studies, we seek functionally dense, heteroatom-rich environments where a kinetic barrier prevents two otherwise reactive functional groups from prematurely reacting with each other.[5] Herein we expand the scope of this methodology to include boron-containing isocyanides for use in multicomponent preparation of boropeptides and their derivatives. Our study has resulted in the synthesis of a novel heterocyclic motif—the boromorpholinone. This scaffold has enabled us to identify a novel proteasome inhibitor with nanomolar activity.

Acting as 1,1-amphoteric molecules,[6] isocyanides enable heterocycle synthesis[7] and participate in multicomponent reactions (MCRs) such as Ugi and Passerini processes.[8] As part of our effort to develop amphoteric boron-transfer reagents, we considered an isocyanide/boron combination as an entry into pivotal B-C-N motifs. At the outset, we were aware of the known propensity of tricoordinate boron to react with isocyanides.[9] Rapid decomposition upon exposure to air has been an additional impediment to synthetic application of boron-containing isocyanides.[10] To circumvent this undesired reactivity, we focused our search on fragments with tetracoordinate boron. In *N*-methyliminodiacetyl (MIDA) boronates, an intramolecular coordinative stabilization of the empty p orbital on boron effectively masks its Lewis acidity.[11] The tetracoordinate boronate fragment tolerates a diverse range of functional-group transformations, thus allowing access to a variety of borylated derivatives. These include α-boryl aldehydes,[12] which contain a carbon–boron bond adjacent to an electrophilic aldehyde, and α-boryl isocyanates **1** (for structure see Table 1), reagents which are now readily available.[13]

The structural stability of the α-boryl isocyanates **1** in various reactions prompted us to attempt a trichlorosilane-mediated deoxygenation,[14] which afforded the corresponding isocyanides **2** as solid materials stable to column chromatography (Table 1). To explore the properties of these compounds we first investigated the possibility of deprotonation α to the isocyanide nitrogen atom.[7a] During an attempted α-deprotonation using weak bases (10 equiv of Et_3N or 15 equiv of $NaHCO_3$) in deuterated solvents (D_2O or $[D_4]$MeOH) there was no observable decrease in the integration of the α-proton signal in the ^1H NMR spectra. Under strongly basic conditions (1 equiv of potassium *tert*-butoxide) and subsequent exposure to $[D_3]$MeCN, a similar stability towards α deprotonation was observed. Interestingly, tetra-

Table 1: Preparation of MIDA α-boryl isocyanides.[a]



1 **2**

Starting Material	R	Product	Yield [%][b]
1a	isobutyl	**2a**	75
1b	cyclohexyl	**2b**	31
1c	phenyl	**2c**	30

[a] The reactions were carried out by stirring α-boryl isocyanate (1.0 equiv), trichlorosilane (1.6 equiv), and triethylamine (3.6 equiv) in anhydrous CH_2Cl_2 at 0 °C for 30 min and subsequent stirring for 6 h at 23 °C. [b] Yields of isolated products after silica gel chromatography.

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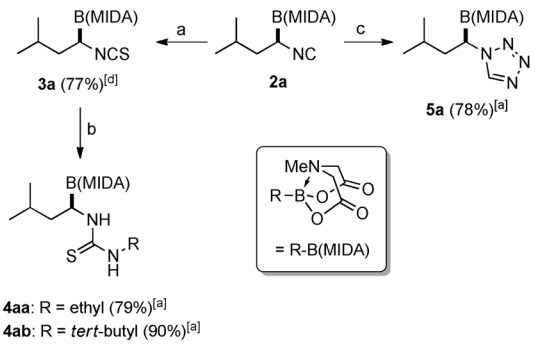
[**] We would like to thank the Natural Science and Engineering Research Council (NSERC) and Canadian Institutes of Health Research (CIHR) for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201302818.

deuteration of the MIDA moiety was seen in both the ^{1}H NMR and HRMS spectra. This example supports the notion that competitive enolization of the MIDA protons offers a protective function.[15]

The configurational stability of the α proton led us to focus our efforts on a variety of isocyanide functionalizations (Scheme 1). Selenium-catalyzed sulfurization gave rise to the

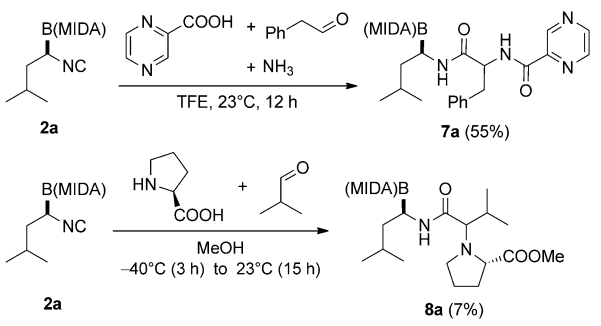


Scheme 1. Functionalization of **2a**. a) α-Boryl isocyanide **2a** (1.0 equiv), sulfur (1.2 equiv), selenium (5.0 mol%) and triethylamine (2.4 equiv) in THF at 80°C for 15 min. b) α-Boryl isothiocyanate **3a** (1.0 equiv) and amine (2.0 equiv) in THF at 23°C. c) α-Boryl isocyanide **2a** (1.0 equiv), HCl (2.0 mol%), and $TMSN_3$ (1.5 equiv) in THF/Et_2O (1:1) at 60°C for 6.5 h. [a] Yields of isolated products after silica gel chromatography. TMS = trimethylsilyl.

α-boryl isothiocyanate **3a** in moderate yield.[16] Reaction of **3a** with various amines afforded the corresponding thioureas **4aa** and **ab** in excellent yields.[17] Reaction of the isocyanide **2a** with in situ generated hydrazoic acid yielded the α-boryl tetrazole **5a** in moderate yield.[7b]

Successful retention of the carbon–boron bond during functionalization of the isocyanide moiety further prompted us to investigate more challenging transformations. We found that **2a** participated in an Ugi four-component reaction (U4CR) with 2-pyrazinyl carboxylic acid, phenylacetaldehyde, and ammonia. This reaction affords a streamlined approach to the bortezomib[18] analogue **7a** in 55% yield upon isolation (Scheme 2).

We attempted to generalize the U4CR reaction of **2a** by employing amino acids as both the acid and amine components. When **2a** was reacted with L-proline and isobutyraldehyde, the borodipeptide **8a** was obtained in 7% yield upon

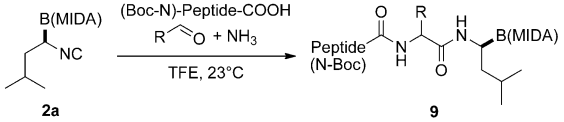


Scheme 2. U4CRs involving **2a**.

isolation (Scheme 2).[19] In a number of other reactions, we have found that methanol solvolyzes the MIDA moiety, thus yielding decomposition products. The reaction was attempted in 2,2,2-trifluoroethanol (TFE) given its decreased nucleophilicity relative to methanol. However, the desired product was not obtained.

We shifted our focus to U4CRs using *N*-protected amino acids or peptides as the carboxylic acid component and ammonia as the amine.[8e] The reactions proceeded at room temperature to give the desired diastereomers of the protected boropeptides **9** in moderate to excellent yields (Table 2). In most cases, the diastereomers were separable by HPLC. For larger peptides separation became more difficult as a result of considerable peak overlap.

Table 2: Preparation of protected boropeptides using **2a**.[a]



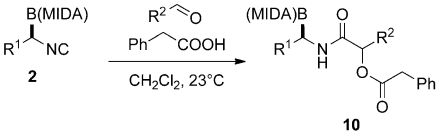
Entry	Peptide/AA[b]	R	Product	*t* [d]	Yield [%][c]
1	G	benzyl	**9a**	7	69
2	G	isopropyl	**9b**	6	79
3	F	isopropyl	**9c**	10	74
4	V	benzyl	**9d**	6	57
5	GG	benzyl	**9e**	6	92
6	FA	benzyl	**9f**	6	91
7	PLF	benzyl	**9g**	7	63
8	PGLF	benzyl	**9h**	12	76

[a] The reactions were carried out by stirring α-boryl isocyanide **2a** (1.0 equiv), aldehyde (1.0 equiv), ammonia (1.5 equiv, 7 N solution in MeOH), and peptide (1.0 equiv) in TFE at 23°C. [b] Boc-protected at N terminus; written from N to C terminus using standard one-letter amino acid abbreviations. [c] Yield of diastereomeric products determined by comparison of the integration of the ^{1}H NMR signals of the product with that for 3,4,5-triiodobenzoic acid, which was used as an internal standard.

The successful participation of **2a** in U4CRs led us to explore its applicability in the Passerini three-component reaction (P3CR).[8e–g] We found this reaction to proceed smoothly with a variety of aldehydes, thus affording minimal by-products (Table 3). Generally, the P3CR products **10** could be isolated in an acceptably pure form with simple aqueous workup. The two diastereomers could be separated by flash column chromatography on silica gel in the vast majority of cases. The reaction proceeded with moderate to excellent yields. The rate of the reaction could be increased at elevated temperature and pressure (100°C, μwave, 25 min), however, this occurred at the expense of selectivity for the desired product. Dichloromethane was found to be an ideal solvent as protic solvents did not yield the desired product and the isocyanide was not soluble in diethyl ether or tetrahydrofuran.

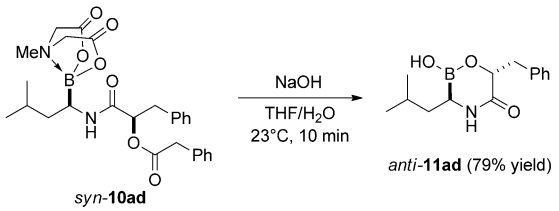
We then attempted to remove the MIDA group from the the P3CR product *syn* **10ad** under aqueous basic conditions to afford the corresponding free boronic acid (Scheme 3).[12c] We found that under the deprotection conditions, hydrolysis

Table 3: P3CRs involving α-boryl isocyanides.[a]



Entry	R^1	R^2	Product	*t* [d]	Yield [%][b]
1	isobutyl	phenyl	**10aa**	7	81
2[c]	isobutyl	isopropyl	**10ab**	4	68
3	isobutyl	4-FC_6H_4	**10ac**	4	60
4	isobutyl	benzyl	**10ad**	4	56
5	isobutyl	3-pyridinyl	**10ae**	2	79
6	isobutyl	4-MeC_6H_4	**10af**	4	50
7	isobutyl	2-BrC_6H_4	**10ag**	7	93
8	cyclohexyl	phenyl	**10ba**	7	53
9	cyclohexyl	isopropyl	**10bb**	7	46
10	cyclohexyl	benzyl	**10bd**	4	57
11	cyclohexyl	3-pyridinyl	**10be**	2	42
12	phenyl	benzyl	**10ca**	7	61

[a] The reactions were carried out by stirring α-boryl isocyanide (1.0 equiv), aldehyde (1.0 equiv), and phenylacetic acid (1.0 equiv) in CH_2Cl_2 at 23 °C. [b] Yields of isolated products after silica gel chromatography. [c] The two diastereomeric products could not be separated by silica gel chromatography. Boc = *tert*-butoxycarbonyl.



Scheme 3. Deprotection/condensation of P3CR product *syn*-**10ad**.

of the ester also occurred, followed by condensation of the resulting free hydroxyl group with the newly formed boronic acid. This process yielded the disubstituted 6-boromorpholinone *anti*-**11ad** as an air-stable white solid. The relative stereochemistry of the novel borocycle *anti*-**11ad** was determined by computational modeling of the starting material. Computational predictions (MPW1PW91, 6-311G(2d, p))[20] of several ^{1}H NMR chemical-shift differences between the two diastereomers (*syn* and *anti*) of **10ad** correlated well with experimental observations, thus allowing an inference of the relative stereochemistry. We determined the pK_a value of the boron center in *anti*-**11ad** to be approximately 9.0 in aqueous methanol by using a titration monitored by ^{11}B NMR/ESI MS.[21] This is an important value towards the prediction of 6-boromorpholinone behavior during in vitro and in vivo studies based on accessible pH.

Given the known propensity of boropeptide analogues to inhibit members of the 20S proteasome[3e–g] we decided to investigate the interaction of *anti*-**11ad** with various members of this protease family. We found that *anti*-**11ad** inhibited the chymotrypsin-like (CT-L)[21] members of the 20S proteasome with an IC_{50} value of 19 nM (Figure 2). In the same assay, bortezomib gave an IC_{50} value of 0.4 nM. The boromorpholinone *anti*-**11ad** selectively inhibited the CT-L enzymes over both the caspase-like (C-L) and trypsin-like (T-L) enzymes with a C-L IC_{50} value of 2.0 μM (bortezomib: 3.2 nM) and no observable inhibition of the T-L enzymes under 10 μM (see the Supporting Information). The diastereomer *syn*-**11ad** was prepared from *anti*-**10ad** and exhibited inhibition of the CT-L enzymes with an IC_{50} value roughly 20 times greater than that of the *anti*-**11ad** (52 nM versus 2.9 nM in the same assay), thus suggesting that the correct relative stereochemistry is critical to activity.

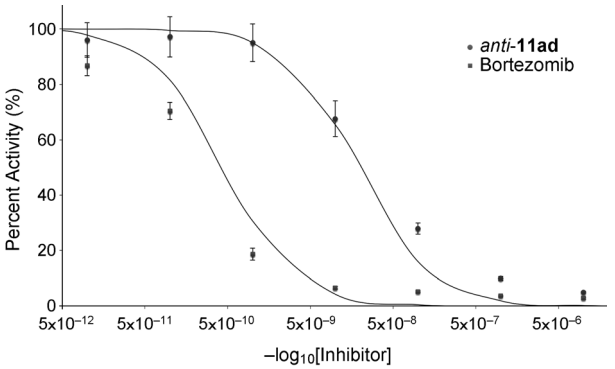


Figure 2. *In vitro* cytosolic chymotrypsin-like 20S proteasome inhibition by *anti*-**11ad**. The results were obtained in triplicate and averaged. Errors shown indicate one standard deviation.

While unprotected boropeptides are known to inhibit members of the 20S proteasome, the instability of the free boronic acid moiety under biological conditions[1] limits the feasibility of oral administration. We therefore questioned whether the protected nature of MIDA-protected boropeptides, which exhibit improved stability under biological conditions,[1] would shut down their biological activity. To investigate this, we subjected each diastereomer of **7a** to the CT-L 20S proteasome inhibition assay with unprotected bortezomib as a control. We observed low nanomolar inhibition of the CT-L enzymes for both diastereomers (IC_{50} values of 22 and 71 nM for diastereomers A and B, respectively; bortezomib 0.15 nM).

The similarity in potency and selectivity of *anti*-**11ad** and **7a** compared to bortezomib led us to question whether their structural differences might give rise to differences in cell permeability. We subjected each of these compounds to a Caco-2 screening assay[22] and found that *anti*-**11ad** exhibited greatly improved cell permeability compared to both **7a** and bortezomib. The latter two yielded similar cellular permeability (see the Supporting Information). In a control experiment, we found that in the absence of cells and cell lysates, **7a** is partially hydrolyzed to the free boronic acid when incubated at 37 °C in buffered aqueous solution (see the Supporting Information). We therefore attribute the results of both the 20S proteasome inhibition and Caco-2 assays for this compound to its buffer-mediated hydrolysis forming the active species during the assay.

In summary, we have outlined the preparation and utility of bench-stable α-boryl isocyanides. These novel amphoteric reagents can be applied to the synthesis of boron-containing building blocks (tetrazoles, isothiocyanates, and thioureas)

and as boron transfer agents in MCR-based preparation of biologically active boropeptides. As part of this study we have demonstrated a one-step synthesis of MIDA-protected bortezomib diastereomers. Our studies of α-boryl isocyanides also afforded a new class of boron-containing heterocycles (6-boromorpholinones). These air-stable solids exhibited selective inhibition of CT-L members of the 20S proteasome with IC_{50} values in the low nanomolar range. We expect that α-boryl isocyanides will enable access to many other novel biologically active boropeptide derivatives using readily available starting materials and will enable synthesis of biological probes of proteasome function.[23]

Received: April 5, 2013
Revised: May 24, 2013
Published online: ■■ ■■, ■■■■

Keywords: boron · inhibitors · isocyanides · multicomponent reactions · peptides

[1] *Boronic Acids: Preparation and Applications in Organic Synthesis Medicine and Materials*, 2nd ed. (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2011**.

[2] For reviews on boron-containing chemosensors, see: a) C. L. Fraser, G. Zhang, *Mater. Today* **2009**, *12*, 38 – 40; b) E. Galbraith, Y. D. James, *Chem. Soc. Rev.* **2010**, *39*, 3831 – 3842; c) T. A. Houston, S. M. Levonic, M. J. Keifel, *Aust. J. Chem.* **2007**, *60*, 811 – 815L; d) V. M. Dembitsky, A. A. A. A. Quntar, M. Srebnik, *Chem. Rev.* **2011**, *111*, 209 – 237; e) C. R. Wade, A. E. Broomsgrove, S. Aldridge, F. P. Gabbaï, *Chem. Rev.* **2010**, *110*, 3958 – 3984.

[3] a) J. M. Fevig, M. M. Abelman, D. R. Britelli, C. A. Kettner, R. M. Knabb, P. C. Weber, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 295 – 300; b) C. Dominguez, D. J. Carini, P. C. Weber, R. M. Knabb, R. S. Alexander, C. A. Kettner, R. R. Wexler, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 79 – 84; c) J. M. Fevig, J. Buriak, Jr., J. Cacciola, R. S. Alexander, C. A. Kettner, R. M. Knabb, J. R. Pruitt, P. C. Weber, R. R. Wexler, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 301 – 306; d) A. B. Shevni, *Biochemistry* **1986**, *25*, 1286 – 1291; e) S. Touchet, F. Carreaux, B. Carboni, A. Bouillon, J.-L. Boucher, *Chem. Soc. Rev.* **2011**, *40*, 3895 – 3914; f) R. J. R. Rao, A. K. S. B. Rao, K. Swapna, B. B. Rani, S. P. Kumar, S. Awantika, Y. L. N. Murthy, *J. Korean Chem. Soc.* **2011**, *55*, 765 – 775; for reviews, see: g) A. Rentsch, D. Landsberg, T. Brodmann, L. Bülow, A.-K. Girbig, M. Kalesse, *Angew. Chem.* **2013**, *125*, 5560 – 5599; *Angew. Chem. Int. Ed.* **2013**, *52*, 5450 – 54881.

[4] a) M. J. Jebrail, N. Assem, J. M. Mudrik, M. D. M. Dryden, K. Lin, A. K. Yudin, A. R. Wheeler, *J. Flow Chem.* **2012**, *2*, 103 – 107; b) N. Assem, A. Natarajan, A. K. Yudin, *J. Am. Chem. Soc.* **2010**, *132*, 10986 – 10987; c) X. Li, A. K. Yudin, *J. Am. Chem. Soc.* **2007**, *129*, 14152 – 14153.

[5] a) M. J. Jebrail, A. H. C. Ng, V. Rai, R. Hili, A. K. Yudin, A. R. Wheeler, *Angew. Chem.* **2010**, *122*, 8807 – 8811; *Angew. Chem. Int. Ed.* **2010**, *49*, 8625 – 8629; b) C. C. G. Scully, V. Rai, G. Poda, S. Zaretsky, D. C. Burns, R. S. Houliston, T. Lou, A. K. Yudin, *Chem. Eur. J.* **2012**, *18*, 15612 – 15617; c) A. Roxin, J. Chen, C. C. G. Scully, B. H. Rotstein, A. K. Yudin, *Bioconjugate Chem.* **2012**, *23*, 1387 – 1395; d) R. Hili, V. Rai, A. K. Yudin, *J. Am. Chem. Soc.* **2010**, *132*, 2889 – 2891; e) N. Assem, A. K. Yudin, *Nat. Protoc.* **2012**, *7*, 1327 – 1334; f) B. H. Rotstein, D. J. Winterheimer, L. M. Yin, C. M. Deber, A. K. Yudin, *Chem. Commun.* **2012**, *48*, 3775 – 3777; g) B. H. Rotstein, V. Rai, R. Hili, A. K. Yudin, *Nat. Protoc.* **2010**, *5*, 1813 – 1822.

[6] a) R. Hili, A. K. Yudin, *Chem. Eur. J.* **2007**, *13*, 6538 – 6542; b) V. V. Tumanov, A. A. Tishkov, H. Mayr, *Angew. Chem.* **2007**, *119*, 3633 – 3636; *Angew. Chem. Int. Ed.* **2007**, *46*, 3563 – 3566.

[7] a) U. Schöllkopf, H.-H. Lau, K.-H. Scheunemann, E. Blume, K. Madawinata, *Liebigs Ann. Chem.* **1980**, 600 – 610; b) Y. Jin, S. Kamijo, Y. Yamamoto, *Tetrahedron Lett.* **2004**, *45*, 9435 – 9437; for reviews, see: c) U. Schöllkopf, *Angew. Chem.* **1977**, *89*, 351 – 360; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 339 – 348; d) Y. Ito, K. Kobayashi, T. Saegusa, *J. Am. Chem. Soc.* **1977**, *99*, 3532 – 3534; e) Q. Cai, F. Zhou, T. Xu, L. Fu, K. Ding, *Org. Lett.* **2011**, *13*, 340 – 343; f) H. Takaya, S. Kojima, S.-I. Murahashi, *Org. Lett.* **2001**, *3*, 421 – 424; g) Q. Xia, B. Ganem, *Org. Lett.* **2002**, *4*, 1631 – 1634; h) L. E. Kaim, L. Grimaud, P. Patil, *Org. Lett.* **2011**, *13*, 1261 – 1263; i) S. Kamijo, C. Kanazawa, Y. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 9260 – 9266; j) M. Suginome, T. Fukuda, Y. Ito, *Org. Lett.* **1999**, *1*, 1977 – 1979; k) Y. Li, X. Xu, J. Tan, C. Xia, D. Zhang, Q. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 1775 – 1777; l) T. Yue, M.-X. Wang, D.-X. Wang, G. Masson, J. Zhu, *Angew. Chem.* **2009**, *121*, 6845 – 6849; *Angew. Chem. Int. Ed.* **2009**, *48*, 6717 – 6721; m) P. Janvier, X. Sun, H. Bienaymé, J. Zhu, *J. Am. Chem. Soc.* **2002**, *124*, 2560 – 2567.

[8] a) *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**; for U4CRs, see: b) I. Ugi, F. K. Rosendahl, F. Bodesheim, *Justus Liebigs Ann. Chem.* **1963**, *666*, 54 – 61; c) S. Lehnhoff, M. Goebel, R. M. Karl, R. Klösel, I. Ugi, *Angew. Chem.* **1995**, *107*, 1208 – 1211; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1104 – 1107; d) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300 – 3344; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168 – 3210; e) M. Waki, J. Meienhofer, *J. Am. Chem. Soc.* **1977**, *99*, 6075 – 6082; f) E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem.* **2011**, *123*, 6358 – 6371; *Angew. Chem. Int. Ed.* **2011**, *50*, 6234 – 6246; for P3CRs, see: g) R. H. Baker, A. H. Schlesinger, *J. Am. Chem. Soc.* **1945**, *67*, 1499 – 1500; h) R. H. Baker, D. Stanonis, *J. Am. Chem. Soc.* **1951**, *73*, 699 – 702; i) S.-X. Wang, M.-X. Wang, D.-X. Wang, J. Zhu, *Angew. Chem.* **2008**, *120*, 394 – 397; *Angew. Chem. Int. Ed.* **2008**, *47*, 388 – 391; j) I. Ugi, *Angew. Chem.* **1962**, *74*, 9 – 22; *Angew. Chem. Int. Ed.* **1962**, *1*, 8 – 21; for reviews, see: k) A. Dömling, *Comb. Chem. High Throughput Screening* **1998**, *1*, 1 – 22; l) F. De Moliner, L. Banfi, R. Riva, A. Basso, *Comb. Chem. High Throughput Screening* **2011**, *14*, 782 – 810; m) C. Hulme, T. Nixey, *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 921 – 929; n) A. Dömling, *Curr. Opin. Chem. Biol.* **2000**, *4*, 318 – 323.

[9] H. Witte, P. Mischke, G. Hesse, *Leibigs Ann. Chem.* **1969**, *722*, 21 – 28.

[10] J. P. G. Versleijen, P. M. Faber, H. H. Bodewes, A. H. Braker, D. van Leusen, A. M. van Leusen, *Tetrahedron Lett.* **1995**, *36*, 2109 – 2112.

[11] a) T. Mancilla, R. Contreras, *J. Organomet. Chem.* **1986**, *307*, 1 – 6; b) B. Garrigues, M. Mulliez, A. Raharinirina, *J. Organomet. Chem.* **1986**, *302*, 153 – 158; c) G. R. Dick, D. M. Knapp, E. P. Gillis, M. D. Burke, *Org. Lett.* **2010**, *12*, 2314 – 2317; d) D. M. Knapp, E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2009**, *131*, 6961 – 6963; e) E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2008**, *130*, 14084 – 14085; for reviews, see: f) Q. I. Churches, *Aust. J. Chem.* **2011**, *64*, 1474; g) E. P. Gillis, M. D. Burke, *Aldrichimica Acta* **2009**, *42*, 17 – 27; h) E. M. Woerly, A. H. Cherney, E. K. Davis, M. D. Burke, *J. Am. Chem. Soc.* **2010**, *132*, 6941 – 6943; i) S. Fujii, S. Y. Chang, M. D. Burke, *Angew. Chem.* **2011**, *123*, 8008 – 8010; *Angew. Chem. Int. Ed.* **2011**, *50*, 7862 – 7864; j) G. R. Dick, E. M. Woerly, M. D. Burke, *Angew. Chem.* **2012**, *124*, 2721 – 2726; *Angew. Chem. Int. Ed.* **2012**, *51*, 2667 – 2672.

[12] a) J. D. St. Denis, Z. He, A. K. Yudin, *Org. Biomol. Chem.* **2012**, *10*, 7900 – 7902; b) Z. He, A. K. Yudin, *J. Am. Chem. Soc.* **2011**, *133*, 13770 – 13773; c) J. Li, M. D. Burke, *J. Am. Chem. Soc.* **2011**, *133*, 13774 – 13777.

[13] Z. He, A. Zajdlik, J. D. St. Denis, N. Assem, A. K. Yudin, *J. Am. Chem. Soc.* **2012**, *134*, 9926 – 9929.
[14] a) J. E. Baldwin, J. C. Bottaro, P. D. Riordan, A. E. Derome, *J. Chem. Soc. Chem. Commun.* **1982**, 942 – 943; b) J. E. Baldwin, A. E. Derome, P. D. Riordan, *Tetrahedron* **1983**, *39*, 2989 – 2994; c) J. E. Baldwin, Y. Yamaguchi, *Tetrahedron Lett.* **1989**, *30*, 3335 – 3338.
[15] J. E. Grob, M. A. Dechantsreiter, R. B. Tichkule, *Org. Lett.* **2012**, *14*, 5578 – 5581.
[16] S.-I. Fujiwara, T. Shin-Ike, *Tetrahedron Lett.* **1991**, *32*, 3503 – 3506.
[17] a) H. Takahashi, K. Takeda, N. Nimura, H. Ogura, *Chem. Pharm. Bull.* **1979**, *27*, 1137 – 1142; b) V. P. Arya et al., *Indian J. Chem.* **1972**, *10*, 686 – 690.
[18] B. Greener, D. S. Millan in *Modern Drug Synthesis* (Eds.: J. J. Li, D. S. Johnson), Wiley, Hoboken, **2010**, chap. 8, pp. 99 – 110.
[19] For the original use of L-Pro in an U4CR, see: A. Demharter, W. Hörl, E. Herdtweck, I. Ugi, *Angew. Chem.* **1996**, *108*, 185 – 187; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 173 – 175.
[20] Gaussian 09, Revision A.1, M. J. Frisch et al., Gaussian, Inc., Wallingford CT, **2009**.
[21] D. Nandi, P. Tahiliani, A. Kumar, D. Chandu, *J. Biosci.* **2006**, *31*, 137 – 155.
[22] a) P. Artursson, *J. Pharm. Sci.* **1990**, *79*, 476 – 482; b) S. Yee, *Pharm. Res.* **1997**, *14*, 763 – 766.
[23] W. W. Kallemeijn, K.-Y. Li, M. D. Witte, A. R. A. Marques, J. Aten, S. Scheij, J. Jiang, L. I. Willems, T. M. Voorn-Brouwer, C. P. A. A. van Roomen et al., *Angew. Chem.* **2012**, *124*, 12697 – 12701; *Angew. Chem. Int. Ed.* **2012**, *51*, 12529 – 12533.

