Conformational control of nonplanar free base porphyrins: towards bifunctional catalysts of tunable basicity

This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Quaternary \( \beta^{2,2} \)-Amino Acid Derivatives by Asymmetric Addition of Isoxazolidin-5-ones to para-Quinone Methides

Andreas Eitzinger, Michael Winter, Johannes Schörgenhumer, and Mario Waser

The highly enantioselective (>99.5% ee) synthesis of a new class of densely functionalized \( \beta^{2,2} \)-amino acid derivatives by reacting isoxazolidin-5-ones with para-quinone methides in the presence of chiral ammonium salt phase-transfer catalysts was developed. The reaction proceeds with exceptionally low catalyst loadings down to 20 ppm on gram scale and the utilization of the primary addition products towards further manipulations was demonstrated for selected examples.

Chiral \( \beta \)-amino acids (AA) are very interesting structural motives which have attracted significant attention over the last decades. Their high value is because \( \beta \)-AA-containing compounds show unique biological properties combined with increased metabolic stability and, in addition, it turned out that their incorporation into peptides results in well-defined and more rigid secondary structures, compared to \( \alpha \)-AA-based ones. It is thus not surprising that the development of novel synthesis methods to access those valuable targets has become a very important topic. While syntheses of \( \beta \)-AA containing only one substituent in the \( \alpha \)- and/or \( \beta \)-position (\( \beta^{3} \), \( \beta^{3,3} \) or \( \beta^{2,2} \)-AA) have been well-established, the asymmetric syntheses of \( \beta \)-AA containing an all-carbon \( \alpha \)-quaternary stereocenter but no further substituents in the \( \beta \)-position (\( \beta^{2,2,2} \)-AA), remain a synthetic challenge.

An elegant and straightforward strategy to access masked \( \beta^{2,2} \)-AA in an asymmetric catalytic manner relies on the use of easily accessible isoxazolidin-5-ones as pronucleophiles (Scheme 1A). These compounds can be directly accessed from Meldrum acid derivatives via an elegant route developed by Briere and co-workers. The same group also pioneered the use of compounds 1 for asymmetric transformations to access \( \alpha \)-sulfanlylated, \( \alpha \)-aminated, and \( \alpha \)-alkylated derivatives under asymmetric phase-transfer catalysis (PTC). In addition, they demonstrated the utilization of the hereby obtained products towards chiral \( \beta^{2,2} \)-AA derivatives (i.e. by reductive cleavage of the N-O bond), giving access to chiral \( \beta^{2,2} \)-AA that are not accessible by other common strategies. Shortly after these initial reports the groups of Shibasaki and Cossey independently reported transition metal-catalysed asymmetric \( \alpha \)-allylation reactions of compounds 1, as well as organocatalytic Michael and Mannich reactions. In addition Noda and Shibasaki recently also demonstrated that isoxazolidinones 1 can undergo intramolecular electrophilic aromatic aminations (by N-O bond cleavage), providing another powerful application for these unique compounds. Our group has a long-standing interest in asymmetric PTC, and we recently reported the enantioselective addition of 1 to MBH carbonates in the presence of chiral PTCs. However, apart from those few very recent reports describing the utilization of pronucleophiles 1 to access (masked) all-carbon quaternary \( \beta^{2,2,2} \)-AA no further asymmetric approaches relying on the use of compounds 1 have been reported so far (to the best of our knowledge). We thus wondered if we would be able to develop a broadly applicable and highly stereoselective method to access a new family of densely functionalized (masked) \( \beta^{2,2} \)-AA. We were especially interested in the synthesis of novel \( \beta^{3,3} \)-diarylated- \( \beta^{2,2} \)-amino acids as it was recently shown that \( \beta^{3,3} \)-diarylated-\( \alpha \)-AA possess very promising biological properties, and we thus reasoned that the so far unknown homologous \( \beta \)-AA would be worthwhile targets.

Scheme 1. Asymmetric \( \beta^{2,2} \)-AA syntheses starting from isoxazolidin-5-ones 1.

One class of acceptor molecules that turned out to be highly versatile are p-quinone methides (p-QMs; 2). These easily accessible and reasonably electrophilic compounds have...
we changed for Et2O in those experiments. Gratifyingly, we dioxane made lowering the reaction temperature not possible, lowering temperatures as well. However, as the melting point of at -20°C (24 h) gives product (entries 7 and 9). The high selectivity obtained with Cs2CO3 was allows for high enantio- and moderate diastereoselectivities.

We started by carrying out the reaction between the α-benzyl isoxazolidin-5-one 1a and the parent p-quinone methide 2a in the presence of a variety of different achiral and chiral phase-transfer catalysts (Table 1 gives the most significant results). First racemic experiments using K2CO3 and Cs2CO3 showed that Cs2CO3 alone allows for product 3a formation (entry 2), while K2CO3 requires the addition of a quaternary ammonium salt to promote the target reaction (entries 1 and 3). To suppress the uncatalyzed background reaction as good as possible, we thus carried out the further screening using K2CO3 first (entries 4-8). In analogy to our recent observations when reacting compounds 1 with MBH carbonates, the only catalysts that allowed for high selectivities were Maruoka’s commercially available binaphthyl-based spiro ammonium salts A. Those gave promising enantioselectivities already under the unoptimized conditions (entries 4 and 5), with the 3,4,5-trifluorophenyl-based A1 being slightly better suited then A2. Noteworthy, the reaction also gave high enantioselectivities when using a catalytic amount of base, albeit processing significantly slower (entry 6). In order to improve diastereo- and enantioselectivity, we screened different solvents and bases and found that dioxane in combination with a catalytic amount of either K2CO3 or Cs2CO3 allows for high enanti- and moderate diastereoselectivities (entries 7 and 9). The high selectivity obtained with Cs2CO3 was especially encouraging, as it demonstrates a very high catalytic activity when considering the fact that the reaction proceeds well in the absence of ammonium salts as well (compare with entry 2). Unfortunately, reactions with catalytic amounts of base turned out to be rather slow (requiring > 72 h to complete) and in general reactions using Cs2CO3 were found to be more robust and better reproducible (compared to other bases).

In order to improve ee and especially dr further, we tested lower temperatures as well. However, as the melting point of dioxane made lowering the reaction temperature not possible, we changed for Et2O in those experiments. Gratifyingly, we finally found that the use of a stoichiometric amount of Cs2CO3 at -20°C (24 h) gives product 3a with excellent enantioselectivity (>99.5% ee), high diastereoselectivity (10:1), and in literally quantitative yield (97%) (entry 10, please note that the uncatalyzed background reaction becomes significantly slower at -20 °C compared to room temperature conditions).

With these operationally simple conditions at hand, we next investigated the influence of the catalyst loading (Scheme 2). As the Maruoka catalyst A1 is only rather sparingly soluble in Et2O we reasoned that the undissolved catalyst may only serve as a reservoir for the catalytically relevant dissolved ammonium salt. In addition, given the high selectivities observed when using this catalyst under conditions where the uncatalyzed racemic background is relatively fast as well, we were hoping that we could reduce the catalyst loading significantly. Remarkably, we were able to carry out the reaction with exceptionally low catalyst loadings of down to 0.002 mol% (20 ppm), without significantly affecting the selectivity. We only observed that the conversion became slightly slower, requiring 48 h of reaction time to give 90% isolated yield for this 20 ppm experiment, while “higher” catalyst loadings resulted in full conversions after 12-24 h. Autocatalysis could be ruled out by control experiments and thus this high selectivity is really a consequence of a very remarkable catalyst control herein. To the best of our knowledge, this is one of the lowest asymmetric phase-transfer catalyst loadings reported so far, resulting in an efficient process to access the target 3a with very high ee.

Table 1. Identification of the best-suited catalyst and conditions for the addition of 1a to 2a.

| Entry | Cat. | Solv. | Base (eq.) | Yield [%]b | drc | ee/d |
|-------|------|------|------------|------------|-----|-----|
| 1     | -    | THF  | K2CO3 (1.1) | <5         | -   | -   |
| 2     | -    | THF  | Cs2CO3 (1.1) | 89         | 1:1.7 | - |
| 3     | TEBACd | THF  | K2CO3 (1.1) | 94         | 1:1.6 | - |
| 4     | A1   | THF  | K2CO3 (1.1) | 90         | 2.7:1 | 93 |
| 5     | A2   | THF  | K2CO3 (1.1) | 91         | 1.8:1 | 90 |
| 6    | A1    | THF  | K2CO3 (0.2) | 28         | 3.2:1 | 95 |
| 7    | A1    | dioxane | K2CO3 (0.2) | 92         | 5.4:1 | 99 |
| 8    | A1    | Et2O | K2CO3 (0.2) | 91         | 4.8:1 | 95 |
| 9    | A1    | dioxane | Cs2CO3 (0.1) | 94         | 4.5:1 | 98 |
| 10   | A1    | Et2O | Cs2CO3 (1.1) | 97         | 10:1 | >99.5 |

a All reactions were run for 24 h at room temperature unless otherwise stated using 0.1 mmol 1a, 0.15 mmol 2a and 5 mol% of the catalyst (0.1 M with respect to 1a).b Isolated Yields; c Determined by 1H NMR of the crude product; d Determined by HPLC using a chiral stationary phase; e Triethylbenzylammonium chloride; f Reactions had to be run for more than 72 h to ensure full conversion; g Run at -20 °C.

Scheme 2. Low catalyst loading gram scale synthesis of almost enantiopure 3a.

To demonstrate the generality of this reaction we next investigated the application scope by using a broad variety of differently substituted pronucleophiles 1 and acceptors 2 (Table...
We first screened a variety of differently substituted nucleophiles 1 (entries 1-14). All of them performed similarly well, giving access to the products 3a-3m (differing in their R1 substituents) in almost quantitative yields and with excellent enantioselectivities and high diastereo selectivities. To elucidate the relative and the absolute configuration of the newly formed products 3 we performed X-ray analysis of single crystals of the major stereoisomer of the bromo-derivative 3j. This allowed for an unambiguous elucidation of the configuration of this derivative and the configuration of the other targets was assigned in analogy (we also carried out X-ray analysis of single crystals of racemic 3b confirming the relative configuration of this derivative as well).21 Next, we varied the quinone methide acceptors 2 (entries 15-25). Besides the bis-t-butyl-containing QMs also differently R2-substituted derivatives, as shown in entries 15 and 16, can be successfully employed with high selectivities and high yields. Alternative aromatic R3 groups were well accepted too, as outlined in entries 17-23. Here we also carried out one experiment with N-Cbz-protected 1a (entry 20), which resulted in a similarly high enantioselectivity (compared to the parent N-Boc protected derivative), but gave the product in lower yield, mainly because of the formation of notable amounts of unidentified side-products. We were also pleased to see that vinylogous QMs were equally well tolerated too (entry 24). Finally, one novel acceptor that we were especially interested in is the CF3-containing QM 2x, which we herein report for the first time22 as a versatile building block for asymmetric catalysis. The use of this unique QM allows for the synthesis of the CF3-containing masked β-amino acid 3y in very high selectivity as well (entry 25), giving access to an interesting new class of CF3-containing β-amino acid derivatives.

To demonstrate the versatility of products 3 for further manipulations we carried out the test reactions shown in Scheme 3. The N-O bond could easily be cleaved under Pd-catalyzed hydrogenation conditions (either using H2 or HCO2NH)8,9 to get access to the N-protected β2-amino acid 4a straightforwardly (Scheme 3A). This compound could then be deprotected and debutylated using AlCl3 (giving 8a). In addition, as demonstrated by Noda and Shibasaki recently,7a isoxazolidinones can be directly employed for KAH-type ligations.7b We were glad to see that this strategy can also be applied to utilize 3a to access the dipeptide 7a in high isolated yield upon treatment of the in situ formed deprotected isoxazolidinone 5a with ω-ketoacid 6 (Scheme 3B).

2. Application scope.

Table 2. Application scope.*

| Entry | R1 | R2 | R3 | I [%] | ee [%] |
|-------|----|----|----|-------|--------|
| 1     | 2-Bn | t-Bu | Ph | 99 (3b) | >99.5 |
| 2     | 4-Ph-C6H4-Ch2 | t-Bu | Ph | 97 (3c) | >99.5 |
| 3     | 4-Ph-C6H4-Ch2 | t-Bu | Ph | 99 (3d) | >99.5 |
| 4     | 4-Ph-C6H4-Ch2 | t-Bu | Ph | 97 (3e) | >99.5 |
| 5     | 4-Ph-C6H4-Ch2 | t-Bu | Ph | 97 (3f) | >99.5 |
| 6     | 4-Ph-C6H4-Ch2 | t-Bu | Ph | 96 (3g) | >99.5 |
| 7     | 4-Ph-C6H4-Ch2 | t-Bu | Ph | 94 (3h) | >99.5 |
| 8     | 4-Ph-C6H4-Ch2 | t-Bu | Ph | 93 (3i) | >99.5 |

Scheme 3. Further transformations of 3a.
In conclusion, we have developed the highly enantioselective (> 99.5% ee) synthesis of a new class of densely functionalized \( \beta^2 \)-AA derivatives 3 by reacting isoxazolidin-5-ones 1 with para-quinone methides 2 in the presence of commercially available Maruoka PTCs. The reaction tolerates a broad variety of differently substituted starting materials and proceeds with exceptionally low catalyst loadings down to 0.002 mol% (20 ppm) on gram scale. Furthermore, we demonstrated the utilization of the primary addition products towards further manipulations, like KAHAs-type ligations, hydrogenation reactions, and aryl-debutylations.

Financial support by the Austrian Science Funds (FWF), Project No. P30237, is gratefully acknowledged. The used NMR spectrometers were acquired in collaboration with the University of South Bohemia (CZ) with financial support from the European Union through the EFRE INTERREG IV ETC-AT-CZ program (project M00146, “RERI-usb”).

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 Selected reviews: a) R. P. Cheng, S. H. Gellman, and W. F. DeGrado, Chem. Rev. 2001, 101, 3219-3232; b) G. Lelais and D. Seebach, Peptide Science, 2004, 76, 206-243; c) M.-I. Aguilar, A. W. Purcell, R. Devi, R. Lew, J. Rossjohn, A. I. Smith, and P. Perlmutter, Org. Biomol. Chem. 2007, 5, 2884-2890; d) D. Seebach and J. Gardiner, Acc. Chem. Res. 2008, 41, 1366-1375; e) Y.-D. Wu, W. Han, D.-P. Wang, Y. Gao, and Y.-L. Zhao, Acc. Chem. Res. 2008, 41, 1418-1427.

2 D. Seebach, S. Abele, T. Sifferlen, M. Hänggi, S. Gruner, and P. Seiler, Helv. Chim. Acta 1998, 81, 2218-2243

3 E. Juaristi and V. A. Soloshonok, Editors Enantioselective Synthesis of \( \beta \)-Amino Acids, Second Edition, John Wiley & Sons, 2005.

4 Reviews on \( \beta \)-AA syntheses: a) S. Abele and D. Seebach, Eur. J. Org. Chem. 2000, 1-15; b) J.-A. Ma, D. Seebach and J. Gardiner, Adv. Synth. Catal. 2008, 1499-1509.

5 For selected pioneering reports relying on conjugate additions to \( \beta \)-disubstituted nitroalkenes: a) H.-H. Lu, F.-G. Zhang, X.-G. Meng, S.-W. Duan, and W.-J. Xiao, Org. Lett. 2009, 11, 3946-3949; b) R. Kastl, and H. Wennisers, Angew. Chem. Int. Ed. 2013, 52, 7228-7223; c) K. Mori, M. Wakawaka, and T. Akiyama, Chem. Sci. 2014, 5, 1799-1803.

6 For a pioneering report relying on the use of \( \omega \)-cyanooacetates: T.-Y. Liu, R. Li, Q. Chai, J. Long, B.-J. Li, Y. Wu, L.-S. Ding, and Y.-C. Chen, Chem. Eur. J. 2007, 13, 319-327.

7 a) J.-S. Yu, H. Noda, and M. Shibasaki, Angew. Chem. Int. Ed. 2018, 57, 818-822. b) M. N. de Oliveira, S. Arseniyadis, and J. Willis, Chem. Soc. Rev. 2010, 39, 1456-1691. c) W. Li, X. Xu, Y. Liu, H. Gao, and G. Zhao, J. Org. Chem. 2016, 81, 9315-9325; c) Y.-J. Fan, L. Zhou, and S. Liu, Org. Chem. Front. 2018, 5, 1820-1824.

8 Addition of masked \( \beta \)-amino acid derivatives to p-QMs: a) X.-Z. Zhang, Y.-H. Deng, X. Yan, K.-Y. Du, G.-B. Zhang, F.-X. Wang, X.-Y., and C.-A. Fan, Angew. Chem. Int. Ed. 2013, 52, 9229-9233; b) L. Ge, X. Lu, C. Cheng, J. Chen, W. Cao, X. Wu, and G. Zhao, J. Org. Chem. 2016, 81, 9315-9325; c) Y.-J. Fan, L. Zhou, and S. Liu, Org. Chem. Front. 2018, 5, 1820-1824.

9 a) W.-D. Chu, L.-F. Zhang, X. Bao, X.-H. Zhao, C. Zeng, J.-Y. Du, G.-B. Zhang, F.-X. Wang, X.-Y., and C.-A. Fan, Angew. Chem. Int. Ed. 2013, 52, 9229-9233; b) L. Ge, X. Lu, C. Cheng, J. Chen, W. Cao, X. Wu, and G. Zhao, J. Org. Chem. 2016, 81, 9315-9325; c) Y.-J. Fan, L. Zhou, and S. Liu, Org. Chem. Front. 2018, 5, 1820-1824.
Novel densely functionalized $\beta^{2,2}$-amino acids were obtained in almost enantiopure form using down to 20 ppm of a chiral phase-transfer catalyst.