ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Chem. Commun.*, 2020, 56, 579

Received 27th November 2019,
Accepted 6th December 2019

DOI: 10.1039/c9cc09239k

rsc.li/chemcomm

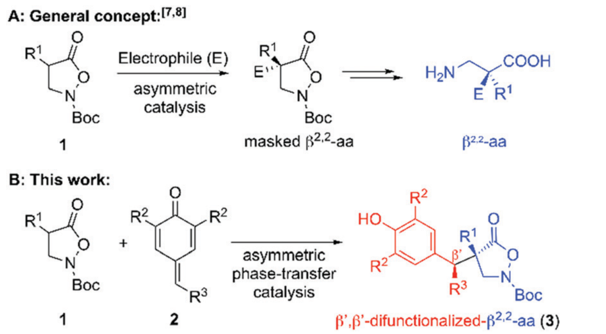
Quaternary $\beta^{2,2}$-amino acid derivatives by asymmetric addition of isoxazolidin-5-ones to *para*-quinone methides†

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

The highly enantioselective (>99.5% ee) synthesis of a new class of densely functionalized β[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 β-amino acids (AA) are very interesting structural motifs which have attracted significant attention over the last decades.[1–4] Their high value is because β-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 α-AA-based ones.[1,2] It is thus not surprising that the development of novel synthesis methods to access those valuable targets has become a very important topic.[3,4] While syntheses of β-AA containing only one substituent in the α- and/or β-position (β^2, β^3 or $\beta^{2,3}$-AA) have been well-established,[3,4] the asymmetric syntheses of β-AA containing an all-carbon α-quaternary stereocenter but no further substituents in the β-position ($\beta^{2,2}$-AA) remain a synthetic challenge.[5–8]

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 **1** as pronucleophiles (Scheme 1A).[7,8] These compounds can be directly accessed from Meldrum acid derivatives *via* an elegant route developed by Briere and co-workers.[9] The same group also pioneered the use of compounds **1** for asymmetric transformations to access α-sulfanylated, α-aminated, and α-alkylated derivatives[8] under asymmetric phase-transfer catalysis (PTC).[10] In addition, they



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

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 Cossy independently reported transition metal-catalysed asymmetric α-allylation reactions of compounds **1**,[7a,b] as well as organocatalytic Michael and Mannich reactions.[7c] 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.[11] Our group has a long-standing interest in asymmetric PTC,[12] and we recently reported the enantioselective addition of **1** to MBH carbonates in the presence of chiral PTCs.[7d] However, apart from those few very recent reports describing the utilization of pronucleophiles **1** to access (masked) all-carbon quaternary $\beta^{2,2}$-AA,[7,8] 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 β′,β′-diarylated-$\beta^{2,2}$-amino acids as it was recently shown that β,β-diarylated-α-AA possess very promising biological properties,[13] and we thus

Johannes Kepler University Linz, Institute of Organic Chemistry, Altenbergerstraße 69, 4040 Linz, Austria. E-mail: mario.waser@jku

† Electronic supplementary information (ESI) available: Detailed experimental procedures, analytical details, copies of NMR spectra, HPLC traces and X-ray crystallographic data. CCDC 1911984 (**3j**) and 1943927 (**3b**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc09239k

reasoned that the so far unknown homologous β-AA would be worthwhile targets.

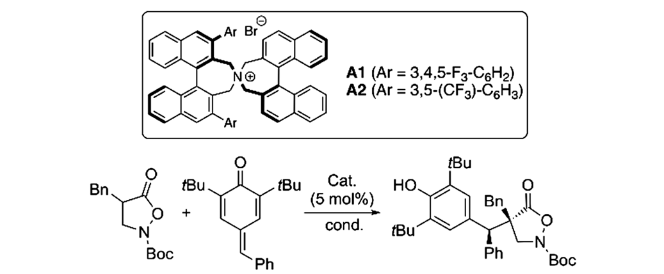
One class of acceptor molecules that turned out to be highly versatile are *p*-quinone methides (*p*-QMs; **2**).[14] These easily accessible and reasonably electrophilic[15] compounds have recently emerged as outstanding acceptors to access high levels of structural complexity upon reaction with different (pro)-nucleophiles[16,17] and we reasoned that the development of a stereoselective catalytic protocol for the addition of masked β-AA **1** to *p*-QMs **2** would result in a unique and powerful approach to access a new class of highly functionalized dissymmetric β′,β′-difunctionalized-β^{2,2}-AA **3** (Scheme 1B).

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).[18] First racemic experiments using K_2CO_3 and Cs_2CO_3 showed that Cs_2CO_3 alone allows for product **3a** formation (entry 2), while K_2CO_3 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 K_2CO_3 first (entries 4–8). In analogy to our recent observations when reacting compounds **1** with MBH carbonates,[7d] and Briere's results when using **1** under asymmetric phase-transfer catalysis,[8] the only catalysts that allowed for high selectivities were Maruoka's commercially available binaphthyl-based spiro ammonium salts **A**.[18,19] 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 K_2CO_3 or Cs_2CO_3 allows for high enantio- and moderate diastereoselectivities (entries 7 and 9). The high selectivity obtained with Cs_2CO_3 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 Cs_2CO_3 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 Et_2O in those experiments. Gratifyingly, we finally found that the use of a stoichiometric amount of Cs_2CO_3 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[18]). As the Maruoka catalyst **A1** is only rather sparingly soluble in Et_2O 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.[18] 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.[20]

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



1a **2a** **3a**

Entry	Cat.	Solv.	Base (eq.)	Yield[b] [%]	dr[c]	ee[d]
1	—	THF	K_2CO_3 (1.1)	<5	—	—
2	—	THF	Cs_2CO_3 (1.1)	89	1 : 1.7	—
3	TEBAC[e]	THF	K_2CO_3 (1.1)	94	1 : 1.6	—
4	**A1**	THF	K_2CO_3 (1.1)	90	2.7 : 1	93
5	**A2**	THF	K_2CO_3 (1.1)	91	1.8 : 1	90
6[f]	**A1**	THF	K_2CO_3 (0.2)	28	3.2 : 1	95
7[f]	**A1**	Dioxane	K_2CO_3 (0.2)	92	5.4 : 1	99
8[f]	**A1**	Et_2O	K_2CO_3 (0.2)	91	4.8 : 1	95
9[f]	**A1**	Dioxane	Cs_2CO_3 (0.1)	94	4.5 : 1	98
10[g]	**A1**	Et_2O	Cs_2CO_3 (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 ^{1}H 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.

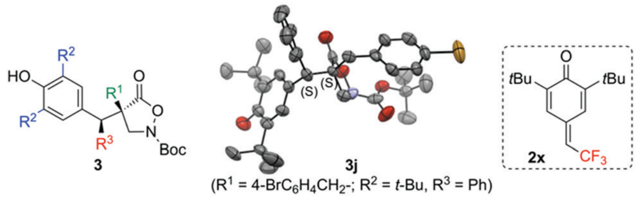
1a 1.38 g 5 mmol

2a 2.21 g 7.5 mmol

3a 2.57 g; 4.5 mmol (90%) *dr* = 10:1, *ee* = 99%

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

Table 2 Application scope[a]

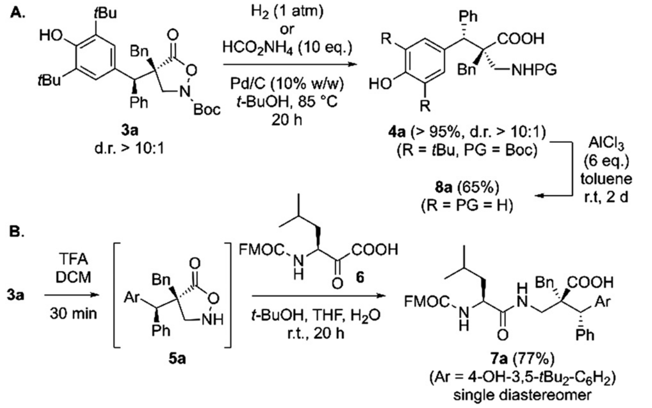


Entry	R^1	R^2	R^3	3^b [%]	dr[c]	ee[d,e]
1	Bn	t-Bu	Ph-	97 (**3a**)	10 : 1	> 99.5
2	4-Ph-C_6H_4-CH_2-	t-Bu	Ph-	99 (**3b**)	10 : 1	> 99.5
3	2-Naphthyl-CH_2-	t-Bu	Ph-	97 (**3c**)	10 : 1	> 99.5
4	2-Furanyl-CH_2-	t-Bu	Ph-	98 (**3d**)	11 : 1	> 99.5
5	4-Me-C_6H_4-CH_2	t-Bu	Ph-	97 (**3e**)	10 : 1	> 99.5
6	2-Me-C_6H_4-CH_2	t-Bu	Ph-	96 (**3f**)	3 : 1	> 99.5
7	4-t-Bu-C_6H_4-CH_2	t-Bu	Ph-	94 (**3g**)	14 : 1	> 99.5
8	4-MeO-C_6H_4-CH_2	t-Bu	Ph-	99 (**3h**)	9 : 1	> 99.5
9	4-Cl-C_6H_4-CH_2	t-Bu	Ph-	97 (**3i**)	8 : 1	99.3
10[e]	4-Br-C_6H_4-CH_2	t-Bu	Ph-	95 (**3j**)	7 : 1	99.4
11	4-F-C_6H_4-CH_2	t-Bu	Ph-	99 (**3k**)	7 : 1	99.1
12	(E)-Ph–CH═CH–CH_2	t-Bu	Ph-	95 (**3l**)	9 : 1	99.4
13	Cyclopropyl-CH_2	t-Bu	Ph-	90 (**3m**)	9 : 1	98.0
14	Cyclohexyl-CH_2	t-Bu	Ph-	91 (**3n**)	7 : 1	> 99.5
15	Bn	i-Pr	Ph-	90 (**3o**)	5 : 1	98.9
16	Bn	t-Bu, Me	Ph-	99 (**3p**)	10 : 1	99.5
17	Bn	t-Bu	4-MeO-C_6H_4-	95 (**3q**)	6 : 1	99.1
18	Bn	t-Bu	2-MeO-C_6H_4-	99 (**3r**)	6 : 1	> 99.5
19	Bn	t-Bu	4-Cl-C_6H_4-	99 (**3s**)	20 : 1	> 99.5
20[f]	Bn	t-Bu	4-Cl-C_6H_4-	35 (**3s-Cbz**)	14 : 1	99.0
21	Bn	t-Bu	4-CF_3-C_6H_4-	99 (**3t**)	6 : 1	> 99.5
22	Bn	t-Bu	2-Naphthyl-	99 (**3u**)	11 : 1	> 99.5
23	Bn	t-Bu	2-Pyridyl-	97 (**3v**)	4 : 1	96.5
24	Bn	t-Bu	(E)-Ph-CH═CH-	70 (**3w**)	5 : 1	98.5
25	Bn	t-Bu	CF_3-	97 (**3x**)	10 : 1	> 99.5

[a] For ease of comparison all reactions were run for 24 h at −20 °C in Et_2O (0.1 M with respect to **1**) using 0.1 mmol **1**, 0.15 mmol **2**, 0.11 mmol Cs_2CO_3, and 5 mol% of **A1** (selected examples were repeated using 1 mol% **A1** without affecting the outcome). [b] Isolated yields. [c] Determined by NMR of the crude product. [d] Determined by HPLC using a chiral stationary phase. [e] The relative and absolute configuration of **3j** was proven by X-ray single crystal diffraction analysis[23] and all other compounds were assigned in analogy. [f] Using N-Cbz-protected **1a**.

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 2). 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–3n** (differing in their R^1 substituents) in almost quantitative yields and with excellent enantioselectivities and high diastereoselectivities. 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 R^2-substituted derivatives, as shown in entries 15 and 16, can be successfully employed with high selectivities and high yields. Alternative aromatic R^3 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 CF_3-containing QM **2x**, which we herein report for the first time[22] as a versatile building block for asymmetric catalysis. The use of this unique QM allows for the synthesis of the CF_3-containing masked β-aa **3x** in very high selectivity as well (entry 25), giving access to an interesting new class of CF_3-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 H_2 or HCO_2NH_4)[8,9] to get access to the N-protected $\beta^{2,2}$-amino acid **4a** straightforwardly (Scheme 3A). This compound could then be deprotected and debutylated using $AlCl_3$ (giving **8a**). In addition, as demonstrated by Noda and Shibasaki recently,[7a] isoxazolidinones can be directly employed for KAHA-type ligations.[23] 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 β-ketoacid **6** (Scheme 3B).



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 $\beta^{2,2}$-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 KAHA-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-uasb").

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, *Pept. Sci.*, 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 *Enantioselective Synthesis of β-Amino Acids*, ed. E. Juaristi and V. A. Soloshonok, 2nd edn, John Wiley & Sons, 2005.
4 Reviews on β-AA syntheses: (*a*) S. Abele and D. Seebach, *Eur. J. Org. Chem.*, 2000, 1–15; (*b*) J.-A. Ma, *Angew. Chem., Int. Ed.*, 2003, **42**, 4290–4299; (*c*) D. Seebach, A. K. Beck, S. Capone, G. Deniau, U. Groselj and E. Zass, *Synthesis*, 2009, 1–32; (*d*) B. Weiner, W. Szymanski, D. B. Janssen, A. J. Minnaard and B. L. Feringa, *Chem. Soc. Rev.*, 2010, **39**, 1656–1691.
5 For selected pioneering reports relying on conjugate additions to β,β-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. Wennemers, *Angew. Chem., Int. Ed.*, 2013, **52**, 7228–7232; (*c*) K. Mori, M. Wakazawa and T. Akiyama, *Chem. Sci.*, 2014, **5**, 1799–1803.
6 For a pioneering report relying on the use of α-cyanoacetates: 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. Cossy, *Chem. – Eur. J.*, 2018, **24**, 4810–4814; (*c*) J.-S. Yu, H. Noda and M. Shibasaki, *Chem. – Eur. J.*, 2018, **24**, 15796–15800; (*d*) V. Capaccio, K. Zielke, A. Eitzinger, A. Massa, L. Palombi, K. Faust and M. Waser, *Org. Chem. Front.*, 2018, **5**, 3336–3340; (*e*) F. Amemiya, H. Noda and M. Shibasaki, *Chem. Pharm. Bull.*, 2019, **67**, 1046–1049.
8 (*a*) T. Cadart, C. Berthonneau, V. Levacher, S. Perrio and J.-F. Briere, *Chem. – Eur. J.*, 2016, **22**, 15261–15264; (*b*) T. Cadart, V. Levacher, S. Perrio and J.-F. Briere, *Adv. Synth. Catal.*, 2018, **360**, 1499–1509.
9 (*a*) T. Tite, M. Sabbah, V. Levacher and J.-F. Briere, *Chem. Commun.*, 2013, **49**, 11569–11571; (*b*) N. Lespes, E. Pair, C. Maganga, M. Bretier, V. Tognetti, L. Joubert, V. Levacher, M. Hubert-Roux, C. Afonso, C. Loutelier-Bourhis and J.-F. Briere, *Chem. – Eur. J.*, 2018, **24**, 4086–4093.
10 Recent reviews on asymmetric PTCs: (*a*) J.-F. Briere, S. Oudeyer, V. Dalla and V. Levacher, *Chem. Soc. Rev.*, 2012, **41**, 1696–1707; (*b*) S. Shirakawa and K. Maruoka, *Angew. Chem., Int. Ed.*, 2013, **52**, 4312–4348; (*c*) J. Tan and N. Yasuda, *Org. Process Res. Dev.*, 2016, **20**, 129–139; (*d*) L. Zong and C.-H. Tan, *Acc. Chem. Res.*, 2017, **50**, 842–856; (*e*) J. Schörgenhumer, M. Tiffner and M. Waser, *Beilstein J. Org. Chem.*, 2017, **13**, 1753–1769; (*f*) H. Wang, *Catalysts*, 2019, **9**, 244.
11 (*a*) J.-S. Yu, M. Espinosa, H. Noda and M. Shibasaki, *J. Am. Chem. Soc.*, 2019, **141**, 10530–10537; (*b*) M. Espinosa, H. Noda and M. Shibasaki, *Org. Lett.*, 2019, **21**, 9296–9299.
12 For a recent example see: J. Novacek, J. A. Izzo, M. J. Vetticatt and M. Waser, *Chem. – Eur. J.*, 2016, **22**, 17339–17344.
13 For two examples: (*a*) M. Nilsson, M. Hämäläinnen, M. Ivarsson, J. Gottfries, Y. Xue, S. Hansson, R. Isaksson and T. Fex, *J. Med. Chem.*, 2009, **52**, 2708–2715; (*b*) D. E. Patterson, J. D. Powers, M. LeBlanc, T. Sharkey, E. Boehler, E. Irdam and M. H. Osterhout, *Org. Process Res. Dev.*, 2009, **13**, 900–906.
14 (*a*) W.-J. Bai, J.-G. David, Z.-G. Feng, M. G. Weaver, K.-L. Wu and T. R. R. Pettus, *Acc. Chem. Res.*, 2014, **47**, 3655–3664; (*b*) N. J. Willis and C. D. Bray, *Chem. – Eur. J.*, 2012, **18**, 9160–9173; (*c*) M. S. Singh, A. Nagaraju, N. Anand and S. Chowdhury, *RSC Adv.*, 2014, **4**, 55924–55959; (*d*) L. Caruana, M. Fochi and L. Bernardi, *Molecules*, 2015, **20**, 11733–11764; (*e*) D. V. Osipov, V. A. Osyanin and Y. N. Klimochkin, *Russ. Chem. Rev.*, 2017, **86**, 625–687.
15 (*a*) R. Lucius, R. Loos and H. Mayr, *Angew. Chem., Int. Ed.*, 2002, **41**, 91–95; (*b*) D. Richter, N. Hampel, T. Singer, A. R. Ofial and H. Mayr, *Eur. J. Org. Chem.*, 2009, 3203–3211.
16 Phase transfer-catalyzed additions to *p*-QMs: (*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. Ma 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. Li, *Org. Chem. Front.*, 2018, **5**, 1820–1824.
17 Addition of masked α-amino acid derivatives to *p*-QMs: (*a*) X.-Z. Zhang, Y.-H. Deng, X. Yan, K.-Y. Yu, F.-X. Wang, X.-Y. Ma and C.-A. Fan, *J. Org. Chem.*, 2016, **81**, 5655–5662; (*b*) F.-S. He, J.-H. Jin, Z.-T. Yang, X. Yu, J. S. Fossey and W.-P. Deng, *ACS Catal.*, 2016, **6**, 652–656; (*c*) W. Li, X. Xu, Y. Liu, H. Gao, Y. Cheng and P. Li, *Org. Lett.*, 2018, **20**, 1142–1145; (*d*) Z.-P. Zhang, K.-X. Xie, C. Yang, M. Li and X. Li, *J. Org. Chem.*, 2018, **83**, 364–373.
18 For further details see the online ESI†.
19 (*a*) T. Ooi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.*, 1999, **121**, 6519–6520; (*b*) T. Ooi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.*, 2003, **125**, 5139–5151.
20 Asymmetric PTC reactions using 0.01 mol% of a chiral PTC: (*a*) M. Kitamura, S. Shirakawa and K. Maruoka, *Angew. Chem., Int. Ed.*, 2005, **44**, 1549–1551; (*b*) Z. Han, Y. Yamaguchi, M. Kitamura and K. Maruoka, *Tetrahedron Lett.*, 2005, **46**, 8555–8558; (*c*) M. Kitamura, S. Shirakawa, Y. Arimura, X. Wang and K. Maruoka, *Chem. – Asian J.*, 2008, **3**, 1702–1714.
21 CCDC 1911984 (www.ccdc.cam.ac.uk) contains the crystallographic data for **3j** and CCDC 1943927 those for **3b**†.
22 For the intermediate formation of a similar CF_3-*p*-QM: Y. Gong and K. Kato, *Synlett*, 2002, 431–434.
23 (*a*) J. W. Bode, R. M. Fox and K. D. Baucom, *Angew. Chem., Int. Ed.*, 2006, **45**, 1248–1252; (*b*) T. G. Wucherpfennig, V. R. Pattabiraman, F. R. P. Limberg, J. Ruiz-Rodriguez and J. W. Bode, *Angew. Chem., Int. Ed.*, 2014, **53**, 12248–12252.

