Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2019, **17**, 5731

Synthesis of α-CF_3-proline derivatives by means of a formal (3 + 2)-cyclisation between trifluoropyruvate imines and Michael acceptors†

Michael Winter,[a] Kirill Faust,[b] Markus Himmelsbach [c] and Mario Waser *[a]

Received 15th May 2019,
Accepted 24th May 2019

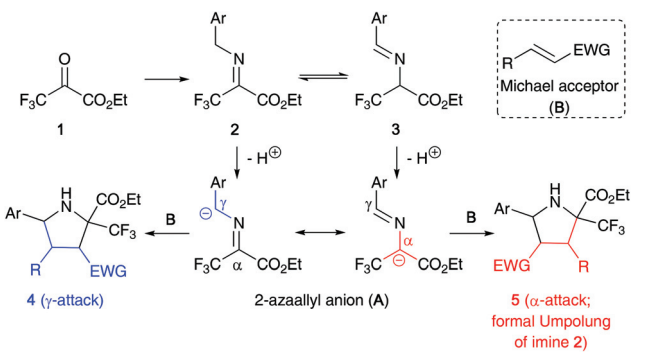
DOI: 10.1039/c9ob01134j

rsc.li/obc

We herein report the first formal (3 + 2)-cyclisation between 3,3,3-trifluoropyruvate-derived imines and indandione-based Michael acceptors. This reaction gives access to a novel class of spirocyclic α-CF_3-α-proline derivatives with complete control of the diastereoselectivity under phase transfer-catalysed reaction conditions.

Introduction

The synthesis of fluorine-containing α-amino acids became a heavily investigated topic over the last years.[1–3] The large interest in the hereby accessed fluorinated amino acids is based on the fact that the incorporation of fluorine-containing α- or β-amino acids into peptides and proteins heavily effects their (bio)-chemical and (bio)-physical properties.[3] One particularly appealing approach to alter the nature of biologically active molecules is the introduction of a trifluoromethyl group.[4,5] A broad variety of different synthesis strategies to install either a single fluorine atom, or a polyfluorinated group have been developed in the past.[6–9] Concerning the synthetic introduction of the trifluoromethyl group, one could either rely on a nucleophilic[8] or electrophilic[7] trifluoromethylation of a given compound, or, alternatively, one uses simple CF_3-containing building blocks to access further structural complexity. One commercially readily available CF_3-starting material is ethyl 3,3,3-trifluoropyruvate (**1**), which has been commonly used for further (asymmetric) transformations in the past.[10–12] Hereby the use of (protected or unprotected) trifluoropyruvate-derived imines is an especially interesting strategy to access (chiral) α-trifluoromethylated α-amino acids.[11] Very interestingly, pyruvate **1**-based imines have recently also been used as dipolarophiles for formal (3 + 2)-cyclisations upon reactions with suited 1,3-dipolar compounds.[12] Alternatively, besides their use as dipolarophiles in (3 + 2)-annulations, imines can also serve as precursors for the *in situ* generation of 1,3-dipolar azomethine ylides or 2-azaallyl anions, which then may react with suited dipolarophiles in a (3 + 2)-fashion.[13] In this regard also the use of CF_3-containing imines for the construction of 2-CF_3-substituted pyrrolidines has been described.[14] Very interestingly however, and to the best of our knowledge, the trifluoropyruvate-based benzylic imines **2**[15] or the isomeric imines **3** have so far not been used as precursors for the *in situ* generation an utilisation of 1,3-dipolar species. This comes as a surprise, as an (3 + 2)-annulation reaction of 2-azaallyl anions **A** with suited (Michael) acceptors **B** would give access to α-CF_3-containing α-proline derivatives **4** or **5** straightforwardly (Scheme 1). Spurred by the recent progress in the use of *in situ* generated 2-azaallyl anions for (enantioselective) C–C bond forming reactions (often involving a formal Umpolung of the inherent starting imine reactivity),[16–18] we became interested in investigating the potential of trifluoropyruvate-based benzylic imines **2** for formal (3 + 2)-cyclisations with different Michael acceptors to access a novel class of α-CF_3-substituted



Scheme 1 Targeted use of trifluoropyruvate **1**-based imines to access α-CF_3-α-proline derivatives **4** and/or **5**.

[a]*Institute of Organic Chemistry, Johannes Kepler University Linz, Altenbergerstr. 69, 4040 Linz, Austria. E-mail: Mario.waser@jku.at*
[b]*Institute of Catalysis, Johannes Kepler University Linz, Altenbergerstr. 69, 4040 Linz, Austria*
[c]*Institute of Analytial Chemistry, Johannes Kepler University Linz, Altenbergerstr. 69, 4040 Linz, Austria*

†Electronic supplementary information (ESI) available. CCDC 1911986. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ob01134j

α-proline derivatives **4** (*via* γ-attack of the starting imine) or **5** (*via* Umpolung of the initial imine **2**).

Results and discussion

The formation of benzylic imines **2** from pyruvate **1** was investigated in the past, but the synthetic use of these imines has so far only sparingly been evaluated.[19] In these initial reports, Soloshonok and co-workers also found that isolation of imines **2** is hardly possible, as these compounds tend to undergo a very rapid double bond migration to the isomeric benzaldimines **3** under basic and/or higher temperature reaction conditions.[19] Keeping this observation in mind, we reasoned that the α-position of the corresponding 2-azaallyl anions (that will be obtained under basic reaction conditions) will be the preferred nucleophilic site, which should then provide a route towards proline derivatives **5**, rather than **4**.

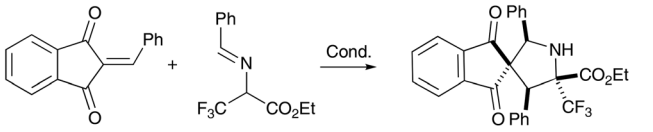
We started our investigations by carrying out the reaction between the phenyl-based imine **3a** (obtained directly from **1** upon reaction with benzylamine)[19,20] and the benzylidene indandione **6a** as the acceptor[21] (Table 1 gives an overview of the most significant results obtained in this screening). Already our initial experiments showed that the targeted (3 + 2)-annulation is possible, giving the α-attack-derived spiro compound **5a** as the sole cyclization product. It should be noted that in neither case any formation of the corresponding γ-addition product **4** or any classical Michael addition product were observed. As expected, the presence of a simple ammonium salt phase-transfer catalyst (PTC) significantly improved the conversion (compare entries 1 and 2) and the reaction proceeded with full conversion and a promising initial yield and diastereoselectivity in the presence of a catalytic amount of aqueous base (entry 2). In order to improve yield and dr we next screened different bases (in all these cases CH_2Cl_2 was used as the solvent, but we of course also tested other solvents like toluene or THF later on, which however did not allow for better results!).

By increasing the amount of base, we found that solid KOH allows for a slightly higher diastereoselectivity than aqueous KOH (entries 3 and 4). When using different solid bases (entries 4–7) it turned out that LiOH allows for complete control of the diastereoselectivity combined with a reasonable isolated yield of 68% (entry 7). When testing other simple ammonium salt PTCs we found that benzyltriethylammonium bromide performs more or less similarly as tetrahexylammonium bromide (entries 7 and 8) and we later on also realized that the corresponding ammonium chlorides allow for the same outcome. In order to improve the yield further, we increased the amount of base and catalyst (entries 9–11) and finally used a twofold excess of the acceptor **6a** combined with three equivalents of solid LiOH in the presence of 30 mol% ammonium salt catalyst, which gave **5a** in literally quantitative isolated yield on 1 mmol reaction scale (entry 9).

The relative configuration of the major diastereomer was first investigated by NOESY NMR experiments. Here we observed NOEs between the two benzylic protons (substantiating a *cis*-configuration of the two phenyl rings) as well as a weak NOE between the ester group and one phenyl group (supporting a *cis* relationship between the ester and the phenyls as well).[20] We later on were able to carry out single crystal X-ray analysis of the bromo-derivative **5b**[22] (compare with Scheme 3), which unambiguously proved the same relative configuration for that derivative as well, supporting our earlier NOESY results.

Having identified high yielding and highly diastereoselective racemic phase transfer-catalysed conditions for the (3 + 2)-cyclisation between **3a** and **6a**, we next screened a variety of different chiral ammonium salt phase transfer catalysts under different conditions for this reaction.[20,23] Unfortunately however, all these efforts were rather disappointing, as we were not able to obtain any reasonable enantioselectivity for this reaction. Scheme 2 gives the best result obtained with a Cinchona alkaloid-based chiral phase transfer catalyst, but a variety of other catalyst systems under different conditions were tested as well, but none of them gave any satisfying selectivity (as shown in the online ESI†).[20]

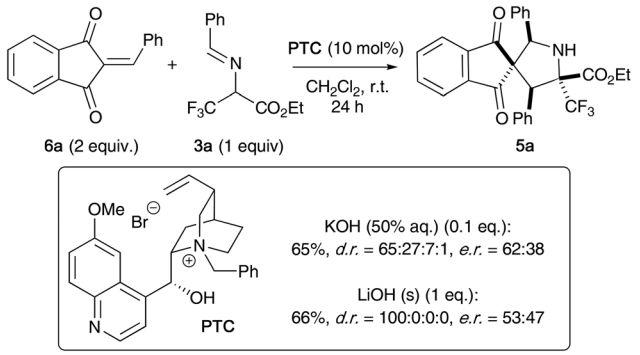
Table 1 Identification of the optimum conditions for the diastereoselective (3 + 2)-cyclisation of the azaallyl anion precursor **3a** and acceptor **6a**



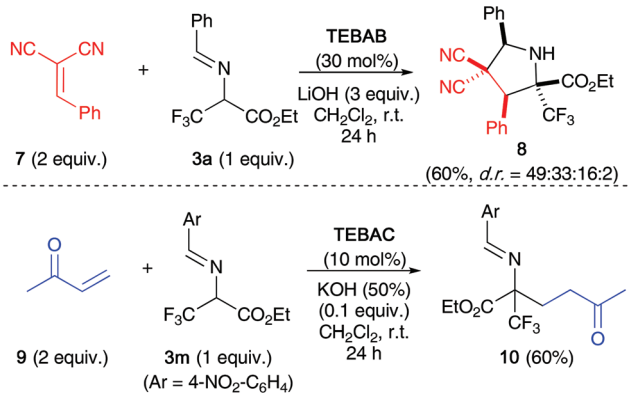
6a 3a 5a

Entry[a]	Cat.[b]	Base	Conv. (%)[c]	Yield[d] (%)	dr[c]
1	—	KOH (50%) (0.1 eq.)	15	n.d.	84 : 0 : 16 : 0
2	THAB	KOH (50%) (0.1 eq.)	>99	57	82 : 12 : 5 : 1
3	THAB	KOH (50%) (1 eq.)	91	74	80 : 12 : 7 : 1
4	THAB	KOH (s) (1 eq.)	93	72	94 : 3 : 3 : 0
5	THAB	Cs_2CO_3 (s) (1 eq.)	>99	79	95 : 4 : 1 : 0
6	THAB	K_3PO_4 (s) (1 eq.)	95	51	83 : 10 : 6 : 1
7	THAB	LiOH (s) (1 eq.)	90	68	100 : 0 : 0 : 0
8	TEBAB	LiOH (s) (1 eq.)	>99	70	100 : 0 : 0 : 0
9	TEBAB	LiOH (s) (2 eq.)	>99	70	100 : 0 : 0 : 0
10	TEBAB[e]	LiOH (s) (2 eq.)	>99	75	100 : 0 : 0 : 0
11[f]	TEBAB[g]	LiOH (s) (3 eq.)	>99	98	100 : 0 : 0 : 0

[a] Unless otherwise stated all reactions were carried out by stirring a mixture of 0.1 mmol **3a** and 1.2 equiv. **6a** with 10 mol% of catalyst in the presence of base in CH_2Cl_2 at room temperature for 24 hours. [b] THAB (tetrahexylammonium bromide), TEBAB (benzyltriethylammonium bromide). [c] Determined by ^1H and ^{19}F NMR of the crude product. [d] Isolated yields. [e] Using 20 mol% TEBAB. [f] Using 1 mmol **3a** and 2 equiv. **6a**. [g] Using 30 mol% TEBAB or the analogous chloride TEBAC.



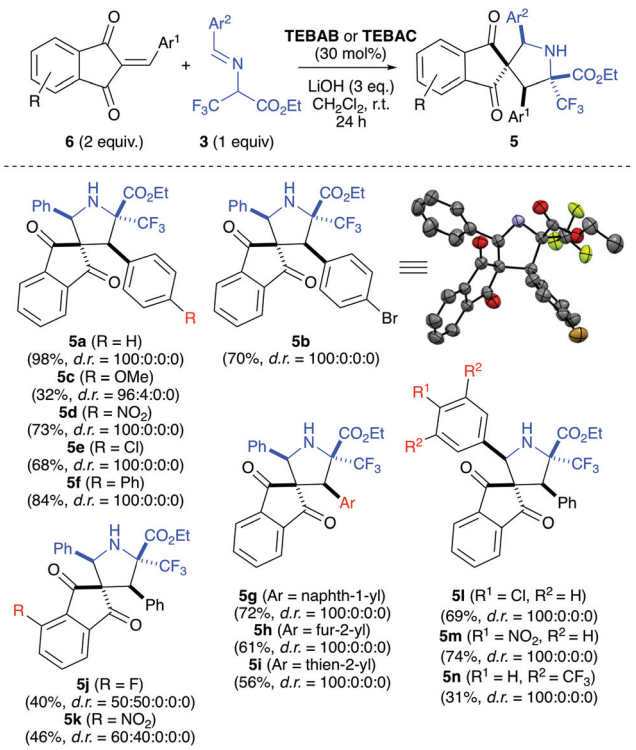
Scheme 2 Attempted chiral phase transfer-catalysed enantioselective (3 + 2)-cyclization.



Scheme 4 Reaction of imines **3** with alternative acceptors **7** and **9**.

As we were not successful in developing a satisfyingly enantioselective protocol, we investigated the application scope for the reaction between imines **3** and 1,3-indandiones **6** using achiral ammonium salt PTCs only (Scheme 3).

A variety of acceptors with different Ar^1-groups were tolerated well (giving products **5a–5i**). Only the methoxy-containing **5c** was obtained in a lower yield, mainly because of a significantly slower conversion in that specific case. As mentioned above, **5b** could be analysed by single crystal X-ray analysis and the relative configuration of the other products was assigned in analogy. When using alternative Ar^2-groups on the donor side, the products **5l** and **5m** were obtained in similar yields and with the same high diastereoselectivity. Surprisingly, the bis-CF_3-containing **5n** was obtained in a lower yield only, mainly because of the accompanying formation of unidentified side-products (most probably originating from background hydrolysis of the starting imine). Unfortunately, the introduction of other substituents on the indandione side resulted in slightly reduced yields (see products **5j** and **5k**). Furthermore, these products were also obtained as mixtures of diastereomers (differing in the configuration of the spiro carbon). The fact that the configuration of this additional stereogenic center was not controlled in this otherwise highly diastereoselective reaction came as a surprise, and unfortunately we were not able to overcome this issue.



Scheme 3 Application scope of the diastereoselective (3 + 2)-cyclisation of imines **3** and acceptors **6**.

Finally, we also tested if other Michael acceptors may be used for this (3 + 2)-cyclisation with imines **3**. As shown in Scheme 4, the arylidene malonitrile **7** gave the (3 + 2)-product **8** as well, but with very low diastereoselectivity and in this case also significant amounts of different not identified impurities were formed. In sharp contrast, methyl vinyl ketone **9** was the only acceptor so far that did not give the cyclisation product, but rather underwent a reasonably high yielding Michael addition when reacted with the NO_2-containing imine **3m** (the same conjugated addition reaction, but significantly slower, was observed with the phenyl-based **3a**).

Conclusions

The reaction between 3,3,3-trifluoropyruvate (**1**)-derived imines **3** and indandione-based Michael acceptors **6** allows for a formal (3 + 2)-cyclisation which gives access to an unprecedented class of α-CF_3-α-proline derivatives **5**. By choice of the proper phase transfer-catalysed reaction conditions (*i.e.* the used base) this reaction performs with literally complete diastereoselectivity. Unfortunately, the use of chiral ammonium salt catalysts turned out to be not satisfying so far. Other acceptors were tested as well and arylidene malonitrile **7** undergoes this type of (3 + 2)-cyclization as well, but with relatively poor diastereoselectivity, while methyl vinylketone (**9**) acted as a Michael acceptor only.

Experimental details[20]

General procedure

The arylidene indandiones **6a–k** (0.2 mmol) were dissolved in dry CH_2Cl_2 (2 mL), followed by the addition of LiOH (0.3 mmol, 7.2 mg), TEBAC (30 mol%, 0.03 mmol, 7.8 mg) and imines **3a–d** (0.1 mmol). The reaction mixture was stirred for 24 h at room temperature followed by filtration over a pad of silica and washing with Et_2O. After evaporation of the solvent, the product was purified by column chromatography with a gradient of heptanes and EtOAc (20 : 1–10 : 1–5 : 1) to yield products **5a–n** in the reported yields and diastereomeric ratios.

Analytical data for 5a (this compound was also synthesised on 1 mmol scale)

^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ 7.76–7.73 (m, 1H), 7.60–7.52 (m, 3H), 7.15–7.06 (m, 10H), 4.93–4.83 (m, 2H), 4.65 (s, 1H), 4.31–4.20 (m, 1H), 3.96–3.86 (m, 1H), 0.94 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (176 MHz, $CDCl_3$, 298 K) δ 199.4, 199.4, 166.7, 142.6, 142.1, 135.9, 135.6, 133.5, 133.5, 130.3, 128.4, 128.4, 128.2, 127.9, 126.7, 126.2 (q, J = 298 Hz), 124.1, 122.0, 122.9, 74.6 (q, J = 28 Hz), 72.1, 71.3, 63.0, 60.7, 14.2, 13.4 ppm; ^{19}F-NMR (282 MHz, $CDCl_3$, 298 K): δ = −74.22 (s, 3F) ppm; HRMS (ESI): m/z calcd for $C_{28}H_{22}F_3NO_4$ $[M + H]^+$ = 494.1574, found: 494.1580.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was generously supported by the Austrian Science Funds (FWF): Project No. P30237 (financed by the Austrian National Foundation for Research, Technology and Development and Research Department of the State of Upper Austria). 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").

Notes and references

1 V. P. Kukhar and V. A. Soloshonok, in *Fluorine Containing Amino Acids: Synthesis and Properties*, Wiley, New York, 1995.
2 (*a*) X.-L. Qiu, W.-D. Meng and F.-L. Qing, *Tetrahedron*, 2004, **60**, 6711; (*b*) X.-L. Qiu and F.-L. Qing, *Eur. J. Org. Chem.*, 2011, 3261; (*c*) R. Smits, C. D. Cadicamo, K. Burger and B. Koksch, *Chem. Soc. Rev.*, 2008, **37**, 1727; (*d*) J. L. Acena, A. Simon-Fuentes and S. Fustero, *Curr. Org. Chem.*, 2010, **14**, 928; (*e*) T. L. March, M. R. Johnston, P. J. Duggan and J. Gardiner, *Chem. Biodiversity*, 2012, **9**, 2410; (*f*) A. M. Remete, M. Nonn, S. Fustero, F. Fülöp and L. Kiss, *Tetrahedron*, 2018, **74**, 6367.
3 (*a*) N. C. Yoder and K. Jumar, *Chem. Soc. Rev.*, 2002, **31**, 335; (*b*) G. Akcay and K. Kumar, *J. Fluorine Chem.*, 2009, **130**, 1178; (*c*) M. Salwiczek, E. K. Nyakatura, U. I. M. Gerling, S. Ye and B. Koksch, *Chem. Soc. Rev.*, 2012, **41**, 2135; (*d*) E. N. G. Marsh, *Acc. Chem. Res.*, 2014, **47**, 2878; (*e*) A. A. Berger, J.-S. Völler, N. Budisa and B. Koksch, *Acc. Chem. Res.*, 2017, **50**, 2093; (*f*) S. Huhmann and B. Koksch, *Eur. J. Org. Chem.*, 2018, 3667.
4 Y. Zhou, j. Wang, Z. gu, S. Wang, W. Zhu, J. L. Acena, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422.
5 R. Smits, C. D. Cadicamo, K. Burger and B. Koksch, *Chem. Soc. Rev.*, 2008, **37**, 1727.
6 (*a*) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214; (*b*) X. Yang, T. Wu, R. J. Phipps and F. D. Toste, *Chem. Rev.*, 2015, **115**, 826.
7 For illustrative reviews on electrophilic trifluoromethylations: (*a*) S. Barata-Vallejo, B. Lantano and A. Postigo, *Chem. – Eur. J.*, 2014, **20**, 16806; (*b*) J. Charpentier, N. Früh and A. Togni, *Chem. Rev.*, 2015, **115**, 650; (*c*) T. Umemoto, in *Modern Synthesis Processes and Reactivity of Fluorinated Compounds – Progress in Fluorine Science*, ed. H. Groult, F. R. Leroux and A. Tressaud, Elsevier, 2017, pp. 265–287.
8 For selected reviews on nucleophilic trifluoromethylations: (*a*) B. R. Langlois, T. Billard and S. Roussel, *J. Fluorine Chem.*, 2005, **126**, 173; (*b*) X. Liu, C. Xu, M. Wang and Q. Liu, *Chem. Rev.*, 2015, **115**, 683.
9 X.-H. He, Y.-L. Ji, C. Peng and B. Han, *Adv. Synth. Catal.*, 2019, **361**, 1923.
10 For selected recent asymmetric examples using trifluoropyruvate: (*a*) K. Fujity and K. Mikami, *J. Fluorine Chem.*, 2019, **219**, 50; (*b*) Y. Tang, J. Xu, J. Yang, L. Lin, X. Feng and X. Liu, *Chem.*, 2018, **4**, 1658; (*c*) T. P. Le, K. Higashita, S. Tanaka, M. Yoshimura and M. Kitamura, *Org. Lett.*, 2018, **20**, 7149; (*d*) K. Aikawa, K. Yabuuchi, K. Torii and K. Mikami, *Beilstein J. Org. Chem.*, 2018, **14**, 576; (*e*) B.-B. Huang, L. Wu, R.-R. Liu, L.-L. Xing, R.-X. Liang and Y.-X. Jia, *Org. Chem. Front.*, 2018, **5**, 929.
11 For selected recent asymmetric examples using trifluoropyruvate-based imines: (*a*) M. Sawa, K. Morisaki, Y. Kondo, H. Morimoto and T. Ohshima, *Chem. – Eur. J.*, 2017, **23**, 17022; (*b*) R. Yonesaki, Y. Kondo, W. Akkad, M. Sawa, K. Morisaki, H. Morimoto and T. Ohshima, *Chem. – Eur. J.*, 2018, **24**, 15211; (*c*) M. Frias, A. C. Carrasco, A. Fraile and J. Aleman, *Chem. – Eur. J.*, 2018, **24**, 3117; (*d*) K. Morisaki, M. Sawa, R. Yonesaki, H. Morimoto, K. Mashima and T. Ohshima, *J. Am. Chem. Soc.*, 2016, **138**, 6194.
12 (*a*) Y. V. Rassukana, L. V. Bezgubenko, O. V. Stanko, E. B. Rusanov, I. B. Kulik and P. P. Onys'ko, *Tetrahedron: Asymmetry*, 2017, **28**, 555; (*b*) L. Wei, Q.-H. Li and C.-J. Wang, *J. Org. Chem.*, 2018, **83**, 11814; (*c*) A. Sanz-Vidal, J. Miro, M. Sanchez-Rosello, C. del Pozo and S. Fustero, *J. Org. Chem.*, 2016, **81**, 6515.
13 (*a*) C. Najera and J. M. Sansano, *Curr. Org. Chem.*, 2003, **7**, 1105; (*b*) I. Coldham and R. Hufton, *Chem. Rev.*, 2005, **105**,

2765; (*c*) J. Adrio and J. C. Carretero, *Chem. Commun.*, 2011, **47**, 6784; (*d*) T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2015, **115**, 5366; (*e*) A. G. Meyer and J. H. Ryan, *Molecules*, 2016, **21**, 935.

14 For selected recent examples: (*a*) M. Ma, Y. Zhu, Q. Sun, X. Li, J. Su, L. Zhao, Y. Zhao, S. Qiu, W. Yan, K. Wang and R. Wang, *Chem. Commun.*, 2015, **51**, 8789; (*b*) Q. Sun, X. Li, J. Su, L. Zhao, M. Ma, Y. Zhu, Y. Zhao, R. Zhu, W. Yan, K. Wang and R. Wang, *Adv. Synth. Catal.*, 2015, **357**, 3187; (*c*) A. Ponce, I. Alonso, J. Adrio and J. C. Carretero, *Chem. – Eur. J.*, 2016, **22**, 4952; (*d*) Z. Dong, Y. Zhu, B. Li, C. Wang, W. Yan, K. Wang and R. Wang, *J. Org. Chem.*, 2017, **82**, 3482; (*e*) Q. Liu, K. Zhao, Y. Zhi, G. Raabe and D. Enders, *Org. Chem. Front.*, 2017, **4**, 1416; (*f*) H.-Z. Gui, Y.-N. Gao, Y. Wei and M. Shi, *Chem. – Eur. J.*, 2018, **24**, 10038; (*g*) Y. You, W.-Y. Lu, Z.-H. Wang, Y.-Z. Chen, X.-Y. Xu, X.-M. Zhang and W.-C. Yuan, *Org. Lett.*, 2018, **20**, 4453; (*h*) B. Li, J. Liu, F. Gao, M. Sun, Y. Guo, Y. Zhou, D. Wen, Y. Deng, H. Chen, K. Wang and W. Yan, *Org. Biomol. Chem.*, 2019, **17**, 2892; (*i*) B. Li, F. Gao, X. Feng, M. Sun, Y. Guo, D. Wen, Y. Deng, J. Huang, K. Wang and W. Yan, *Org. Chem. Front.*, 2019, **6**, 1567.

15 For the addition of C-nucleophiles to imines **2** and subsequent α-CF_3-proline formation: (*a*) M. Eckert, S. Moulin, F. Monnier, I. D. Titanyuk, S. N. Osipov, T. Roisnel, S. Derien and P. H. Dixneuf, *Chem. – Eur. J.*, 2011, **17**, 9456; (*b*) G. Huang, Z. Yin and X. Zhang, *Chem. – Eur. J.*, 2013, **19**, 11992; (*c*) G. Chaume, M.-C. van Severen, S. Marinkovic and T. Brigaud, *Org. Lett.*, 2016, **8**, 6123.

16 For overviews on imine Umpolung: (*a*) D. Seebach and D. Enders, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 15; (*b*) J. Novacek and M. Waser, *Angew. Chem., Int. Ed.*, 2015, **54**, 14228.

17 (*a*) M. Liu, J. Li, X. Xiao, Y. Xie and Y. Shi, *Chem. Commun.*, 2013, **49**, 1404; (*b*) Y. Wu, L. Hu, Z. Li and L. Deng, *Nature*, 2015, **523**, 445; (*c*) L. Hu, Y. Wu, Z. Li and L. Deng, *J. Am. Chem. Soc.*, 2016, **138**, 15817; (*d*) P. Chen, Z. Yue, J. Zhang, X. Lv, L. Wang and J. Zhang, *Angew. Chem., Int. Ed.*, 2016, **55**, 13316; (*e*) Y.-L. Su, Y.-H. Li, Y.-G. Chen and Z.-Y. Han, *Chem. Commun.*, 2017, **53**, 1985; (*f*) Y. Yoshida, T. Mino and M. Sakamoto, *Chem. – Eur. J.*, 2017, **23**, 12749; (*g*) B. Hu and L. Deng, *Angew. Chem., Int. Ed.*, 2018, **57**, 2233; (*h*) Y. Yoshida, Y. Moriya, T. Mino and M. Sakamoto, *Adv. Synth. Catal.*, 2018, **360**, 4142.

18 (3 + 2)-cyclizations: (*a*) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao and L.-Z. Gong, *J. Am. Chem. Soc.*, 2009, **131**, 13819; (*b*) C. Guo, J. Song and L.-Z. Gong, *Org. Lett.*, 2013, **15**, 2676; (*c*) L. Tian, X.-Q. Hu, Y.-H. Li and P.-F. Xu, *Chem. Commun.*, 2013, **49**, 7213.

19 (*a*) V. A. Soloshonok and V. P. Kukhar, *Tetrahedron*, 1997, **53**, 9307; (*b*) H. Ohkura, D. O. Berbasov and V. A. Soloshonok, *Tetrahedron*, 2003, **59**, 1647.

20 Further details can be found in the online ESI.†

21 For selected recent reports describing the use of compounds **6** for (3 + 2)-cyclizations: (*a*) Y.-R. Chen, M. R. Ganapuram, K.-H. Hsieh, K.-H. Chen, P. Karanam, S. S. Vagh, Y.-C. Liou and W. Lin, *Chem. Commun.*, 2018, **54**, 12702; (*b*) J.-K. Yu, H.-W. Chien, Y.-J. Lin, P. Karanam, Y.-H. Chen and W. Lin, *Chem. Commun.*, 2018, **54**, 9921; (*c*) Y. Huang, J. Sun and C.-G. Yan, *ChemistrySelect*, 2017, **2**, 10496; (*d*) R.-G. Shi, J. Sun and C.-G. Yan, *ACS Omega*, 2017, **2**, 7820.

22 CCDC 1911986 (Cambridge Crystallographic Data Centre, https://www.ccdc.cam.ac.uk) contains the supplementary crystallographic data for **5b**.†

23 For two recent asymmetric PTC contributions by our group: (*a*) J. Novacek, J. A. Izzo, M. J. Vetticatt and M. Waser, *Chem. – Eur. J.*, 2016, **22**, 17339; (*b*) V. Capaccio, K. Zielke, A. Eitzinger, A. Massa, L. Palombi, K. Faust and M. Waser, *Org. Chem. Front.*, 2018, **5**, 3336.