

Synthesis of a Precursor to Sacubitril Using Enabling Technologies

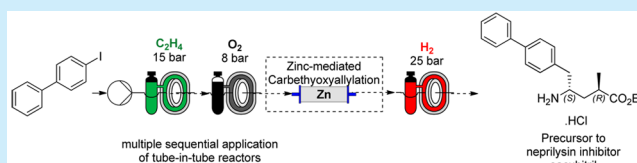
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S Supporting Information

ABSTRACT: An efficient preparation of a precursor to the neprilysin inhibitor sacubitril is described. The convergent synthesis features a diastereoselective Reformatsky-type carboxyallylation and a rhodium-catalyzed stereoselective hydrogenation for installation of the two key stereocenters. Moreover, by integrating machine-assisted methods with batch processes, this procedure allows a safe and rapid production of the key intermediates which are promptly transformed to the target molecule (3·HCl) over 7 steps in 54% overall yield.



LCZ696 (sacubitril/valsartan) is a first-in-class combination of the angiotensin II receptor-blocker valsartan and the neprilysin inhibitor sacubitril. A recent head-to-head comparison of LCZ696 with enalapril in a double-blind trial was stopped early because the boundary for an overwhelming benefit with LCZ696 was crossed.¹ As a result of this, LCZ696 was reviewed under the FDA's priority review program and was granted approval on the July 7, 2015 to reduce the risk of cardiovascular death and hospitalization for HF in patients with chronic HF (NYHA Class II–IV) and reduced ejection fraction.²

LCZ696 is a complex aggregate comprised of the anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5, respectively (Figure 1).³

Active components of LCZ696

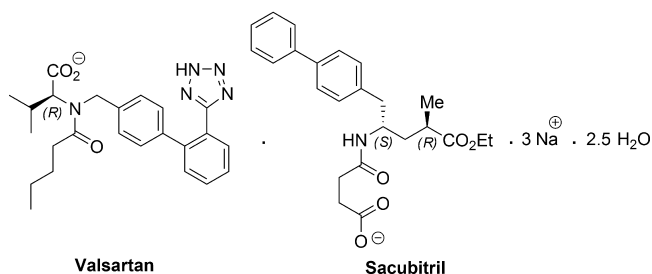
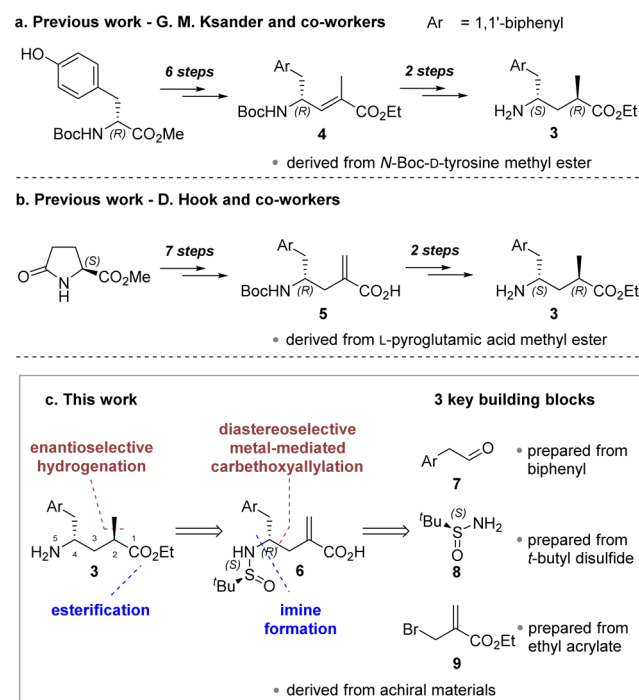


Figure 1. Valsartan (1) and sacubitril (2).

Developed by G. M. Ksander and co-workers in the early 1990s, sacubitril (2) was identified as a novel neprilysin inhibitor with promising pharmacological properties.⁴ Advanced intermediate ester 3 was prepared in eight linear synthetic steps from the unnatural *N*-Boc-D-tyrosine methyl ester. The key steps involved a Wittig reaction between biphenyl amino aldehyde and (carbethoxyethylidene)triphenylphosphorane followed by a stereoselective hydrogenation of the resulting internal double bond of acrylic ester 4 (Scheme 1a). An alternative approach, starting from *L*-pyroglutamic acid methyl ester, also employs

Scheme 1. (a and b) Previous Preparations of Intermediate Ester (3); (c) This Work



stereoselective hydrogenation of the structurally similar acrylic ester 5 (Scheme 1b).⁵

In our retrosynthetic analysis to 3 (inspired by the route via acrylic acid 5 as an intermediate), we would install the stereochemistry at the C2 carbon via a stereoselective hydrogenation of *N*-sulfinyl protected acrylic acid 6. We then

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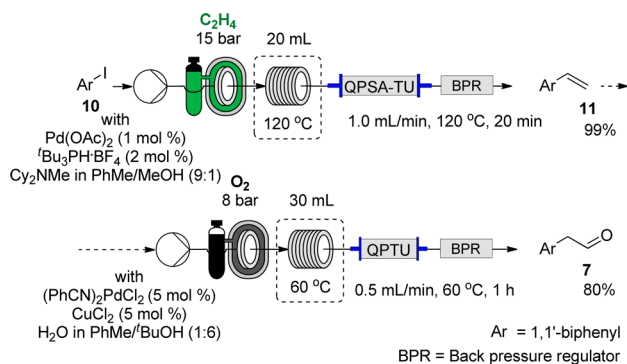
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envisaged a diastereoselective Reformatsky-type carbethoxyallylation of the imine, derived from biphenyl acetaldehyde **7** and enantiopure *tert*-butyl sulfinamide **8**, with bromide **9**. This strategy therefore afforded three key building blocks which can be prepared from inexpensive, commercially available materials (Scheme 1c).¹²

Traditional batch methods are sometimes laborious and time-consuming, whereas flow chemistry can be a solution to these problems by improving downstream processing and reaction telescoping.⁶ Over the past 15 years our laboratory has explored the benefits of using continuous flow techniques⁷ to facilitate chemical processes, for instance, in gas-flow reactors,⁸ inline analytical tools,⁹ cryogenic reactors,¹⁰ and computational software.¹¹ With the spotlight on LCZ696, we describe herein an alternative synthetic strategy for the synthesis of sacubitril precursor **3** via a machine-assisted approach.

According to our previous work on gas–liquid reactions in flow, we decided to use tube-in-tube gas reactors for the synthesis of aldehyde **7** (Scheme 2).^{13,14} An ethylene Heck coupling

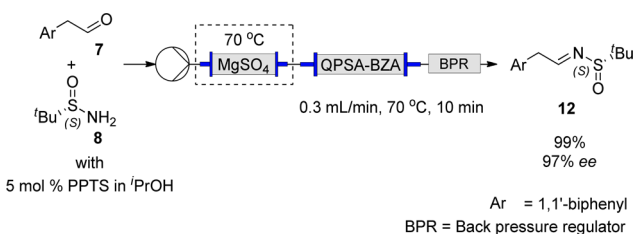
Scheme 2. Synthesis of Acetaldehyde **7**



process allowed the preparation of styrene **11** from 4-iodobiphenyl **10** in almost quantitative yield. With a simple solvent switch to PhMe/*t*BuOH (1:6), an aerobic *anti*-Markovnikov Wacker oxidation could then be employed to furnish acetaldehyde **7** in 80% yield after column chromatography with a selectivity of 86:14 for the aldehyde over the ketone in the unpurified reaction product. Waste metal and base was easily removed from the reaction stream by passage through a column of QuadraPure polymer supported sulfonic acid (QP-SA) and/or polymer supported thiourea (QP-TU).

Condensation of acetaldehyde **7** with (*S*)-*tert*-butanesulfinamide (**8**)¹⁵ to afford imine **12** was achieved by passing the reagent stream through a column of MgSO₄ at 70 °C in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) with a residence time of less than 10 min (Scheme 3). In addition, a scavenger cartridge containing QP-SA and polymer

Scheme 3. Flow Condensation of Acetaldehyde **7** and Sulfinamide **8** To Prepare Imine **12**

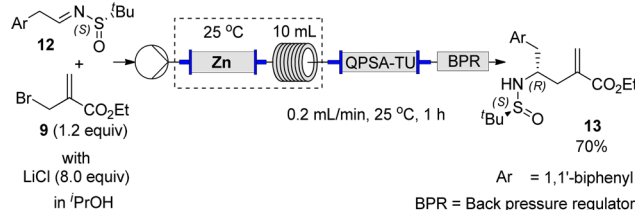


supported benzyl amine (QP-BZA) effectively removed unreacted sulfinamide **8** along with catalytic PPTS. Evaporation of the reactor output gave **12**, which could be used in the next stage without any further purification.

Next, we commenced an investigation of the zinc-mediated Reformatsky-type carbethoxyallylation reaction.¹⁶ After optimizations in batch,¹⁷ we found that addition of bromide **9** (1.2 equiv) to imine **12** in a slurry of activated zinc (4.0 equiv), potassium carbonate (0.5 equiv) and lithium chloride (4.0 equiv) in isopropanol provides acrylic ester **13** in 82% yield with excellent 99:1 dr. However, inefficient mixing of the slurry led to uncontrolled exotherms of the reaction mixture on large scale which led to increased byproduct formation and hence the reaction was not reproducible on scale. To resolve these problems we developed a flow protocol using a column of activated zinc.

At the outset of our flow investigations, we adopted the flow setup which had been previously described in the group for the generation of the reactive organozinc species.^{18,19} A reaction solution (0.2 M) containing **9** (1.2 equiv) and **12** (1.0 equiv) with LiCl (4.0 equiv) was pumped at a flow rate of 0.2 mL/min through the zinc column followed by a scavenger cartridge containing QP-SA and QP-TU. In the first attempt we obtained only a 40% yield and recovered unreacted imine **9**. However, as no bromide was recovered, it suggested that rapid organozinc formation is followed by a relatively slow carbethoxyallylation. To our delight, we were able to achieve full conversion by increasing the residence time to 1 h with the incorporation of a 10 mL reaction coil into the flow setup after the zinc column. In addition, increasing the amount of LiCl to 8 equiv further decreased impurities and improved the yield. Acrylic ester **13** was obtained in 70% yield and 99:1 dr (Scheme 4). This flow

Scheme 4. Carbethoxyallylation of Bromide **9** and Imine **12** To Afford Acrylic Ester **13**

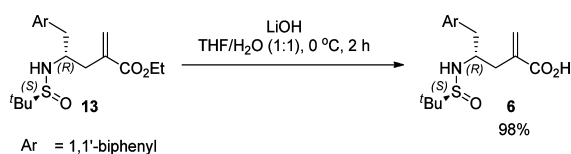


protocol offers several benefits compared to batch mode: (i) the reaction in batch mode was run as a slurry, which led to inconsistent mixing and therefore reproducibility issues, whereas yields from the flow procedure were more consistent; (ii) slow addition of the bromide **9** in batch mode was required to avoid formation of side products due to the exothermic formation of the organozinc species, whereas the use of a narrow zinc packed column in flow allowed the efficient dissipation of heat via simple air flow; and (iii) the residence time of the reaction in flow is 1 h compared to several hours, including reagent addition time, in batch.

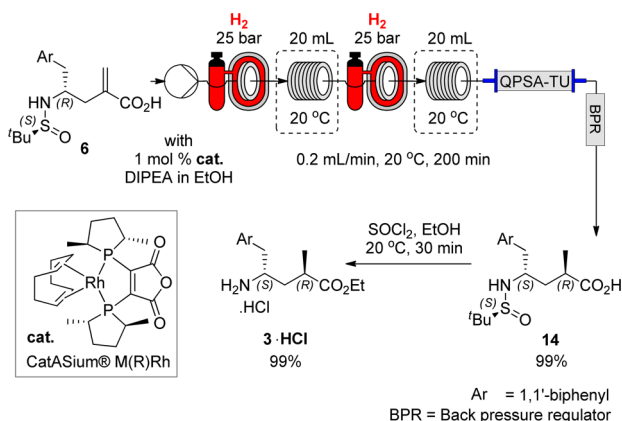
Acrylic ester **13** was then converted into acrylic acid **6** in batch using a tetrahydrofuran/water (1:1) solution of lithium hydroxide (Scheme 5).

With the use of tube-in-tube gas reactors, continuous hydrogenation can be achieved without the need for installing a costly high pressure autoclave. We then investigated the optimum conditions for the homogeneous stereoselective hydrogenation²⁰ of acrylic acid **6** in flow (Scheme 6).²¹ In the

Scheme 5. Hydrolysis of Acrylic Ester 13 To Provide Acrylic Acid 6



Scheme 6. Synthesis of Amino Ester 3·HCl Salt via Enantioselective Hydrogenation of Acrylic Acid 6



initial attempt, a 0.05 M solution of acrylic acid **6** in EtOH with 0.2 mol % catalyst was passed through a tube-in-tube reactor that was charged with 25 bar of H₂ with a residence time of 3 h. The reaction gave only a 78% conversion due to the depletion of H₂ in the reaction stream.²² We were able to solve this problem by using two sequential tube-in-tube reactors to provide a sufficient supply of H₂. Pleasingly, after optimizations with the modified system, a 0.2 M solution of acrylic acid **6** with 1 mol % catalyst produced acrylic acid **14** in 99% isolated yield and 93:7 dr (Scheme 6). It was possible to continuously process 2 g of starting material at a slightly lower concentration (0.075 M of acrylic acid **6**), producing acid **14** with a throughput of 0.45 g h⁻¹.²³ Crystallization of **14** provided diastereo- and enantiomerically pure material but for our purposes the material was of sufficient purity to carry through to the next step. The correct absolute and relative configuration of the two stereogenic centers in acid **14** was confirmed by single crystal X-ray crystallography.

The synthesis of **3** was completed with the esterification of acid **14** to the corresponding ethyl ester using thionyl chloride in ethanol and concomitant cleavage of the sulfinyl group in batch mode. After the removal of all volatiles the desired product **3**·HCl was obtained in essentially quantitative yield (99%) without further purification. The stereoisomeric purity (93:7) was confirmed by comparison to known standards by chiral HPLC analysis.

In summary, we have developed a synthesis of (2*R*,4*S*)-5-(4-biphenyl)-4-amino-2-methylpentanoic acid ethyl ester (**3**·HCl), a precursor to the neprilysin inhibitor sacubitril (**2**), prepared in 54% overall yield over 7 steps from commercially available 4-iodobiphenyl **10**. We have demonstrated that flow chemistry methodology can be used to enhance several steps in the synthesis. The development of a telescoped process of sacubitril (**2**) is currently under investigation in our laboratories.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02806.

Characterization data for all the compounds (also see <http://www.repository.cam.ac.uk/handle/1810/251223>) (PDF)

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Author Contributions

§S.-H.L. and S.L.B. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) McMurray, J. J. V.; Packer, M.; Desai, A. S.; Gong, J.; Lefkowitz, M. P.; Rizkala, A. R.; Rouleau, J. L.; Shi, V. C.; Solomon, S. D.; Swedberg, K.; Zile, M. R. *N. Engl. J. Med.* **2014**, *371*, 993–1004.
- (2) Novartis AG, Novartis' new heart failure medicine LCZ696, now called Entresto, approved by FDA to reduce risk of cardiovascular death and heart failure hospitalization, <https://www.novartis.com/news/media-releases/novartis-new-heart-failure-medicine-lcz696-now-called-entrestotm-approved-fda> (accessed Jul 29, 2015).
- (3) Packer, M.; McMurray, J. J. V.; Desai, A. S.; Gong, J.; Lefkowitz, M. P.; Rizkala, A. R.; Rouleau, J. L.; Shi, V. C.; Solomon, S. D.; Swedberg, K.; Zile, M.; Andersen, K.; Arango, J. L.; Arnold, J. M.; Bělohávek, J.; Böhm, M.; Boytsov, S.; Burgess, L. J.; Cabrera, W.; Calvo, C.; Chen, C.-H.; Dukat, A.; Duarte, Y. C.; Erglis, A.; Fu, M.; Gomez, E.; González-Medina, A.; Hagège, A. A.; Huang, J.; Katova, T.; Kiatchoosakun, S.; Kim, K.-S.; Kozan, Ö.; Llamas, E. B.; Martinez, F.; Merkely, B.; Mendoza, I.; Mosterd, A.; Negrusz-Kawecka, M.; Peuhkurinen, K.; Ramires, F. J. A.; Refsgaard, J.; Rosenthal, A.; Senni, M.; Sibulo, A. S., Jr.; Silva-Cardoso, J.; Squire, I. B.; Starling, R. C.; Teerlink, J. R.; Vanhaecke, J.; Vinereanu, D.; Wong, R. C.-C. *Circulation* **2015**, *131*, 54–61.
- (4) Ksander, G. M.; Ghai, R. D.; DeJesus, R.; Diefenbacher, C. G.; Yuan, A.; Berry, C.; Sakane, Y.; Trapani, A. *J. Med. Chem.* **1995**, *38*, 1689–1700.
- (5) Hook, D.; Riss, B.; Kaufmann, D.; Napp, M.; Bappert, E.; Polleux, P.; Medlock, J. Zanoliti-Gerosa, A. Process and intermediates for the preparation of 5-biphenyl-4-yl-2-methylpentanoic acid derivatives. World Patent, 2009,090,251 A2, Jul 23, 2009.
- (6) Selected publications on continuous flow systems: (a) Ley, S. V.; Fitzpatrick, D. E.; Ingham, R. J.; Myers, R. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 3449–3464. (b) Valera, F. E.; Quaranta, M.; Moran, A.; Blacker, J.; Armstrong, A.; Cabral, J. T.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2010**, *49*, 2478–2485. (c) Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Commun.* **2011**, *47*, 4583–4592. (d) Pastre, J. C.; Browne, D. L.; Ley, S. V. *Chem. Soc. Rev.* **2013**, *42*, 8849–8869. (e) Hessel, V.; Gursel, I. V.; Wang, Q.; Noël, T.; Lang, J. *Chem. Eng. Technol.* **2012**, *35*, 1184–1204.
- (7) For recent contributions of our group in this field see: (a) Ingham, R. J.; Battilocchio, C.; Fitzpatrick, D. E.; Sliwinski, E.; Hawkins, J. M.; Ley, S. V. *Angew. Chem., Int. Ed.* **2015**, *54*, 144–148. (b) Tran, D. N.; Battilocchio, C.; Lou, S.; Hawkins, J. M.; Ley, S. V. *Chem. Sci.* **2015**, *6*, 1120–1125. (c) Newby, J. A.; Blaylock, D. W.; Witt, P. M.; Turner, R.

- M.; Heider, P. L.; Harji, B. H.; Browne, D. L.; Ley, S. V. *Org. Process Res. Dev.* **2014**, *18*, 1221–1228. (d) Kabeshov, M. A.; Musio, B.; Murray, P. R. D.; Browne, D. L.; Ley, S. V. *Org. Lett.* **2014**, *16*, 4618–4621. (e) Newton, S.; Carter, C. F.; Pearson, C. M.; Alves, L. C.; Lange, H.; Thansandote, P.; Ley, S. V. *Angew. Chem., Int. Ed.* **2014**, *53*, 4915–4920. (f) Battilocchio, C.; Hawkins, J. M.; Ley, S. V. *Org. Lett.* **2014**, *16*, 1060–1063. (g) Lau, S.-H.; Galván, A.; Merchant, R. R.; Battilocchio, C.; Souto, J. A.; Berry, M. B.; Ley, S. V. *Org. Lett.* **2015**, *17*, 3218–3221.
- (8) (a) Cranwell, P. B.; O'Brien, M.; Browne, D. L.; Koos, P.; Polyzos, A.; Peña-López, M.; Ley, S. V. *Org. Biomol. Chem.* **2012**, *10*, 5774–5779. (b) O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2010**, *12*, 1596–1598. (c) Polyzos, A.; O'Brien, M.; Petersen, T. P.; Baxendale, I. R.; Ley, S. V. *Angew. Chem., Int. Ed.* **2011**, *50*, 1190–1193. (d) O'Brien, M.; Taylor, N.; Polyzos, A.; Baxendale, I. R.; Ley, S. V. *Chem. Sci.* **2011**, *2*, 1250–1257. (e) Petersen, T. P.; Polyzos, A.; O'Brien, M.; Ulven, T.; Baxendale, I. R.; Ley, S. V. *ChemSusChem* **2012**, *5*, 274–277. (f) Koos, P.; Gross, U.; Polyzos, A.; O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2011**, *9*, 6903–6908. (g) Browne, D. L.; O'Brien, M.; Koos, P.; Cranwell, P. B.; Polyzos, A.; Ley, S. V. *Synlett* **2012**, *23*, 1402–1406. (h) Pastre, J.; Browne, D. L.; O'Brien, M.; Ley, S. V. *Org. Process Res. Dev.* **2013**, *17*, 1183–1191. (i) Kasinathan, S.; Bourne, S. L.; Tolstoy, P.; Koos, P.; O'Brien, M.; Bates, R. W.; Baxendale, I. R.; Ley, S. V. *Synlett* **2011**, *2011*, 2648–2651. (j) Battilocchio, C.; Baxendale, I. R.; Biava, M.; Kitching, M. O.; Ley, S. V. *Org. Process Res. Dev.* **2012**, *16*, 798–810. (k) Mallia, C. J. Baxendale, I. R. The Use of Gases in flow Synthesis. *Org. Process Res. Dev.* [Online early access]. DOI: ASAP10.1021/acs.oprd.5b00222 Published Online: August 4, 2015. <http://pubs.acs.org/doi/10.1021/acs.oprd.5b00222> (accessed Oct 19, 2015).
- (9) (a) Carter, C. F.; Lange, H.; Ley, S. V.; Baxendale, I. R.; Wittkamp, B.; Goode, J. G.; Gaunt, N. L. *Org. Process Res. Dev.* **2010**, *14*, 393–404. (b) Qian, Z.; Baxendale, I. R.; Ley, S. V. *Chem. - Eur. J.* **2010**, *16*, 12342–12348. (c) Malet-Sanz, L.; Madrzak, J.; Ley, S. V.; Baxendale, I. R. *Org. Biomol. Chem.* **2010**, *8*, 5324–5332. (d) Smith, C. J.; Baxendale, I. R.; Lange, H.; Ley, S. V. *Org. Biomol. Chem.* **2011**, *9*, 1938–1947. (e) Koos, P.; Gross, U.; Polyzos, A.; O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2011**, *9*, 6903–6908. (f) Brodmann, T.; Koos, P.; Metzger, A.; Knochel, P.; Ley, S. V. *Org. Process Res. Dev.* **2012**, *16*, 1102–1113. (g) Lange, H.; Carter, C. F.; Hopkin, M. D.; Ley, S. V. *Chem. Sci.* **2011**, *2*, 765–769.
- (10) (a) Browne, D. L.; Harji, B. H.; Ley, S. V. *Chem. Eng. Technol.* **2013**, *36*, 959–967. (b) Browne, D. L.; Baumann, M.; Harji, B. H.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2011**, *13*, 3312–3315. (c) Nakayama, K.; Browne, D. L.; Baxendale, I. R.; Ley, S. V. *Synlett* **2013**, *24*, 1298.
- (11) The Ley Group, Organic Chemistry Science Gateway, <http://leysci.gateway.ch.cam.ac.uk> (accessed Jul 29, 2015).
- (12) Large-scale synthesis of chiral *tert*-butanesulfinamide from di-*tert*-butyl disulfide was previously described: (a) Weix, D. J.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1317–1320. Ethyl 2-(bromomethyl)acrylate **8** can be produced via a Baylis–Hillman reaction of ethyl acrylate and formaldehyde followed by bromination. See literature: (b) Huang, H.; Liu, X.; Deng, J.; Qiu, M.; Zheng, Z. *Org. Lett.* **2006**, *8*, 3359–3362. (c) Rousseau, A. L.; Buddoo, S. R.; Gordon, G. E. R.; Beemadu, S.; Kupi, B. G.; Lepuru, K. M.; Maumela, M. C.; Parsoo, A.; Sibiya, D. M.; Brady, D. *Org. Process Res. Dev.* **2011**, *15*, 249–257.
- (13) Bourne, S. L.; Koos, P.; O'Brien, M.; Martin, B.; Schenkel, B.; Baxendale, I. R.; Ley, S. V. *Synlett* **2011**, *2011*, 2643–2647.
- (14) Bourne, S. L.; Ley, S. V. *Adv. Synth. Catal.* **2013**, *355*, 1905–1910.
- (15) (a) Maji, M. S.; Froehlich, R.; Studer, A. *Org. Lett.* **2008**, *10*, 1847–1850. (b) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278–1284.
- (16) (a) Shen, A.; Liu, M.; Min, J.; Xu, Z.-S.; Lin, M.-H.; Lin, G.-Q. *Org. Lett.* **2010**, *12*, 5154. (b) Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979.
- (17) For further details on the optimization process, see [Supporting Information](#).
- (18) Alonso, N.; Miller, L. Z.; Muñoz, J.; de, M.; Alcázar, J.; McQuade, D. T. *Adv. Synth. Catal.* **2014**, *356*, 3737–3741.
- (19) Hafner, A.; Ley, S. V. *Synlett* **2015**, *26*, 1470–1474.
- (20) (a) Holz, J.; Zayas, O.; Jiao, H.; Baumann, W.; Spannenberg, A.; Monsees, A.; Riermeier, T. H.; Almendra, J.; Kadyrov, R.; Börner, A. *Chem. - Eur. J.* **2006**, *12*, S001–S013. (b) Almendra, J.; Monsees, A.; Kadyrov, R.; Riermeier, T. H.; Gotov, B.; Holz, J.; Börner, A. *Adv. Synth. Catal.* **2004**, *346*, 1263–1266.
- (21) For further details on the optimization process, see [Supporting Information](#).
- (22) We have previously observed this phenomenon in previous studies on tube-in-tube hydrogenation: Newton, S.; Ley, S. V.; Arce, E. C.; Grainger, D. *Adv. Synth. Catal.* **2012**, *354*, 1805–1812.
- (23) A higher concentration (0.2 M) in continuous flow resulted in 86% conversion due to dispersion.