Organic Syntheses

# Zirconium (IV) chloride catalyzed amide formation from carboxylic acid and amine: (*S*)-*tert*-butyl 2-(benzylcarbamoyl)pyrrolidine-1-carboxylate

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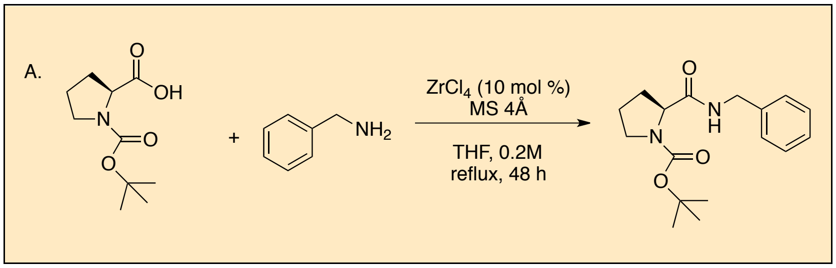
*Checked by Yuxing Wang and Huw M. L. Davies*



## Procedure

*(S)-tert-Butyl 2-(benzylcarbamoyl)pyrrolidine-1-carboxylate* (**2**). Molecular sieves (Note 1) are activated (Note 2) and 18 g are transferred to a 250-mL single-necked, round-bottomed flask equipped with a gas adaptor with stopcock. The flask is filled with argon, charged with Boc-L-proline (4.0 g, 18.6 mmol, 1.0 equiv) (Note 3), a magnetic stir bar (Note 4), and $ZrCl_4$ (0.432 g, 1.86 mmol, 0.1 equiv) (Note 5). Once the addition is complete, the adaptor is replaced with an oven-dried condenser fitted with a rubber septum, and the atmosphere is evacuated and replaced with argon (Note 6). Dry THF (93 mL) (Note 7) is added through the septum of the condenser with a syringe equipped with a long needle and the reaction mixture is then heated to reflux in an oil bath under vigorous stirring (Figure 1). At reflux, benzylamine (2.44 mL, 22.3 mmol, 1.2 equiv) (Note 8) is added over a period of five minutes into the reaction mixture through the septum using a

syringe equipped with a long needle. The rubber septum is replaced with an adaptor connected to an argon line. The mixture is refluxed for 48 h, allowed to cool to room temperature, and filtered through a pad of silica in a sintered glass filter funnel (Note 9), directly into a round-bottomed flask (250 mL) with the aid of water suction (ca. 300 mmHg). The original round-bottomed flask is washed three times with a total of 500 mL EtOAc:$Et_3N$ (200:1), which is subsequently filtered through the silica pad. The solvent is concentrated under reduced pressure (18 mmHg, 35 °C) and the resulting white solid is dissolved in 100 mL EtOAc and washed with 150 mL saturated aqueous NaCl. The aqueous layer is then extracted with EtOAc (2 x 100 mL). The organic layer is combined and dried over $MgSO_4$. The solvent is concentrated under reduced pressure, and the resulting white solid is dissolved in a minimal amount (~ 40 mL) of hot (56 °C) acetone (Note 10), and then allowed to cool to room temperature. A minimal amount (~ 35 mL) of water is added until tiny precipitates begin to appear. The flask is left to stand in a refrigerator at –4 °C for 24 h. The precipitate is collected by vacuum filtration and the filtrate is transferred to another flask. The filtered material is washed with 100 mL deionized water. A portion of the water washings (~ 50 mL) is added to the original filtrate until tiny precipitates begin to appear. The flask is left to stand in a refrigerator for 48 h at –4 °C and the resulting precipitate is collected by vacuum filtration. The combined white solid is dried on a rotary evaporator in a water bath at 65 °C, and then under vacuum (1-2 mmHg) connected to a manifold for 6 h to yield the title compound (**2**) (3.78 g, 67%) (Note 11) as a white solid (Note 12).

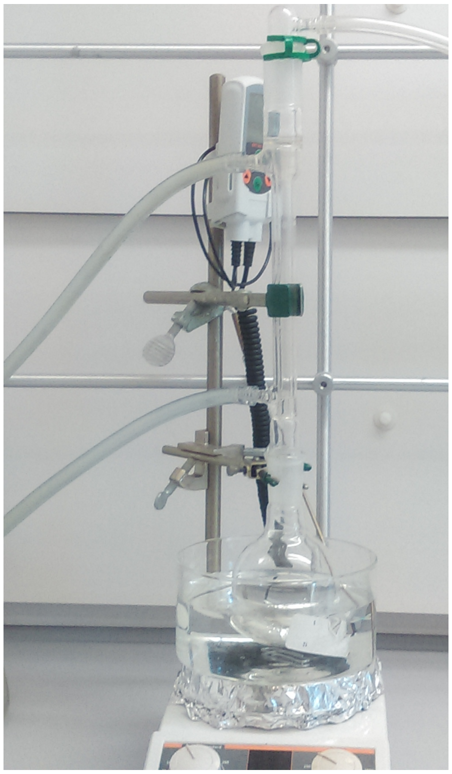


**Figure 1. Reaction Set-up**

## Notes

1. Molecular sieves (pellets, diameter 1.6 mm, pore size 4 Å) were purchased from Sigma Aldrich Co.
2. Molecular sieves (30 g) were oven dried at 140 °C for 2 days, flame-dried (Bunsen-burner) in a 250 mL round-bottomed flask fitted with a stopcock under vacuum (1-2 mmHg) for 7 min. The flask was allowed to cool to room temperature under vacuum and then filled with nitrogen.
3. Boc-L-Pro-OH 99.5% was purchased from Sigma Aldrich Co. and used as received.
4. An oven-dried, Teflon® coated, 35 x 8 mm stir bar was used.
5. Zirconium (IV) chloride ≥ 99.5% trace metals basis was purchased from Sigma Aldrich Co. and used as received. The Zirconium (IV) chloride was stored under a nitrogen atmosphere but weighed under normal atmosphere and quickly transferred to the reaction flask.
6. The atmosphere was exchanged for Ar by means of a needle in the septum, connected to a vacuum manifold. The procedure was repeated three times.
7. THF (≥ 99.9%) was purchased from Sigma Aldrich Co., dried in a Glass Contour solvent purifying system.
8. Benzylamine ≥ 98% was purchased from Sigma Aldrich Co, and was used as received.
9. The sintered glass filter funnel (45 mm h x 55 mm diameter) was filled with 24 g of silica.
10. Acetone (≥ 99.8%) was purchased from E. Merck Co. and used as received.
11. When the reaction was performed at half-scale, a yield of 69% was obtained.
12. IR (neat) 3310, 2976, 2871, 1682, 1652, 1526, 1393, 1370, 1157, 1127, 766, 724, 693 cm$^{-1}$. mp 124–125 °C. $^{1}$H NMR (600 MHz, *d-6* DMSO) Major rotamer δ: 1.28 (s, 6 H), 1.41 (s, 3 H), 1.67 – 1.90 (m, 3 H), 2.04 – 2.18 (m, 1 H), 3.25 – 3.32 (m, 1 H), 3.36 – 3.43 (m, 1 H), 4.08 (dd, *J* = 8.6, 3.1 Hz, 1 H), 4.21 (dd, *J* = 14.0, 5.9 Hz, 1 H), 4.34 (dd, *J* = 14.0, 5.9 Hz, 1 H), 7.20–7.34 (m, 5 H), 8.39 (t, *J* = 5.9 Hz, 1 H). Minor rotamer δ: 1.28 (s, 6 H), 1.41 (s, 3 H), 1.67 – 1.90 (m, 3 H), 2.04 – 2.18 (m, 1H), 3.25 – 3.32 (m, 1 H), 3.36 – 3.43 (m, 1 H), 4.12 (dd, *J* = 8.6, 3.1 Hz, 1 H), 4.19 (dd, *J* = 14.0, 5.9 Hz, 1 H), 4.34 (dd, *J* = 14.0, 5.9 Hz, 1 H), 7.20-7.34 (m, 5 H), 8.34 (t, *J* =

5.9 Hz, 1 H). $^1$H NMR (600 MHz, DMSO, 60 °C) δ: 1.29 (s, 9 H), 1.67 – 1.91 (m, 2 H), 1.99 – 2.20 (m, 1 H), 3.29 (dt, *J* = 10.5, 6.8 Hz, 1 H), 3.38 (ddd, *J* = 10.5, 7.5, 5.1 Hz, 1 H), 4.10 (s, 1 H), 4.21 (dd, *J* = 14.9, 6.0 Hz, 1 H), 4.31 (dd, *J* = 14.9, 6.0 Hz, 1 H), 7.20 (t, *J* = 6.8 Hz, 1 H), 7.23 – 7.31 (m, 4 H), 8.16 (s, 1 H). $^{13}$C NMR (150 MHz, *d-6* DMSO ) Major rotamer δ: 23.6, 28.4, 31.6, 42.5, 47.0, 60.4, 78.9, 127.8, 128.6, 140.1, 153.8, 172.9; Minor rotamer δ: 24.5, 28.66, 30.5, 42.3, 47.2, 60.3, 79.1, 127.0, 127.19, 127.3, 140.1, 154.2, 172.7. HRMS *m*/*z* calcd for $C_{17}H_{25}N_2O_3$ [M + H]$^+$: 305.1860; Found: 305.1856. Anal. calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20; Found: C, 67.02; H, 7.89; N, 9.04. Chiral HPLC AD-H column, 90:10 isohexane:2-PrOH, flow 0.7 mL/min, 30 °C, retention time 18.54 min (Retention times for racemic sample = 7.16 min and 19.93 min).

## Working with Hazardous Chemicals

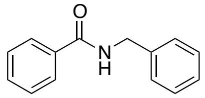
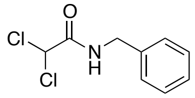
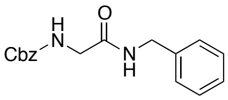
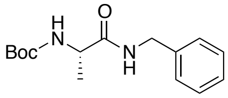
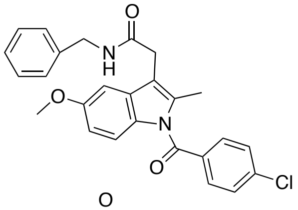
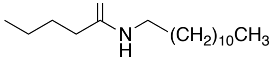
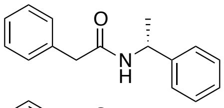
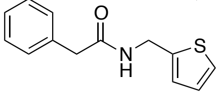
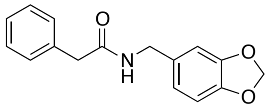
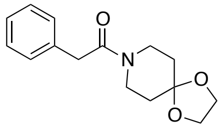
The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red “Caution Notes” within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

## Discussion

The procedure described herein is a direct amide coupling of non-activated carboxylic acids and amines catalyzed by zirconium (IV) chloride. The amide functionality is of major importance in many scientific areas, for example in material science, chemistry, and biology. Furthermore, the amide functionality is one of the most synthesized within the pharmaceutical industry, and it has been estimated that 25% of the pharmaceutical compounds available on the market contain at least one amide bond.[2] The importance of the amide bond is further emphasized by the fact that 2/3 of 128 drug candidates covered in a survey from Process Chemistry R&D departments of GlaxoSmithKline, AstraZeneca and Pfizer in 2006 made use of amide couplings.[3] The most common method for amide coupling is the reaction of an activated carboxylic acid with an amine, mainly by the use of acid chlorides, coupling reagents or mixed anhydride methods, to avoid the salt formation between the carboxylic acid and amine.[3] These methodologies all rely on stoichiometric amounts of additional reagents and equally produces one equivalent of waste along with the desired product. For this reason, catalytic amidations have been considered as greener alternatives.[4] Only a limited number of high-yielding catalytic methods are currently known which employs non-activated carboxylic acids and amines as starting material. The most well-known protocol utilizes boronic acids as catalysts, most commonly performed at high reaction temperatures.[5] In contrast, the method described herein is a mild and selective metal-catalyzed protocol, giving rise to high yields of the desired products at moderate reaction temperatures, and without racemizing chiral amino acids (Table 1). The method stems from our recent work where we have shown that early transition metal complexes such as

**Table 1. Examples of amides formed by $ZrCl_4$-catalysis from carboxylic acids and amines[a]**

| Entry | Amide | Isoated yield (%) |
|---|---|---|
| 1 |  | 85[b,c] |
| 2 |  | >99[d] |
| 3 |  | 63[b] |
| 4 |  | 62[b,c] |
| 5 |  | 97[g] |
| 6 |  | 89[d] |
| 7 |  | 65[b,c] |
| 8 |  | 93[d] |
| 9 |  | 93 |
| 10 |  | 82[b,f] |

[a]Results taken from reference 6. [b]10 mol% $ZrCl_4$. [c]Reaction temperature 100˚C. [d]5 mol% $ZrCl_4$. [e]No racemization was detected with chiral HPLC. [f]Carboxylic acid (1 mmol), amine (1.5 mmol). [g]Carboxylic acid concentration 0.2M

$ZrCl_4$ or Ti(OPr$^i$)$_4$ are excellent catalysts for a range of substrates, including the formation of both secondary and tertiary amides, as well as chiral amides.[6,7] $ZrCl_4$ was recently also shown by Williams and co-workers to catalyze the same reaction at higher reaction temperatures and higher catalyst loadings, however, without molecular sieves.[8]

This journal has previously published a reliable catalytic method for direct amidation of carboxylic acids and amines, employing 3,4,5-(trifluorophenyl)boronic acid as catalyst.[9] This particular protocol requires higher reaction temperatures and higher catalyst loading compared to the method described herein, and the boronic acid catalyst has either to be synthesized, or purchased at a price more than fifteen times higher than that of $ZrCl_4$.[10] A different protocol using boric acid as catalyst has also been published in this journal.[11] The method we present above using $ZrCl_4$ as catalyst has advantages over both protocols based on boron catalysts. The reaction conditions are significantly milder, with lower reaction temperature and no observed racemization of enantiopure starting materials. Furthermore, boric acid is considerably more toxic in comparison to the zirconium-catalyst.[12]

## References

1. Department of Organic Chemistry, Stockholm University, SE-10691 Stockholm, Sweden. hans.adolfsson@su.se This work was supported by the Swedish Research Council, and the K&A Wallenberg foundation.
2. Ghose, A.K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55–68.
3. Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.
4. See the following reviews and references therein: (a) Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, *40*, 3405–3415. (b) Roy, S.; Roy, S.; Gribble, G. W. *Tetrahedron* **2012**, *68*, 9867–9923. (c) Lundberg, H.; Tinnis, F.; Selander, N.; Adolfsson, H. *Chem. Soc. Rev.* **2014**, *43*, 2714–2742.
5. (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196–4197. (b) Maki, T.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, 8, 1431–1434. (c) Al-Zoubi, R. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 2876–2879. (d) Arnold, K.; Davies, B.; Herault, D.; Whiting, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 2673–2676.

6. Lundberg, H.; Tinnis, F.; Adolfsson, H. *Chem. Eur. J.* **2012**, *18*, 3822–3826.
7. Lundberg, H.; Tinnis, F.; Adolfsson, H. *Synlett* **2012**, *23*, 2201–2204.
8. Allen, C. L.; Chhatwal, A. R.; Williams, J. M. J. *Chem. Commun*. **2012**, *48*, 666–668.
9. K. Ishihara, S. Ohara, H. Yamamoto, *Org. Synth.* **2002**, *79*, 176–182.
10. 3,4,5-(Trifluorophenyl)boronic acid (CAS 143418-49-9) is sold from Sigma Aldrich Co. for approximately 745 Euro (July 2015) per five grams, and $ZrCl_4$ (CAS 10026-11-6) has a retail price of approximately 45 Euro for the same amount from the same company during the same period.
11. Tang, P. *Org. Synth.* **2005**, *81*, 262–272.
12. According to the EC Regulation No 1272/2008 [EU-GHS/CLP], and the EU Directives 67/548/EEC or 1999/45/EC, boric acid shows reproductive toxicity (Category 1B), may impair fertility, and may cause harm to the unborn child. Zirconium(IV) chloride has the properties of an acid and should be treated as such, however, there are no long-term biological problems reported upon exposure to the compound.

## Appendix
## Chemical Abstracts Nomenclature (Registry Number)

(Phenylthio)acetic acid: (Phenylmercapto)acetic acid, S-Phenylthioglycolic acid, Thiophenoxyacetic acid; (103-04-8)
$ZrCl_4$: Zirconium(IV) Chloride, Tetrachlorozirconium, Zirconium tetrachloride; (10026-11-6)
Benzylamine: $\alpha$-Aminotoluene; (100-46-9)
$Et_3N$: Triethylamine; (121-44-8)
Boc-L-Proline: Boc-Pro-OH, *N*-(*tert*-Butoxycarbonyl)-L-proline; (15761-39-4)

Fredrik Tinnis obtained his Ph.D. degree from Stockholm University (2014) under the supervision of Prof. Hans Adolfsson, where he focused on the development of catalytic procedures for the formation of amides. Fredrik is now a post-doctoral fellow in the same research group and is currently working on chemoselective reduction of amides.

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Helena Lundberg obtained her Ph. D. degree in June 2015 under the supervision of Professor Hans Adolfsson at the Department of Organic Chemistry, Stockholm University. She is currently pursuing research in the same research group in collaboration with Prof. Fahmi Himo, primarily focusing on the mechanistic aspects of direct catalytic amide formation using group (IV) metal complexes.

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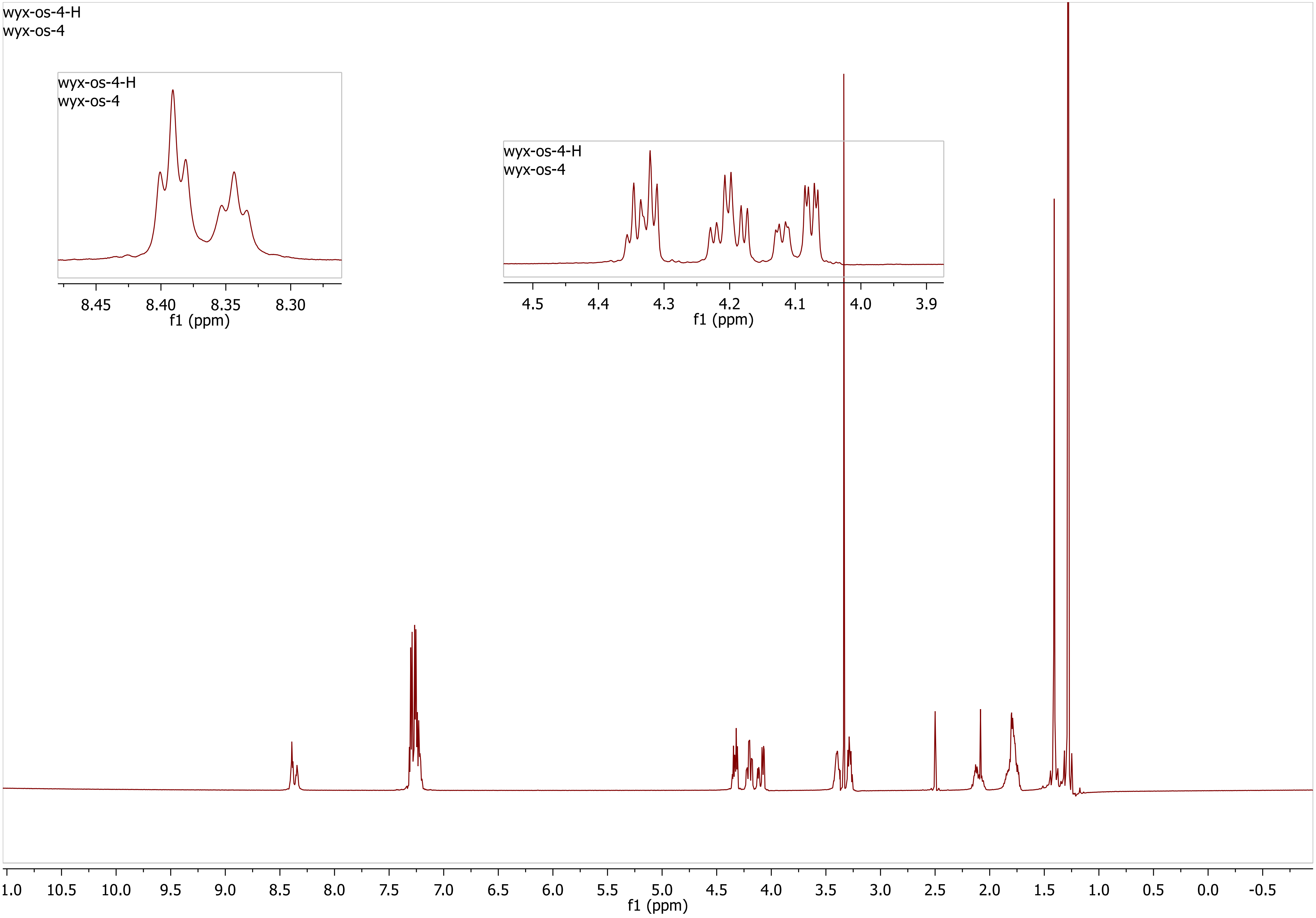
Tove Kivijärvi received her B. Sc. in Environmental Chemistry in June 2013 and her M. Sc. in Organic Chemistry in June 2015 from Stockholm University. Her graduate research under the supervision of Prof. Hans Adolfsson focused on ruthenium-catalyzed asymmetric transfer hydrogenation of sterically demanding ketones.

Hans Adolfsson, professor in organometallic chemistry since 2007, is currently the Pro Vice-Chancellor of Stockholm University. He conducted his undergraduate studies at Stockholm University and graduated in 1989. He moved to the Royal Institute of Technology (KTH) in Stockholm for Ph. D. studies under the guidance of Professor Christina Moberg. After his graduation in November 1995 he continued as a post-doctoral fellow at KTH until August 1996 when he moved to the Scripps Research Institute for a two-year post-doctoral stay with Prof. K. Barry Sharpless. In November 1998 he moved back to Sweden and started as an assistant professor at Stockholm University. In 2002 he was promoted to associate professor, and in 2007 to full professor. His research interests are in the fields of practical and selective catalysis comprising oxidations, reductions and addition reactions.

Yuxing Wang was born in Xi'an, China. He earned his B. Sc. in Chemistry in 2009 and M.Sc. in Organic Chemistry under the guidance of Professor Chanjuan Xi in 2011 from Tsinghua University. The same year he started his Ph. D. studies at Emory University under the guidance of Professor Huw M. L. Davies. His research mainly focuses on the development of transition metal-catalyzed donor-acceptor carbene reactions.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4.1
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9.0
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7.5
7.0
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5.0
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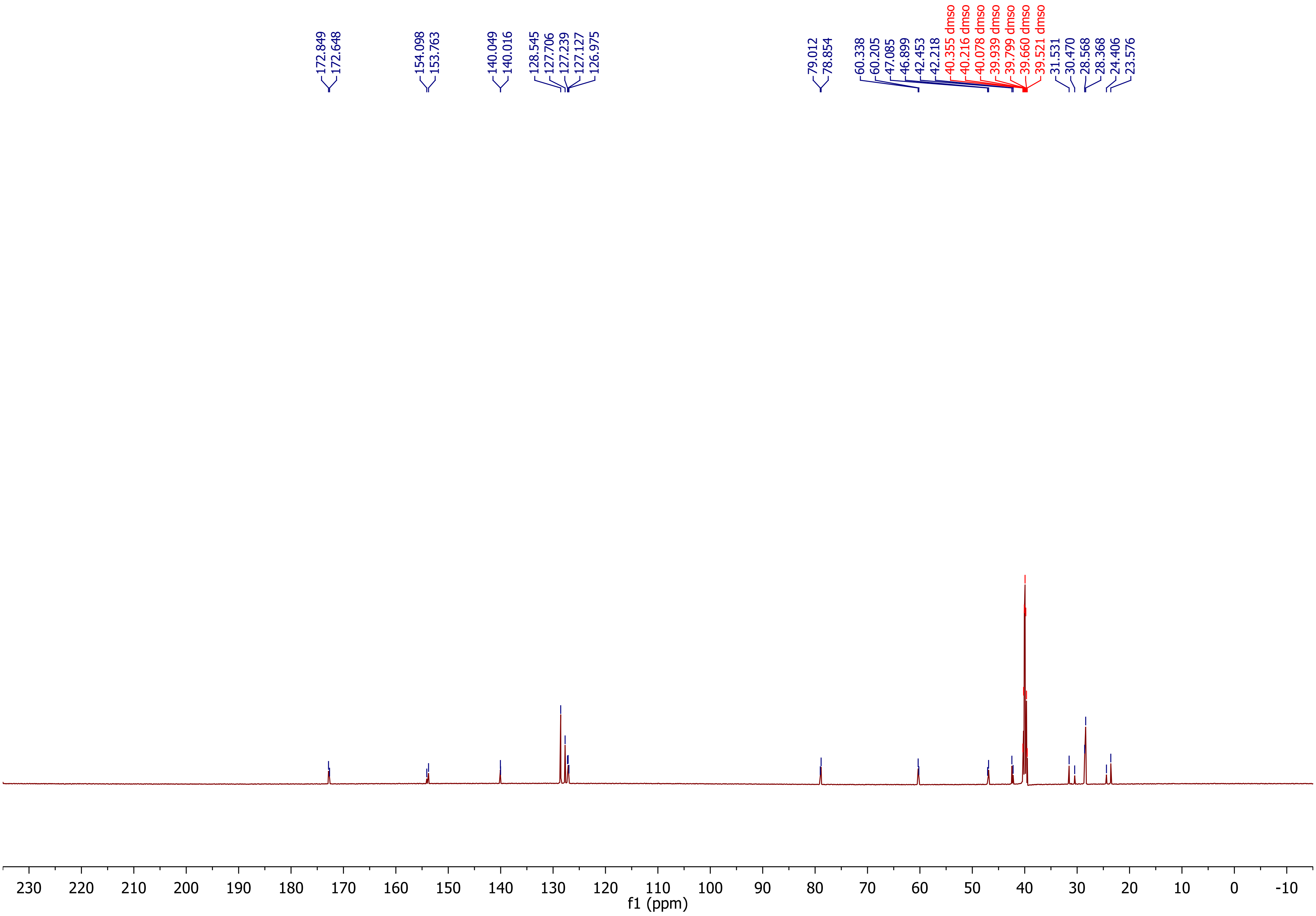
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39.939 dmso
39.799 dmso
39.660 dmso
39.521 dmso
31.531
30.470
28.568
28.368
24.406
23.576
230
220
210
200
190
180
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160
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140
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40
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20
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f1 (ppm)