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Scale-Up of Microwave-Promoted Reactions to the Multigram Level Using a Sealed-Vessel Microwave Apparatus

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Abstract:

A range of synthetic transformations have been scaled up successfully using a sealed-vessel multimode microwave unit. These include metal-catalyzed couplings, synthesis of heterocycles, reactions under an atmosphere of reactive gas and two-step one-pot procedures. Also, observations have been made along the way that are of use to chemists addressing scale-up of microwave-promoted reactions.

Introduction

Microwave heating is proving a valuable tool for synthetic chemists. It is often possible to perform reactions faster and yields can be higher.[1] To this end within industrial settings, for small-scale synthesis microwave heating is often the method of choice. It is possible to prepare a few grams of material using sealed glass tubes up to a working volume of approximately 50 mL or open round-bottom flasks to a volume of up to 125 mL. However, it is going to be necessary to address issues of scale if the technique is going to continue to gain acceptance and become practical at the process level. Possible approaches to scale-up include both batch and continuous-flow processing.[2] Recent work in our laboratory and others has been focused at exploring both possibilities.[3−5] While continuous-flow has advantages in terms of throughput and automation, issues arise when processing heterogeneous reaction mixtures.[6,7] When using a batch approach, issues of microwave penetration into the sample become important. Microwaves penetrate only a few centimetres into a reaction mixture, thus limiting the size of the vessel that can be used. However, it is possible to use batch processing to move into the multigram scale using one large vessel or parallel batch reactors.[8,9] Focusing on single-vessel operation, reactions can be performed open to the atmosphere or else in a sealed pot. Using an open reaction vessel has the advantage of operating at atmospheric pressure.[10] This means that it is possible to work in vessels up to 5 L in capacity without needing special safety precautions. However, many reactions benefit from the elevated temperatures and pressures possible in a sealed vessel. Also, much of the small-scale microwave-promoted chemistry reported in the literature has been performed using sealed vessels. Chemists often would like to be able to take conditions optimized on the small scale to a larger scale without the need for reoptimization. In a study recently undertaken in our laboratory we have probed the scalability of reactions performed in sealed vessels as well as developing scale-up approaches to key organic transformations. We have found that in many cases reactions performed on a small scale can be directly scaled without the need for reoptimization of reaction conditions. However, there are some instances where we, like others,[11] have found that modifications need to be made. In addition, sealed-vessel processing opens up avenues for

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(1) A number of books on microwave-promoted synthesis have been published recently. For examples see: (a) Loupy, A. Ed. *Microwaves in Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, 2006. (b) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, 2005. (c) Lidström, P., Tierney, J. P., Eds.; *Microwave-Assisted Organic Synthesis*; Blackwell: Oxford, 2005.

(2) For reviews see: (a) Lehmann, H. In *New Avenues to Efficient Chemical Synthesis*; Seeberger, P. H., Blume, T.,. Eds.; Springer-Verlag: Berlin, 2007. (b) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653–661.

(3) For a recent report from our laboratories see: Bowman, M. D.; Holcomb, J. L.; Kormos, C. M.; Leadbeater, N. E.; Williams, V. A. *Org. Process. Res. Dev.* **2008**, *12*, 41–57.

(4) For a recent comparison of apparatus for scale-up, see: Moseley, J. D.; Lenden, P.;.; Lockwood, M.; Ruda, K.; Sherlock, J.-P.;.; Thomson, A. D.; Gilday, J. P. *Org. Process Res. Dev.* **2008**, *12*, 30–40.

(5) For an evaluation of microwave reactors for use in a kilolab see: Lehmann, H.; LaVecchia, L. *J. Assoc. Lab. Autom.* **2005**, *10*, 412–417.

(6) For a recent review see: Kappe, C. O.; Glasnov, T. N. *Macromol. Rapid Commun.* **2007**, *28*, 395–410.

(7) For examples of continuous-flow processing see: (a) Moseley, J. D.; Lawton, S. J. *Chem. Today* **2007**, *25*, 16–19. (b) Khadilkar, B. M.; Madyar, V. R. *Org. Process Res. Dev.* **2001**, *5*, 452–455. (c) Kazba, K.; Chapados, B. R.; Gestwicki, J. E.; McGrath, J. L. *J. Org. Chem.* **2000**, *65*, 1210–1214. (d) Esveld, E.; Chemat, F. van Haveren. *J. Chem. Eng. Technol.* **2000**, *23*, 429–435. (e) Marquié, J.; Salmoria, G.; Poux, M.; Laporterie, A.; Dubac, J.; Roques, N. *Ind. Eng. Chem. Res.* **2001**, *40*, 4485–4490.

(8) For examples of batch processing using one vessel see: (a) Raner, K. D.; Strauss, C. R.; Trainor, R. W.; Thorn, J. S. *J. Org. Chem.* **1995**, *60*, 2456–2460. (b) Shackelford, S. A.; Anderson, M. B.; Christie, L. C.; Goetzen, T.; Guzman, M. C.; Hananel, M. A.; Kornreich, W. D.; Li, H.; Pathak, V. P.; Rabinovich, A. K.; Rajapakse, R. J.; Truesdale, L. K.; Tsank, S. M.; Vazir, H. N. *J. Org. Chem.* **2003**, *68*, 267–275. (c) Khadilkar, B. M.; Rebeiro, G. L. *Org. Process Res. Dev.* **2002**, *6*, 826–828. (d) Fraga-Dubreuil, J.; Famelart, M. H.; Bazureau, J. P. *Org. Process Res. Dev.* **2002**, *6*, 374–378. (e) Cleophax, J.; Liagre, M.; Loupy, A.; Petit, A. *Org. Process Res. Dev.* **2000**, *4*, 498–504. (f) Perio, B.; Dozias, M.-J.; Hamelin, J. *Org. Process Res. Dev.* **1998**, *2*, 428–430.

(9) For examples of batch processing using multiple vessels see: (a) Stadler, A.; Yousefi, B. H.; Dallinger, D.; Walla, P.; Van der Eycken, E.; Kaval, N.; Kappe, C. O. *Org. Process Res. Dev.* **2003**, *7*, 707–716. (b) Stadler, A.; Pichler, S.; Horeis, G.; Kappe, C. O. *Tetrahedron* **2002**, *58*, 3177–3183. (c) Alcázar, J.; Diels, G.; Schoentjes, B. *QSAR Comb. Sci* **2004**, *23*, 906–932.

(10) For a recent example see: Barnard, T. M.; Vanier, G.; Collins, M. J. *Org. Process Res. Dev.* **2006**, *10*, 1233–1237.

(11) For an example see: Pawluczyk, J. M.; McClain, R. T.; Denicola, C., Jr.; Rudd, D. J.; Lindsley, C. W. *Tetrahedron Lett.* **2007**, *48*, 1497–1501.

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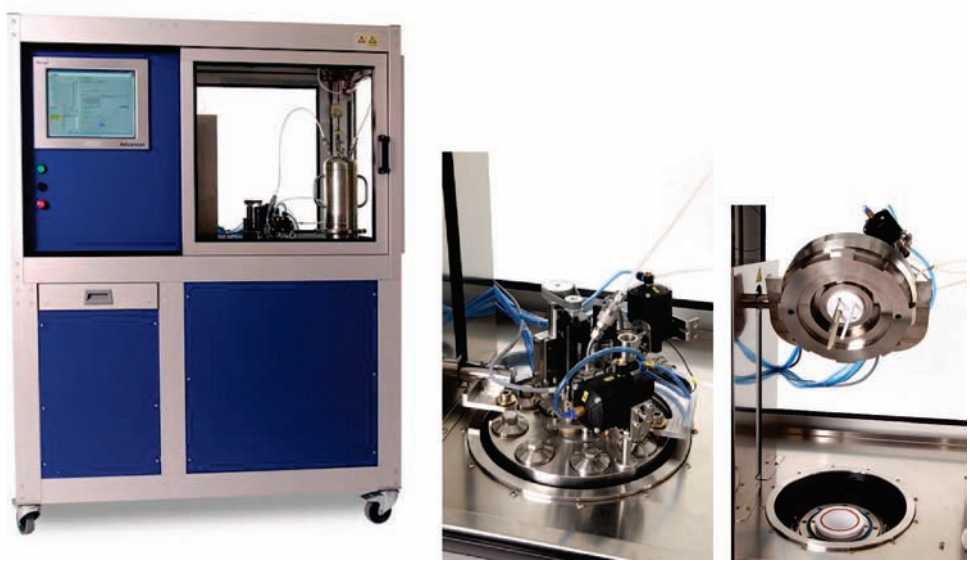


Figure 1. **Biotage Advancer.**

performing reactions under an atmosphere of reactive gas. We present our results from a representative range of reactions in this article.

Results and Discussion

Microwave Apparatus Used. For optimization of reactions on a small scale we used a monomode microwave unit (Biotage Initator). For our scale-up studies we used the Biotage Advancer (Figure 1).[4,12] Reactions are performed in a 350-mL capacity Teflon vessel, temperature being monitored using a fiber-optic probe inserted directly into the mixture by means of a glass thermowell. The unit can operate at temperatures up to 250 °C and pressures up to 20 bar. The contents of the vessel can be stirred by means of a mechanical paddle stirrer. The lid of the reactor also comprises an inlet for gas and three extra available entry/exit ports. Product mixtures can be cooled at the end of a run by using a flash cooling option, the contents of the Teflon reaction vessel being ejected into a stainless steel holding tank. Using this, the temperature of the mixture can be reduced rapidly to the boiling point of the solvent used. This is advantageous since it obviates the long cooling time inherent in other microwave units.

Suzuki−Miyaura Coupling Reaction. A reaction we have focused some considerable attention on previously is the Suzuki−Miyaura coupling.[13] We find that it is possible to perform the reaction using ppm levels of palladium salts in a water/ethanol solvent mixture. Reactions are complete within 5 min heating at 150 °C. We have scaled up the reaction using an open-vessel batch approach and found that a range of aryl bromides can be effectively coupled with phenylboronic acid, reactions taking approximately 20 min to reach completion.[14] Aryl chloride substrates are unreactive in the open-vessel approach but can be coupled using small sealed vessels using Pd/C as the catalyst, water as the solvent, and tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst.[15] The reaction requires the use of simultaneous cooling in conjunction with microwave heating to prolong the lifetime of the aryl chloride substrate in the hot basic aqueous medium. To initiate our current scale-up study using the 350-mL capacity sealed vessel in the Advancer we chose to focus on the coupling of 4-bromoanisole with phenylboronic acid (Scheme 1). We decided first to reoptimize the reaction on the 5 mmol scale with the objective of finding the minimum palladium loading that could be used. Using sodium hydroxide as base and water/ethanol as solvent we were able to obtain a 78% conversion to the desired product in 10 min at 150 °C at a homogeneous palladium catalyst concentration of 100 ppb (0.0004 mol % Pd). Workup of the reaction mixture led to a 77% isolated yield of the biaryl, thus showing that, in the Suzuki reaction, conversions and yields are almost identical. We then performed the coupling of 4-bromoanisole with phenylboronic acid on the 50 mmol scale in the Advancer. We programmed the unit to follow exactly the same heating profile as recorded for our 5 mmol studies in order to see if the conditions were directly scalable. We obtained a 90% yield of the product, the higher recovery being attributed to the larger scale of the reaction and certainly showing that the reaction was directly scalable. We then turned attention to the coupling of 4-chloroanisole with phenylboronic acid, again on the 50 mmol scale and using Pd/C as the catalyst (Scheme 1). Using the Advancer, we did not have the capability to perform the reaction using simultaneous cooling but found that this was not necessary when working on scale. We used exactly the same conditions as for our previously reported protocol (with the exception of not using cooling), thus requiring heating the reaction mixture to 120 °C and holding at this

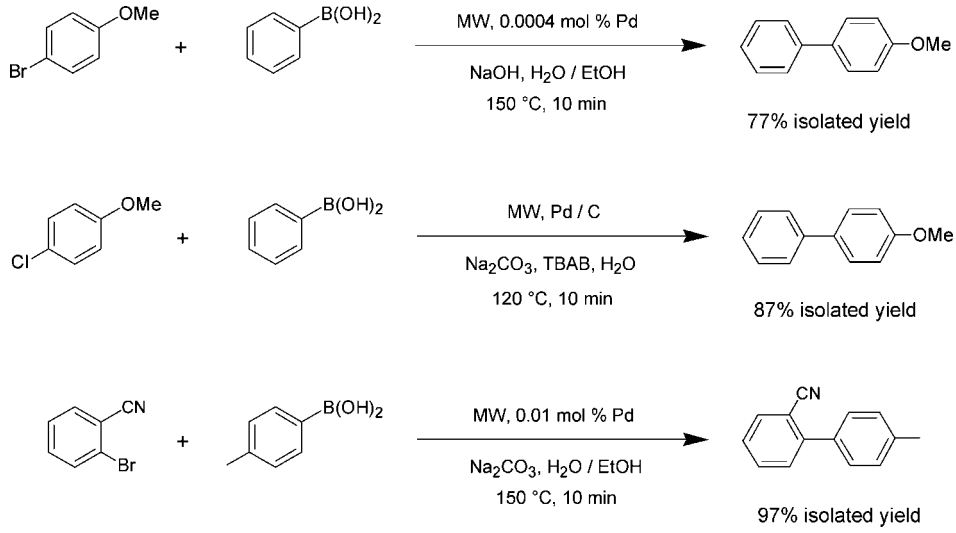
(12) For previous reports using this unit see: (a) Lehmann, F.; Pilotti, Å.; Luthman, K. *Mol. Diversity* **2003**, *7*, 145–152. (b) Ekström, J.; Wettergren, J.; Adolfsson, H. *Adv. Synth. Catal.* **2007**, *349*, 1609–1613. (c) Carlsson, A.-C.; Jam, F.; Tullberg, M.; Pilotti, Å.; Toannidis, P.; Luthman, K.; Grøtli, M. *Tetrahedron Lett.* **2006**, *47*, 5199–5201. (d) Hoogenboom, R.; Paulus, R. M.; Pilotti, Å.; Schubert, U. *Macromol. Rapid Commun.* **2006**, *27*, 1556–1560. (e) Andappan, M. M. S.; Nilsson, P.; von Schenck, H.; Larhed, M. *J. Org. Chem.* **2004**, *69*, 5212–5218.

(13) For a review of the Suzuki−Miyaura reaction using water as a solvent in conjunction with microwave heating see: Leadbeater, N. E. *Chem. Commun.* **2005**, 2881–2902.

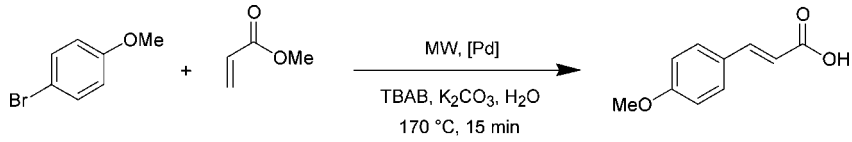
(14) Leadbeater, N. E.; Williams, V. A.; Barnard, T. M.; Collins, M. J. *Org. Process Res. Dev.* **2006**, *10*, 833–837.

(15) Arvela, R. K.; Leadbeater, N. E. *Org. Lett.* **2005**, *7*, 2101–2104.

Scheme 1. **Microwave-promoted Suzuki−Miyaura couplings on the 50 mmol scale**



Scheme 2. **Heck coupling of 4-bromoanisole with methyl acrylate**



sealed glass vessel (5 mmol), 0.002 mol% Pd: 82% isolated yield

sealed Teflon vessel (100 mmol), 0.002 mol% Pd: 93% isolated yield

sealed glass vessel (50 mmol), 0.001 mol% Pd: 82% isolated yield

sealed Teflon vessel (100 mmol), 0.001 mol% Pd: 12% isolated yield

temperature for 10 min. We obtained an 87% yield of 4-methoxybiphenyl and also recovered a small quantity (8%) of unreacted 4-chloroanisole showing that the competitive side reactions of the aryl chloride starting material were not as prevalent on the larger scale.

We completed our focus on the Suzuki−Miyaura reaction by attempting the coupling of 2-bromobenzonitrile and *p*-tolylboronic acid (Scheme 1) since this is more challenging, and also the product formed is the central motif of the hypertension drugs Atacand (Astra-Zeneca), Cozaar (Merck), and Diovan (Novartis).[16] Working on the 50 mmol scale, we performed the reaction in triplicate using sodium carbonate as the base, water/ethanol as the solvent, and a homogeneous palladium catalyst loading of 0.01 mol % and obtained an average yield of 96.6% with a standard deviation of 1.8% showing the reproducibility of the protocol.

Heck coupling. Having scaled the Suzuki−Miyaura reaction successfully, we turned our attention to the Heck coupling of 4-bromoanisole and methyl acrylate. Again we had previously developed conditions for performing the reaction using water as a solvent and low concentrations of ligandless palladium catalyst. On the 1 mmol scale, it is possible to perform the reaction in 5−20 min at 170 °C using 1−10 ppm Pd catalyst loadings; the exact conditions being dependent on the substrates used.[17] However, unlike our analogous Suzuki−Miyaura coupling procedure, the low-catalyst loading Heck coupling is not amenable to scale-up using open-vessel conditions, the elevated temperature obtained under sealed-vessel conditions being required. We have used an automated stop-flow approach to address scale-up of the reaction[18] and have also used the Advancer unit previously for scaling this to the 100 mmol level.[3] On the basis of our smaller-scale protocol, we used 1:2 stoichiometric ratio of aryl bromide (0.1 mol) to methyl acrylate (0.2 mmol), 1 equiv of tetrabutylammonium bromide as phase-transfer agent, 3.7 equiv of potassium carbonate as base, a palladium loading of 0.002 mol % and water as the solvent. We obtained a quantitative conversion to 4′-methoxycinnamic acid and an isolated yield of 93% after 15 min at 170 °C. In our current study we wanted to revisit this reaction, looking particularly at the effects of decreasing the palladium loading since we knew that the Heck coupling was particularly sensitive to changes in catalyst concentration (Scheme 2). Working on the 5 mmol scale in a sealed glass tube using the monomode microwave unit we observed no decrease in product yield when reducing the catalyst loading from 0.002 mol % to 0.001 mol %, an 82% isolated yield being obtained in each case. However,

(16) As an example, for synthetic approaches to Cozaar see: (a) Larsen, R. D.; King, A. O.; Chen, C. Y.; Corley, E. G.; Foster, B. S.; Roberts, F. E.; Yang, C.; Lieberman, D. R.; Reamer, R. A.; Tschaen, D. M.; Verhoeven, T. R.; Reider, P. J.; Young, S. L.; Rossano, L. T.; Brookes, A. S.; Meloni, D.; Moore, J. R.; Amett, J. F. *J. Org. Chem.* **1994**, *59*, 6391–6394. (b) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B., III; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermanns, P. B. M. W. M. *J. Med. Chem.* **1991**, *34*, 2525–2547.

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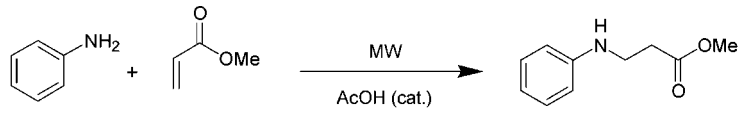
(18) Arvela, R. K.; Leadbeater, N. E.; Collins, M. J. *Tetrahedron* **2005**, *61*, 9349–9355.

Scheme 3. **Synthesis of an *N*-aryl functionalized *β*-amino ester by an aza-Michael addition reaction**



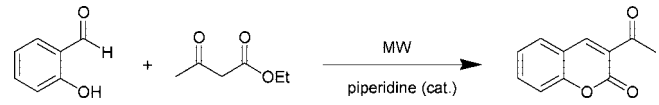
sealed vessel (13 mmol):	heat to 200 °C and hold until a total time of 20 min has elapsed - 81 % yield
eight sealed vessels (8 × 0.35 mol):	irradiate for 20 min (maximum temperature reached is 198 °C) - 78 % yield
one sealed vessel (1.5 mol; flash cooling):	heat to 200 °C and hold until a total time of 20 min has elapsed - 76 % yield

when we repeated the reaction in the Advancer at the 50 mmol scale, we observed only a 12% product conversion. We repeated the reaction a number of times to confirm that indeed it was not directly scalable. During the course of these reactions we began to notice a slight grey coloration on the walls of the previously white Teflon reaction vessel. This led us to believe that a reason for the poor conversions we obtained were due to the fact that the Teflon is slightly permeable to the reaction mixture and adsorbs small quantities of the palladium in solution. Although this is not critical when performing the reaction at higher palladium concentrations, when we were running the reaction at the lower limit of catalyst concentrations, this adsorption of small quantities of metal had the result of impeding the coupling, thus resulting in poor yields. We believe it is necessary to pay some considerable attention to catalyst loading when moving from a sealed glass vessel in a momomode microwave unit to a vessel made from Teflon or other such material such as HDPE or PEEK when the reaction is highly dependent on catalyst concentration.

Synthesis of an *N*-Aryl Functionalized *β*-Amino Ester. We have recently reported the rapid, simple, microwave-promoted synthesis of *N*-aryl functionalized *β*-amino esters using a Michael addition protocol.[19] Reactions are performed using anilines and methyl acrylate as substrates and are catalyzed by acetic acid. They are run solvent-free at 200 °C for 20 min. Significant pressure is generated during the course of the reaction due to the volatility of the methyl acrylate. The chemistry is also highly temperature dependent. Insufficient heating leads to very poor yields, and too much heating leads to side-product formation and decomposition. We believed that the flash cooling possible with the Advancer would be beneficial when scaling up the reaction since the product mixture can be brought from 200 °C down to ambient temperature rapidly, thus preventing over-reaction and formation of byproducts. The fact that we were able to monitor pressure accurately during the course of the reaction would also be beneficial. Using aniline and methyl acrylate as reagents and performing the reaction on the 1.5 mol scale, we obtained a 76% conversion to the desired *N*-aryl functionalized *β*-amino ester product (Scheme 3). This is comparable with that obtained both on the small scale and also in our previous scale-up approach using multiple sealed vessels.[3]

Synthesis of 3-Acetylcoumarin and the Use of in Situ Raman Spectroscopy To Model and Then Scale-Up a Reaction. Coumarins can be prepared using a number of synthetic routes including the Pechmann condensation (reaction of phenols with α-keto esters), Perkin reaction (aldol condensation of aromatic aldehydes and acid anhydrides), and Knoevenagel condensation (base-catalyzed reaction of an aldehyde or ketone with a dicarbonyl compound).[20] Microwave heating has been used as a tool for the synthesis of coumarins.[21] As our model reaction, we chose the reaction of salicylaldehyde with ethylacetoacetate to yield 3-acetylcoumarin since we had studied it previously using in situ reaction monitoring. By interfacing a Raman spectrometer with one of our monomode microwave units it is possible to monitor reactions in real time.[22–24] This makes reaction optimization of reaction parameters possible on the small scale. We wanted to see if we could take a reaction, optimize the reaction conditions on the 1 mmol scale, and then directly scale it. This would make for rapid workflow. Using a 1 M ethyl acetate solution of salicylaldehyde and ethyl acetoacetate and 8 mol % piperidine as a catalyst and performing the reaction at 130 °C, our qualitative in situ monitoring studies of this reaction showed that it took approximately 8 min to reach completion.[25] Using these reaction parameters we performed the reaction on the 0.3 mol scale in the Advancer. A 71% isolated yield of 3-acetylcoumarin was obtained, this being comparable with the small-scale runs.

Scheme 4. **Synthesis of 3-acetylcoumarin**



0.3 mole scale: heat to 130 °C and hold for 8 min - 71 % yield

Synthesis of Allyl Phenyl Ether. To investigate the effects of heterogeneity on product yields we turned attention to the synthesis of allyl phenyl ether using a Williamson etherification

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(22) Leadbeater, N. E.; Smith, R. J. *Org. Lett.* **2006**, *8*, 4588–4591.

(23) Leadbeater, N. E.; Smith, R. J.; Barnard, T. M. *Org. Biomol. Chem.* **2007**, *5*, 822–825.

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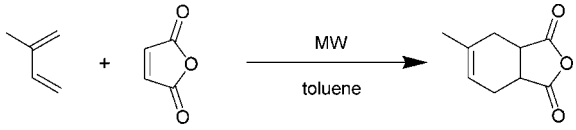
(25) Leadbeater, N. E.; Schmink, J. R. *Nat. Protoc.* **2008**, *3*, 1–7.

Scheme 5. **Synthesis of allyl phenyl ether**

0.2 mole scale: heat to 120 °C and hold for 20 min - 89 % yield

Scheme 6. **Diels−Alder reaction between isoprene and maleic anhydride**

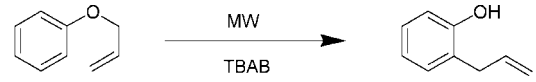


0.1 mole scale: heat to 155 °C and hold for 5 min - 92 % yield

reaction (Scheme 5).[26] We used allyl bromide and phenol as substrates, potassium carbonate as base, and acetone as the solvent. This was a case of a reaction involving a solid component (K_2CO_3), and thus effective stirring was going to be important.[27] Working on the 2 mmol scale we had already screened a series of reaction conditions for similar etherification reactions and found that using 2 equiv of potassium carbonate, heating the mixture to 120 °C, and holding at this temperature for 20 min was optimal.[28] Moving to the Advancer, we performed the etherification of phenol with allyl bromide on the 0.2 mol level and used the same reaction conditions. Efficient agitation was possible using the paddle stirrer. At the end of the reaction we tried using the flash cooling method, but due to the quantity of solid material in the mixture, it did not prove efficient due to clogging of the exit line. A similar problem was encountered previously by Pawluczyk and co-workers[11] in their preparation of supported reagents. We did however obtain a 72% isolated yield of the ether product. We repeated the reaction, reducing the quantity of potassium carbonate to 1.1 equiv and also using passive cooling which, although taking longer (10 min), allowed us to recover all of the product easily. An 89% yield of the desired product was obtained.

Diels−Alder Reaction. To test the heating capability of the Advancer and also in preparation for a later experiment we studied the Diels−Alder reaction between isoprene and maleic anhydride in toluene (Scheme 6). Microwave heating has been used in Diels−Alder reactions before.[29] In our case neither the reagents nor the solvent is particularly microwave absorbent. In addition isoprene is highly volatile (bp 34 °C). We first performed the reaction on a 5 mmol scale in the monomode microwave unit. It was possible to heat the mixture to the desired temperature of 155 °C. After 5 min at 155 °C and then cooling to room temperature, the product crystallized out of solution, and we obtained a 96% yield. We then moved to the Advancer, and performing the reaction on the 0.1 mol level using conditions identical to those of our smaller-scale experiment, we obtained a 92% yield of the desired product.

Scheme 7. **Claisen rearrangement of allyl phenyl ether**



0.44 mole scale: heat to 245 °C and hold for 30 min - 83 % conversion

Claisen Rearrangement. To test further the heating capability of the Advancer as well as working at the temperature limit of the unit we decided to study the Claisen rearrangement of the allyl phenyl ether prepared previously (Scheme 7). There is literature precedent for the use of microwave heating in Claisen rearrangements. Reactions are generally performed using a polar solvent or else on a solid support and require heating to temperatures in the range of 190−250 °C.[30] We wanted to perform the reaction solvent-free. The motivation behind this was that we knew allyl vinyl ether was not particularly microwave absorbent and would require substantial energy input to reach the elevated temperatures required to effect the rearrangement. This would therefore give us an insight into the heating capability of the unit. We initially performed the reaction using an analogous substrate (allyl *p*-tolyl ether) in a monomode microwave unit. Since the temperature ceiling of the unit used was 250 °C, we set the reaction to heat to 247 °C. The target temperature was reached, and after holding at this temperature for 15 min, product was obtained. Moving to the Advancer, we attempted to heat allyl phenyl ether to 245 °C, but the maximum temperature reached was 145 °C. Looking for a reason behind the difference in heating between the small microwave unit and the Advancer, our attention focused on the heating cross section as well as the reaction vessels used. With the monomode microwave unit, the power density is significantly higher than in the multimode Advancer. This certainly plays a role in the difference in heating characteristics. The small-scale experiment was performed in a sealed glass tube, whereas the larger run was performed using a Teflon vessel. Borosilicate glass tubes contain small quantities of salt impurities which can lead to indirect heating of nonpolar reaction mixtures. Teflon, on the other hand, does not contain such impurities. Thus, the vessel material may also have had an effect on the heating profile of the reaction mixture. In order to reach the temperature required for the Claisen rearrangement we repeated the reaction but doped the reaction mixture with tetrabutylammonium bromide (TBAB), this being a highly microwave-absorbent material. We[28] and others[31] have used a similar procedure before for heating nonpolar reaction mixtures using microwave irradiation. We performed the reaction using

(26) For other reports on microwave-promoted ether formation, see: (a) Yadav, G. D.; Desai, N. M. *Catal. Commun.* **2006**, *7*, 325–330. (b) Park, K. K.; Jeong, J. S. *Tetrahedron* **2005**, *61*, 545–553. (c) Lloung, M.; Loupy, A.; Marque, S.; Petit, A. *Heterocycles* **2004**, *63*, 297–308.

(27) For a report on the importance of agitation in microwave-promoted reactions see: Moseley, J. D.; Lenden, P.; Thomson, A. D.; Gilday, J. P. *Tetrahedron Lett.* **2007**, *48*, 6084–6087.

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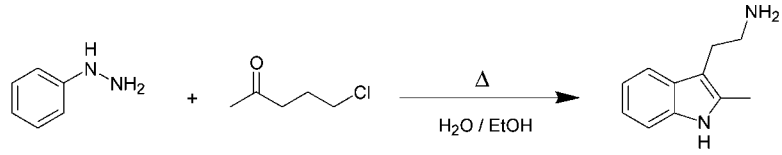
(31) (a) Ley, S. V.; Leach, A. G.; Storer, R. I. *J. Chem. Soc., Perkin Trans. 1* **2001**, 358–361. (b) Van der Eycken, E.; Appukkuttan, P.; De Borggraeve, W.; Dehaen, W.; Dallinger, D.; Kappe, C. O. *J. Org. Chem.* **2002**, *67*, 7904–7907. (c) Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2006**, *71*, 4651–4658.

Scheme 8. **Grandberg synthesis of 2-methyltryptamine**



0.2 mole scale, microwave heating: heat to 75 °C, hold for 5 min then heat to 150 °C over 15 min - 80 % yield

different quantities of TBAB and found that 11 mol % was required in order to be able to heat the reaction mixture to the target temperature of 245 °C. Holding at this temperature for 30 min allowed us to obtain an 83% conversion to the desired rearranged product. This was accompanied with a 17% decomposition of the allyl phenyl ether to phenol.

Synthesis of 2-Methyltryptamine. LBH589, a histone deacetylase (HDAC) inhibitor developed by Novartis, is currently being investigated in phase II clinical trials in cutaneous T-cell lymphoma, chronic myeloid leukemia, and multiple myeloma. HDAC inhibitors have been shown to have multiple effects in tumor cell lines: decreased oncoprotein expression, decreased angiogenesis, induction of apoptosis, induction of cell-cycle arrest, and decreased tumor cell motility and invasion.[32] Of importance to the synthesis of LBH589 is the availability of the key starting material, 2-methyltryptamine. Issues with the initial medicinal chemistry routes to 2-methyltryptamine include poor product purity or the need for expensive starting materials or reagents such as nitromethane or $LiAlH_4$ which, on a larger scale, become serious concerns. Recently a team from Novartis have reported the optimization and scale-up of the Grandberg synthesis of 2-methyltryptamine, which in essence is a modified Fisher indole synthesis (Scheme 8).[33] The chemistry starts with the formation of the hydrazone between the phenylhydrazine and the 5-chloropentan-2-one. After a proton shift and ring formation, a series of rearrangements takes place to afford a tricyclic intermediate which, after loss of a proton, yields 2-methyltryptamine. Prior to the scale-up of the reaction, the team performed a series of experiments in order to optimize the stoichiometry of the phenylhydrazine and ketone. Yields varied from 28−58% and purities from 17 to >99.9%. The stoichiometry chosen for scaling was 1:1, and working at the 20 kg level, a 47% yield was obtained and the purity was in excess of 99%. The addition of the 5-chloropentan-2-one to phenylhydrazine was highly exothermic, and during the course of the reaction (performed in refluxing ethanol) an additional exothermic response was observed. On the basis of observations from the smaller-scale runs, we saw that these exotherms, if not controlled, led to the formation of impurities that were difficult to remove. The fact that the product yield was only moderate together with the observation of exotherms during the course of the reaction attracted our interest in performing the synthesis as part of our current study. We wanted to determine whether the yield could be improved by using microwave heating while at the same time take advantage of the impressive safety features of the Advancer unit in the case of an uncontrollable exothermic incident.

We first performed the reaction on a small scale (5 mmol), using a 1:1.4 stoichiometric ratio of phenylhydrazine to chloroketone and ethanol as solvent.[34] The chloroketone was added slowly to a tube containing phenylhydrazine in ethanol as solvent. The resultant mixture was then sealed and placed into the microwave cavity and the apparatus programmed to heat it to 150 °C. However, once a temperature of 75 °C was reached, the onset of an exotherm was observed, and the heating was stopped. Reports have appeared in the literature suggesting that microwave heating can be used for initiating exothermic reactions and then the power turned off, the temperature rising over the period of a few minutes and the reaction reaching completion without the need for significant energy input.[35] In our mind, this method is highly undesirable when performing a reaction on scale. It is far better to use a slow, controlled heating protocol where the reaction is in complete control during its entirety. However, we went back and attempted the 2-methyltryptamine synthesis using just the first heating stage (i.e., heating to 75 °C then stopping). No product was obtained, showing that either elevated temperature or extended reaction time was going to be necessary. We performed the reaction a third time, heating to 75 °C and holding at this temperature for 10 min before continuing to ramp to 150 °C (using a maximum microwave power of 50 W) and holding for 15 min. Using this two-step protocol it was possible to heat the reaction mixture controllably, and upon workup we obtained an 81% isolated product yield.

The 5-chloropentan-2-one purchased for use in our studies was of technical grade (85−90%). Purification of this proved to be a lengthy process so we wanted to determine whether the material could be used as-purchased without compromising the reaction (taking into account the impurity level in stoichiometry calculations). We found this was indeed the case, and so we used the crude material in all further experiments. A similar observation was made by the Novartis team in their conventional synthetic approach.

We next scaled to the limit possible using the monomode microwave unit which was 15 mmol. The reaction was performed at a phenylhydrazine concentration of 1.25 M in ethanol. Using the same two-stage heating program we obtained

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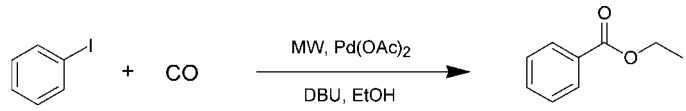
(33) Slade, J.; Parker, D.; Girgis, M.; Wu, R.; Joseph, S.; Repic, O. *Org. Process Res. Dev.* **2007**, *11*, 721–725.

(34) We deviated from the 1:1 stoichiometric ratio used by Slade and coworkers in their scale-up of the reaction since the 1:1.4 ratio was reported by them to give a higher product yield. They chose to use the 1:1 ratio for ease of product isolation in the plant.

(35) See for example: Manhas, M. S.; Ganguly, S. N.; Mukherjee, S.; Jain, A. K.; Bose, A. K. *Tetrahedron Lett.* **2006**, *47*, 2423–2425.

Scheme 9. **Alkoxycarbonylation of iodobenzene**



50 mmol scale, 1 mol% Pd, 200 psi CO: heat to 125 °C and hold for 30 min - quantitative conversion

75 mmol scale, 0.5 mol% Pd, 200 psi CO: heat to 125 °C and hold for 30 min - quantitative conversion

100 mmol scale, 0.1 mol% Pd, 250 psi CO: heat to 125 °C and hold for 30 min - >95 % conversion; 86 % isolated yield

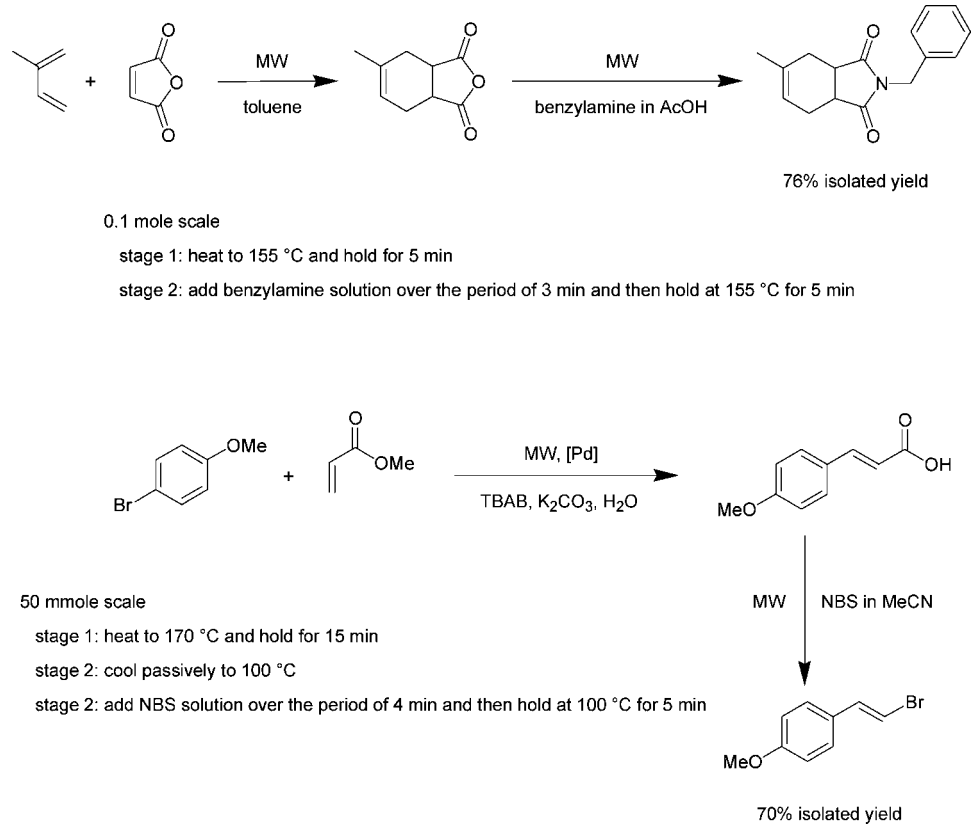
an 85% isolated product yield upon workup. With these results in hand we moved to the Advancer with the objective of performing the reaction on the 0.2 mol scale at the same phenylhydrazine concentration (1.25 M) and the same heating program as used for the small-scale experiments. In our first attempt, while the initial heating stage to 75 °C was smooth, upon initiating the second stage, we found that the heating rate was too fast, and at approximately 120 °C, we observed the onset of an exotherm. The unit is designed to sense such occurrences and released the contents of the reaction vessel into the cooling collection pot, thus quenching the reaction. We performed the reaction a second time, ramping to 75 °C as before and then very gradually increased the reaction temperature to 150 °C over the period of 15 min where it was held for a further 10 min. Using this heating protocol it was possible to heat the mixture controllably. After flash cooling and workup an 80% isolated yield of 2-methyltryptamine was obtained. This shows a rapid approach to the synthesis of this important compound. It should be noted however that we ran into some of the same issues with product purification found by the Novartis team.[33] Our product, while pure by ^{1}H NMR and TLC, was a brown oil. This is indicative of colored impurities from the ketone starting material that were carried through the synthesis and purification procedure, or else polymerization byproducts formed during the course of the reaction.

Preparation of Ethylbenzoate. We have reported the use of microwave heating in small-scale carbonylation reactions using gaseous CO as a reagent.[36−38] When transferring this chemistry from conventional to microwave heating a number of approaches have been developed to circumvent the problem of working with gaseous carbon monoxide.[39] Larhed and co-workers have used $Mo(CO)_6$ as a source of carbon monoxide in conjunction with microwave heating.[40] Advantages of using $Mo(CO)_6$ as a replacement for gaseous CO include the fact that it is a solid and is easily used on a small scale with commercially available monomode microwave apparatus with no modification required. However, $Mo(CO)_6$ is costly and toxic, and its use results in metal waste, these factors being particular problems if the reaction is to be scaled up. In a recent approach we have scaled up our alkoxycarbonylation protocol using a multimode microwave reactor equipped with eight heavy-walled quartz reaction vessels.[3] This gave us the capability to load up to eight reaction vessels and run them simultaneously by means of a reaction carousel. Using the ethoxycarbonylation of iodobenzene as a test reaction and starting with 0.1 mol of iodobenzene across the eight reaction vessels, we obtained an overall conversion of 91% and an isolated yield of 81% after chromatography. The Advancer has the capability for loading the reaction vessel with gas and has been used for performing an oxidative Heck reaction under a pressure of compressed air.[41] For the purposes of our current study we wanted to use the ethoxycarbonylation as a test for the gas-loading feature of the Advancer unit (Scheme 9). We started by performing the reaction on the 50 mmol scale using the optimized conditions from our small-scale protocol. This required using palladium acetate as catalyst and DBU (diaza(1,3)bicyclo[5.4.0]undecene) as base, heating the reaction mixture to 125 °C, and holding at this temperature for 30 min. Under these conditions and using a catalyst loading of 1 mol % and a CO loading of 200 psi (13.8 bar) we obtained a quantitative conversion of iodobenzene to ethyl benzoate. The same was true when we increased the scale to 75 mmol and at the same time decreased the palladium loading to 0.5 mol %. We next wanted to take advantage of the discovery that, on a small scale, the reaction can be run using near-stoichiometric quantities of carbon monoxide.[42] Deciding to perform the reaction on the 100 mmol scale, we calculated that an initial loading of 250 psi (17 bar) of CO would equate to 1.1 equiv. Running the reaction on this scale using a catalyst loading of 0.1 mol % resulted in >95% conversion to product and, after column chromatography, an 86% isolated yield. We could not increase the scale of the reaction any further since at the 0.1 mol level we were approaching the pressure limits of the apparatus.

Two-Step One-Pot Approaches to Synthesis. Taking advantage of the reagent addition port of the Advancer unit, we wanted to see if it was possible to perform a series of two reactions in one-pot (Scheme 10). Our objective was to perform the first reaction and then, while still at temperature, add further reagents and effect a second transformation. Building on our earlier work, we chose as our first case study the Diels−Alder reaction of isoprene and maleic anhydride followed by conversion of the anhydride product to an imide using benzylamine. Working on the 0.1 mol scale, the first step of the sequence

(36) Kormos, C. M.; Leadbeater, N. E. *Org. Biomol. Chem.* **2007**, 65–68.
(37) Kormos, C. M.; Leadbeater, N. E. *Synlett* **2006**, 1663–1666.
(38) For general reviews of palladium-mediated carbonylation chemistry see: (a) Zapf, A.; Beller, M. *Chem. Commun.* **2005**, 431–440. (b) Skoda-Földes, R.; Kollár, L. *Curr. Org. Chem.* **2002**, *6*, 1097–1119.
(39) For a general review of alternatives to CO gas, see: Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int Ed.* **2004**, *43*, 5580.
(40) For examples see: (a) Lagerlund, O.; Larhed, M. *J. Comb. Chem.* **2006**, *8*, 4–6. (b) Wu, X.; Larhed, M. *Org. Lett.* **2005**, *7*, 3327–3329. (c) Wu, X. Y.; Nilsson, P.; Larhed, M. J. *J. Org. Chem.* **2005**, *70*, 346–349. (d) Wannberg, J.; Larhed, M. *J. Org. Chem.* **2003**, *68*, 5750–5753.
(41) Lindh, J.; Enquist, P.-A.; Pilotti, A.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2007**, *72*, 7957–7962.
(42) Kormos, C. M.; Leadbeater, N. E. *Synlett* **2007**, 2006–2010.

Scheme 10. **Two-step one-pot syntheses**



(Diels−Alder reaction) we knew could be performed in 5 min at 155 °C, and so our main challenge was the introduction of benzylamine into the reaction vessel after this was complete. To achieve this, we used a gear pump which we linked to a back-pressure valve using narrow gauge Teflon tubing. This in turn was interfaced with the reagent addition port on the Advancer unit. This then allowed us to introduce the benzylamine (in acetic acid) into the reaction vessel over the period of 3 min while the microwave was still turned on. This was followed by passing nitrogen (75 psi) through the lines to flush any remaining solution into the reaction vessel. The second reagent was added slowly to avoid rapid changes in temperature and pressure inside the reaction vessel. After holding the reaction mixture at 155 °C for a further 5 min, we used flash cooling to return the mixture to room temperature. After workup the desired imide product was obtained in overall 76% yield. This showed us that it was indeed possible to perform two-step one-pot reactions using the apparatus. We decided to perform another two-step one-pot sequence and chose the synthesis of 4-methoxy-β-bromostyrene via a Heck coupling between 4-bromoanisole and methyl acrylate followed by a decarboxylative bromination. Again this builds on our previous work in the study. We knew that the optimum conditions for the Heck coupling involved using water as the solvent and heating the reaction mixture to 170 °C and holding for 15 min. The decarboxylative bromination of cinnamic acid has been the subject of previous research.[43] *N*-Bromosuccinimide (NBS) is used as the brominating agent, and the most common solvent mixture used in this reaction is acetonitrile−water, 97:3. This seemed amenable with our conditions for the Heck coupling step. We performed a series of small-scale reactions and found that the optimum temperature for the reaction was 100 °C. With this in mind, we attempted the complete reaction sequence. Working on the 50 mmol scale, the reaction vessel was loaded with the reagents, catalyst, and solvent for the Heck reaction and then sealed. After heating to 170 °C and holding at this temperature for 15 min, we allowed the mixture to cool passively to 100 °C before introducing NBS in acetonitrile over the period of 4 min using the gear pump. After holding at 100 C for a further 5 min, we used the flash cooling to bring the reaction mixture down to room temperature. After workup an isolated product yield of 70% was obtained.

Summary

In this article we have shown that a range of synthetic transformations can be scaled up successfully using the sealed-vessel multimode microwave unit and have made observations along the way that are of use to chemists addressing scale-up of microwave-promoted reactions. In most cases, reactions can be directly scaled from a small 10-mL capacity sealed glass tube to the larger 350-mL capacity Teflon reaction vessel without need for modification of reaction conditions. In the case of reactions performed using low levels of metal catalysts, a factor that needs to be taken into consideration is that Teflon is slightly permeable to reaction mixtures and adsorbs small quantities of the palladium in solution. Although not critical when performing the reaction at higher catalyst concentrations, when we were running the reaction at the lower limit, this

(43) Bazin, M.-A.; El Kihel, L.; Lancelot, J.-C.; Rault, S. *Tetrahedron Lett.* **2007**, *48*, 4347–4351.

adsorption of small quantities of metal could have the effect of impeding the desired transformation. While microwave heating can be used for scaling up many reactions, if the reaction mixture is highly nonpolar, then an additive may be required in order to heat the reaction mixture to the desired temperature efficiently. Such effects are magnified when moving from small to larger scales. In addition, borosilicate glass tubes contain small quantities of salt impurities which can lead to indirect heating of nonpolar reaction mixtures. Teflon, on the other hand, does not contain such impurities. Thus, the vessel material may also have had an effect on the heating profile of nonpolar reaction mixtures. In cases where the reaction is exothermic, careful microwave heating to the desired temperature is essential when working on larger scales. It is advisable to use multistage heating protocols to ensure smooth and controllable heating of the reaction mixture. It is possible to perform two-step one-pot reactions using the apparatus, this being achieved by addition of the second set of reagents into the reaction vessel while still at elevated temperature and pressure.

Experimental Section

(a) General Experimental. All reagents were obtained from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded at 293 K on a 300 or 400 MHz spectrometer. For reactions involving the use of low concentrations of palladium, an ICP standard was used (Aldrich) and diluted accordingly.

(b) Equipment Used. Small-scale reactions were performed in a Biotage Initiator monomode microwave unit. Larger-scale reactions were performed in a Biotage Advancer multimode microwave unit. The instrument, shown in Figure 1, consists of a continuous microwave power delivery system with power output from 0 to 1200 W. Reactions were performed in a 350-mL capacity Teflon vessel. The temperature of the contents of the vessel was monitored using a fiber-optic probe inserted directly into the reaction mixture by means of a glass thermowell. The contents of the vessel were stirred by means of a mechanical paddle stirrer. The lid of the reactor also comprises an inlet for nitrogen/air and three extra available entry ports. Pressure is monitored using a load cell. Product mixtures were cooled at the end of a run by using the flash cooling capability, the contents of the Teflon reaction vessel being ejected into a stainless steel holding tank. By using this, the temperature of the mixture is rapidly reduced to the boiling point of the solvent used.

(c) Experimental Procedures for the Reactions Performed in This Study. *Suzuki−Miyaura Coupling Reaction between 4-Bromoanisole and Phenylboronic Acid.* In a 350-mL Teflon vessel were combined 4-bromoanisole (6.26 mL, 50 mmol), phenylboronic acid (7.93 g, 65 mmol), 1.0 M sodium hydroxide (100 mL, 100 mmol), 1000 ppm Pd stock solution (20 μL, 188 μmol, 0.0004 mol %), ethanol (100 mL), and water (100 mL). The vessel was placed into the microwave and the reaction mixture heated to 150 °C using an initial microwave power of 1200 W. The contents of the vessel were then held at this temperature for 10 min, agitating using the mechanical stirrer. After cooling, the contents of the collection vessel were added into diethyl ether (400 mL) and water (400 mL), and an aqueous−organic extraction was performed. The aqueous phase was extracted with a further portion (400 mL) of diethyl ether. The organics were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 4-methoxybiphenyl as a white solid (8.30 g, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (m, 2H), 7.52, 6.97 (AA′XX′ peak, $J_{aa'} = J_{xx'} = 1.9$, $J_{ax} = 7.8$, $J_{ax'} = 0.6$ Hz, 4H), 7.40 (m, 2H), 7.28 (m, 1H), 3.84 (s, 3H).

Suzuki−Miyaura Coupling Reaction between 4-Chloroanisole and Phenylboronic Acid. In a 350-mL Teflon vessel were combined 4-chloroanisole (6.12 mL, 50 mmol), phenylboronic acid (7.93 g, 65 mmol), sodium carbonate (19.61 g, 185 mmol), tetrabutylammonium bromide (16.1 g, 50.0 mmol), Pd on carbon (10% Pd/C, 50% water by wt, 1.0 g, 1.0 mol %), and water (100 mL). The vessel was placed into the microwave and the reaction mixture heated to 120 °C using an initial microwave power of 1200 W. The contents of the vessel were then held at this temperature for 10 min, agitating using the mechanical stirrer. After cooling, the contents of the collection vessel were added into diethyl ether (400 mL) and water (400 mL) and an aqueous−organic extraction performed. The aqueous phase was extracted with a further portion (400 mL) of diethyl ether. The organics were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford a white solid. The solid was purified by silica gel chromatography (hexane, then ether) to recover 4-chloroanisole (600 mg, 4.2 mmol, 8% recovery) and 4-methoxybiphenyl (7.70 g, 84% yield).

Suzuki−Miyaura Coupling Reaction between 2-Bromobenzonitrile and p-Tolylboronic Acid. In a 350-mL Teflon vessel were combined 2-bromobenzonitrile (9.10 g, 50 mmol), *p*-tolylboronic acid (7.14 g, 52.5 mmol), sodium carbonate (15.90 g, 150 mmol), 1000 ppm Pd stock solution (500 μL, 0.01 mol %), ethanol (100 mL), and water (100 mL). The vessel was placed into the microwave and the reaction mixture heated to 140 °C using an initial microwave power of 1200 W. The contents of the vessel were then held at this temperature for 10 min, agitating with the mechanical stirrer. After cooling, the product was purified and isolated, in an identical manner to that used in the coupling of 4-bromoanisole and phenylboronic acid, to give 4′-methyl-2-biphenylcarbonitrile as a white solid (9.484 g, 98% yield).

Preparation of 4′-Methoxycinnamic Acid. A 2 ppm Pd standard stock solution was prepared by diluting a commercially available 1000 ppm Pd solution (1.0 mL) to 500 mL with deionized water. 4-Bromoanisole (12.5 mL, 100 mmol), methyl acrylate (18 mL, 200 mmol), potassium carbonate (51.2 g, 370 mmol), tetrabutylammonium bromide (32.2 g, 100 mmol), 2 ppm Pd stock solution (100 mL, 1.88 μmol, 0.002 mol %), and water (100 mL) were combined in a 350-mL Teflon vessel. The vessel was placed into the microwave and the reaction mixture heated to 170 °C using a 0.5 °C/sec ramp (this taking 5 min), agitating using the mechanical stirrer. The contents of the vessel were then held at this temperature for 15 min. After cooling, the contents of the collection vessel were added into dilute hydrochloric acid (600 mL of a 2 M solution), whereupon a white precipitate formed. The mixture was extracted twice with ethyl acetate (500 mL); the organic fractions were combined, dried over magnesium sulfate, filtered, and concen-

trated under reduced pressure. The white solid obtained was recrystallized from ethanol (70 mL) to yield 4′-methoxycinnamic acid (16.6 g, 93% yield) as colorless needles. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 7.64, 6.97 (AA′XX′ peak, $J_{aa'} = J_{xx'} = 2.5$, $J_{ax} = 8.5$, $J_{ax'} = 0.2$ Hz, 4H), 7.55 (d, $J = 15.9$ Hz, 1H), 6.38 (d, $J = 15.9$ Hz, 1H), 3.80 (s, 3H).

Preparation of Methyl N-Phenyl-3-aminopropanoate. In a 350-mL Teflon vessel were combined aniline (137 mL, 1.50 mol), methyl acrylate (135 mL, 1.50 mol),and acetic acid (8.6 mL, 0.15 mol, 10 mol %). The vessel was placed into the microwave and the reaction mixture heated to 200 °C using an initial microwave power of 1200 W. The contents of the vessel were then held at this temperature for 20 min, agitating using the mechanical stirrer. After cooling, the product was obtained in 76% conversion as determined by NMR spectroscopy. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (t, $J = 7.5$ Hz, 2H), 6.70 (t, $J = 7.3$ Hz, 1H), 6.62 (d, $J = 7.7$ Hz, 2H), 4.00 (bs, 1H), 3.70 (s, 3H), 3.46 (t, $J = 6.4$ Hz, 2H), 2.63 (t, $J = 6.4$ Hz, 2H).

Preparation of 3-Acetylcoumarin. In a 350-mL Teflon vessel were combined salicylaldehyde (32.0 mL, 0.30 mol), ethyl acetoacetate (38.5 mL, 0.31 mol), and piperidine (2.36 mL, 8 mol %). Ethyl acetate was added to make a total volume of 300 mL. The vessel was placed into the microwave and the reaction mixture heated to 130 °C using an initial microwave power of 1200 W. The contents of the vessel were then held at this temperature for 8 min, agitating using the mechanical stirrer. After cooling, the product was collected by vacuum filtration and recrystallized from ethanol to give 3-acetylcoumarin in 71% yield (40.10 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.67 (m, 2H), 7.40 (m, 2H), 2.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.4, 159.2, 155.3, 147.4, 134.4, 130.2, 125.0, 124.5, 118.2, 116.7, 30.5.

Synthesis of Allyl Phenyl Ether. In a 350-mL Teflon vessel were combined allyl bromide (24.20 g, 200.0 mmol), phenol (24.40 g, 260.0 mmol, 1.3 equiv), and K_2CO_3 (30.4 g, 220 mmol, 1.1 equiv). Reagent grade acetone (99%) was added to make a total volume of 250 mL. The vessel was placed into the microwave and the reaction mixture heated to 120 °C using an initial microwave power of 1200 W, agitating using the mechanical stirrer. The contents of the vessel were then held at this temperature for 20 min. After this time, the mixture was allowed to cool passively to 60 °C, at which point the reaction chamber was opened. The contents were poured into a separatory funnel containing cold water. The aqueous phase was extracted three times with diethyl ether (100 mL). The organic extracts were combined, washed sequentially with 2.0 M NaOH (25 mL), H_2O (50 mL), and saturated NaCl (50 mL). The organics were dried over $MgSO_4$, and the diethyl ether was removed under reduced pressure until a constant weight was observed to afford allyl phenyl ether (23.86 g, 89%) as an amber-colored oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 2H, $J = 7.5$ Hz), δ 6.95 (m, 3H, $J = 7.0$ Hz), δ 6.12 (m, 1H, $J = 5.7$ Hz), δ 5.45 (d, 1H, $J = 15.8$ Hz), δ 5.31 (d, 1H, $J = 10.5$ Hz), δ 4.59 (2H, d, 5.6 Hz).

Diels−Alder Reaction between Isoprene and Maleic Anhydride. In a 350-mL Teflon vessel were combined isoprene (20.0 mL, 200 mmol), maleic anhydride (9.8 g, 100 mmol), and toluene (100 mL). The vessel was placed into the microwave and the reaction mixture heated to 155 °C using an initial microwave power of 1200 W. The contents of the vessel were then held at this temperature for 5 min, agitating using the mechanical stirrer. After cooling, the solution was concentrated under reduced pressure. Hexane (50 mL) was added to initiate crystallization. The white crystals were filtered and washed with hexane (50 mL) to afford the Diels−Alder adduct 3a,4,7,7a-tetrahydro-5-methylisobenzofuran-1,3-dione (15.3 g, 92% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.62 (m, 1H), 3.39 (ddd, $J = 10.0$, 7.2, 3.1 Hz, 1H), 3.32 (ddd, $J = 9.8$, 7.2, 2.3 Hz, 1H), 2.57 (ddd, $J = 15.8$, 6.1, 2.3 Hz, 1H), 2.49 (dd, $J = 15.8$, 2.6 Hz, 1H), 2.26 (m, 2H), 1.8 (bs, 3H).

Claisen Rearrangement. In a 350-mL Teflon vessel were combined allyl phenyl ether (60 mL, 0.437 mol) and tetrabutylammonium bromide (16.12 g, 50 mmol, 11.4 mol %). The vessel was placed into the microwave and the reaction mixture heated to 245 °C using an initial microwave power of 1200 W. The contents of the vessel were then held at this temperature for 30 min, agitating using the mechanical stirrer. After cooling, NMR spectroscopy showed an 83% conversion to 3-(2-hydroxyphenyl)-1-propene. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.1 (m, 2H), 6.9 (m, 2H), 6.0 (m, 1H), 5.2 (dd, 1H), 5.1 (d, 1H), 3.5 (d, 2H).

Synthesis of 2-Methyltryptamine. In a 350-mL Teflon vessel were combined ethanol (150 mL) and phenylhydrazine (19.78 g, 0.183 mol, 18 mL). To this, 5-chloro-2-pentanone (39.63 g, 37.5 mL of the 85% pure reagent, 0.280 mol) was slowly added with continuous agitation. The vessel was placed into the microwave and the reaction mixture heated to 75 °C over a period of 2 min. The temperature was then slowly raised manually to 150 °C over the period of 15 min where it was held for a further 10 min, agitating using the mechanical stirrer. After cooling, the product mixture was transferred to a round-bottom flask and concentrated to half the volume. This concentrate was placed into a separatory funnel, and water (400 mL) added. The solution was washed three times with ethyl acetate (150 mL) to remove any unreacted chloroketone. Saturated sodium carbonate (50 mL) was added to the aqueous solution. This was again washed three times with ethyl acetate (150 mL). This removed any unreacted phenylhydrazine. Sodium hydroxide (2 M, 200 mL) was then added to the aqueous and the solution extracted three times with ethyl acetate (150 mL). The organic layer was washed with water (150 mL) and brine solution (150 mL). The organic layers were combined and dried over $MgSO_4$, and the diethyl ether was removed under reduced pressure to give 2-methyltryptamine (brown oil, 23.9 g) in 76% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (bs, 1H), 1.1 (bs, 2H), 7.40 (d, 1H), 7.21 (d, 1H), 7.04 (m, 2H), 2.93 (m, 2H), 2.30 (s, 3H), 1.1 (s, 2H).

Ethoxycarbonylation of Iodobenzene. Palladium acetate (22.2 mg, 0.10 mmol) and ethanol (100 mL) were combined in a 350-mL Teflon vessel and stirred. DBU (15.23 g, 100.0 mmol), iodobenzene (20.41 g, 100.0 mmol), and ethanol (80 mL) were combined and then added to the vessel. The vessel was closed and sealed. The toggle valve was opened, the vessel charged with 250 psi carbon monoxide (110 mmol), and then the toggle valve was closed. The mixture was prestirred for 60 s using the mechanical stirrer and then was heated on a slow ramp of

0.5 °C/s to 125 °C and held at this temperature for 30 min. After cooling, water (150 mL) was added and the mixture extracted with diethyl ether/petroleum ether (1:1, 3 × 150 mL). The combined organics were washed with 2 M HCl (2 × 50 mL) and dried over magnesium sulfate, and the solvent was removed under reduced pressure until a constant weight was observed. Silica gel (100 g) chromatography using petroleum ether to elute the remaining iodobenzene followed by ethyl acetate/petroleum ether (90:10) yielded ethyl benzoate (12.88 g, 86% yield) as a clear colorless oil.

Two-Step One-Pot Synthesis of N-Benzyl 3a,4,7,7a-Tetrahydro-5-methylisobenzopyrrole-1,3-dione. In a 350-mL Teflon vessel were combined isoprene (20.0 mL, 200 mmol), maleic anhydride (9.8 g, 100 mmol), and toluene (100 mL). The vessel was placed into the microwave and the reaction mixture heated to 155 °C using an initial microwave power of 1200 W. The contents of the vessel were then held at this temperature for 5 min, agitating using the mechanical stirrer. Upon completion of this heating stage, benzyl amine (20 mL, 183 mL) dissolved in glacial acetic acid (80 mL) was added to the reaction vessel over the period of 3 min using a gear pump while maintaining the temperature at 155 °C. Nitrogen gas (75 psi) was then used to flush any remaining reagent solution from the lines into the reaction flask. The temperature of the reaction mixture was maintained at 155 °C for an additional 5 min before cooling. The solution was washed with 0.2 M HCl (200 mL) and then twice with sat. sodium bicarbonate (200 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the product as a white solid (19.5 g, 76% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (m, 5H), 5.48 (bs, 1H), 4.62, 4.61 (AB peak, J = 14.5 Hz, 2H), 3.08 (td, J = 8.0, 2.4 Hz, 1H), 3.04 (td, J = 8.0, 2.3 Hz, 1H), 2.55 (ddd, J = 15.4, 7.0, 2.2 Hz, 1H), 2.46 (dd, J = 15.4, 2.2 Hz, 1H), 2.19 (m, 2H), 1.64 (bs, 3H).

Two-Step One-Pot Synthesis of trans-4′-Methoxy-β-bromostyrene. A 2 ppm Pd standard stock solution was prepared by diluting a commercially available 1000 ppm Pd solution (1.0 mL) to 500 mL with deionized water. 4-Bromoanisole (12.5 mL, 100 mmol), methyl acrylate (18 mL, 200 mmol), potassium carbonate (51.2 g, 370 mmol), tetrabutylammonium bromide (32.2 g, 100 mmol), 2 ppm Pd stock solution (100 mL, 1.88 μmol, 0.002 mol %), and water (100 mL) were combined in a 350-mL Teflon vessel. The vessel was placed into the microwave and the reaction mixture heated to 170 °C using a 0.5 °C/s ramp (this taking 5 min), agitating using the mechanical stirrer. The contents of the vessel were then held at this temperature for 15 min. The reaction mixture was allowed to cool to 100 °C passively, this taking 8 min. A solution of *N*-bromosuccinimide (10.7 g, 60 mmol) in acetonitrile (150 mL) was added to the vessel over 4 min, using a gear pump while maintaining the mixture at 100 °C. Nitrogen gas (55 psi) was used to flush the remaining solution from the lines into the reaction flask. The temperature of the reaction mixture was maintained at 100 °C for an additional 5 min before cooling. The contents of the collection vessel were added into dilute hydrochloric acid (600 mL of a 2 M solution), whereupon a white precipitate formed. The mixture was extracted twice with ethyl acetate (500 mL), the organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The white solid obtained was recrystallized from ethanol (70 mL) to yield 4′-methoxy-β-bromostyrene (16.6 g, 93% yield) as colorless needles. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 7.64, 6.97 (AA′XX′ peak, $J_{aa'} = J_{xx'}$ = 2.5, J_{ax} = 8.5, $J_{ax'}$ = 0.2 Hz, 4H), 7.55 (d, J = 15.9 Hz, 1H), 6.38 (d, J = 15.9 Hz, 1H), 3.80 (s, 3H).

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