JOC Note

pubs.acs.org/joc

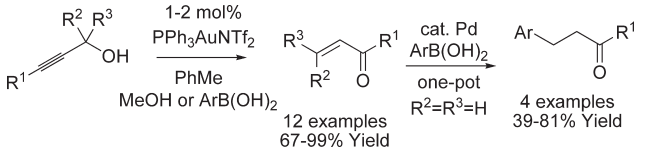
A General Procedure for the Synthesis of Enones via Gold-Catalyzed Meyer−Schuster Rearrangement of Propargylic Alcohols at Room Temperature

Matthew N. Pennell,[†] Matthew G. Unthank,[‡] Peter Turner,[‡] and Tom D. Sheppard*,[†]

[†]*Department of Chemistry, University College London, Christopher Ingold Laboratories, 20, Gordon Street, London WC1H 0AJ, U.K., and* [‡]*GlaxoSmithKline R & D Limited, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts, SG1 2NY, U.K.*

tom.sheppard@ucl.ac.uk

Received November 18, 2010

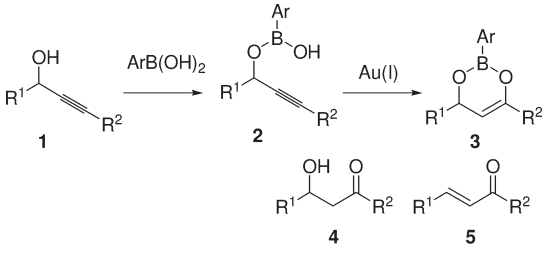


Meyer−Schuster rearrangements of propargylic alcohols take place readily at room temperature in toluene with 1−2 mol % PPh_3AuNTf_2, in the presence of 0.2 equiv of 4-methoxyphenylboronic acid or 1 equiv of methanol. Good to excellent yields of enones can be obtained from secondary and tertiary alcohols, with high selectivity for the *E*-alkene in most cases. A one-pot procedure for the conversion of primary propargylic alcohols into β-arylketones was also developed, via Meyer-Schuster rearrangement followed by Pd-catalayzed addition of a boronic acid.

The synthesis of α,β-unsaturated carbonyl compounds is traditionally achieved via aldol condensation or via a Wittig, Horner−Wadsworth−Emmons or Petersen olefination reaction.[1] A potentially useful alternative strategy is the addition of a metalated alkyne to an aldehyde or ketone, followed by a Meyer−Schuster rearrangement[2,3] of the resulting propargylic alcohol. The classical Meyer−Schuster rearrangement[3] involves heating the alcohol with strong acid which is incompatible with many functional groups. More recently, milder conditions for this reaction have been developed using Au(I) catalysis.[4] The first reports required conversion of the alcohol to the corresponding acetate,[5] but more recently procedures have been developed for the direct rearrangement of the alcohols themselves.[6−10]

During the course of an ongoing research project on the gold-catalyzed generation of boron enolates from alkynes,[11] we explored the reaction of propargylic alcohols with boronic acids in the presence of the commercially available gold catalyst, PPh_3AuNTf_2.[12] We had envisioned that rapid condensation of the alcohol **1** with the boronic acid would lead to an intermediate **2**, which would form the boron enolate **3** after Au(I)-catalyzed cyclization (Scheme 1). We hoped to be able to trap the enolate **3** with an aldehyde but the only products observed were the β-hydroxyketone **4** and the enone **5**. Previous literature reports of gold-catalyzed rearrangements of this type require prolonged heating in methanol,[6] the addition of additives which can hinder purification,[7] or moderately high catalyst loadings and/or noncommercial catalysts.[8,9] In some cases, the procedures are limited to highly activated alkynyl ethers.[9] We therefore reasoned that our boronic acid mediated approach might provide a superior method, especially as it employed a simple and readily available catalyst and appeared to take place rapidly at room temperature.

SCHEME 1. Proposed Gold-Catalyzed Boron Enolate Formation from a Propargylic Alcohol



Propargylic alcohol **6a** was used as a test substrate to optimize the reaction conditions (Scheme 2 and Table 1). A brief examination of solvents (entries 1−5) indicated that

(1) (a) Wittig, G.; Schollkopf, U. *Chem. Ber.* **1954**, *87*, 1318–1330. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927. (c) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780–784. (d) Horner, L.; Hoffmann, H. M. R.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61–63. (e) Wadsworth, W. S., Jr; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738.

(2) For recent reviews, see: (a) Cadierno, V.; Crochet, P.; Garcia-Garrido, S. E.; Gimeno, J. *Dalton Trans.* **2010**, *39*, 4015–4031. (b) Engel, D. A.; Dudley, G. B. *Org. Biomol. Chem.* **2009**, *7*, 4149–4158.

(3) Meyer, K. H.; Schuster, K. *Chem. Ber.* **1922**, *55*, 819–823.

(4) For recent reviews on gold catalysis, see: (a) Shapiro, N. D.; Toste, F. D. *Synlett* **2010**, 675–691. (b) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232–5241. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (d) Muzart, J. *Tetrahedron* **2008**, *64*, 5815–5849. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378. (f) Li, Z; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265. (g) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325. (h) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (i) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449.

(5) (a) Marion, N.; Nolan, S. P *Angew. Chem., Int. Ed.* **2007**, *46*, 2750–2752. (b) Garayalde, D.; Gómez-Bengoa, E.; Huang, X.; Goeke, A.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 4720–4730. (c) Marion, N.; Carlqvist, P.; Gealageas, R.; de Frémont, P.; Maseras, F.; Nolan, S. P. *Chem.—Eur. J.* **2007**, *13*, 6437–6451. (d) Zanoni, G.; D'Alfonso, A.; Porta, A.; Feliciani, L.; Nolan, S. P.; Vidari, G. *Tetrahedron* **2010**, *66*, 7472–7478. (e) Wang, D.; Ye, X.; Shi, X. *Org. lett.* **2010**, *12*, 2088–2091. (f) Hopkinson, M. N.; Giuffredi, G. T.; Gee, A. D.; Gouverneur, V. *Synlett* **2010**, 2737–2742. (g) Nun, P.; Gaillard, S.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Commun* **2010**, *46*, 9113–9115. (h) de Haro, T.; Nevado, C. *Chem. Commun.* **2010**, *46*, 248–249. (i) Wang, Y.; Biao, L.; Zhang, L. *Chem. Commun.* **2010**, *47*, 9179–9181.

(6) Ramón, R. S.; Marion, N.; Nolan, S. P. *Tetrahedron* **2009**, *65*, 1767–1773.

(7) (a) Egi, M.; Yamaguchi, Y.; Fujiwara, N.; Akai, S. *Org. Lett.* **2008**, *10*, 1867–1870. (b) Ye, Y.; Zhang, L. *Org. Lett.* **2009**, *11*, 3646–3649.

DOI: 10.1021/jo102263t Published on Web 01/25/2011

SCHEME 2. Optimization of the Gold-Catalyzed Meyer–Schuster Rearrangement

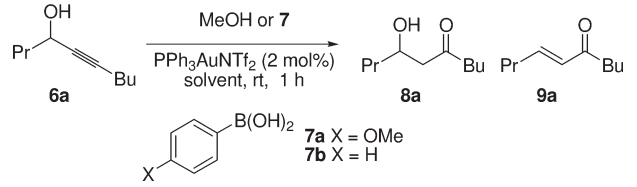


TABLE 1. Optimization of the Gold-Catalyzed Meyer–Schuster Rearrangement in the Presence of Hydroxyl-Containing Additives

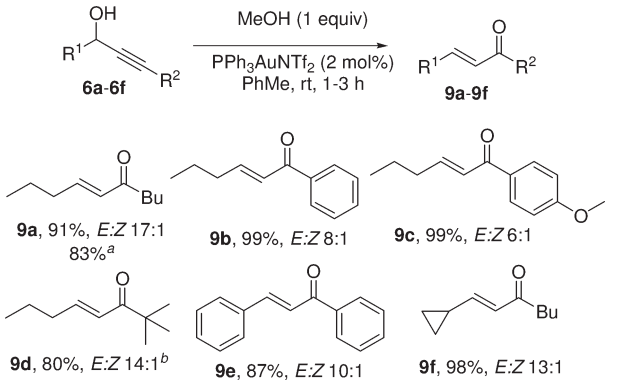
entry	solvent	additive	conversion	**9a**:**8a**	*E*:*Z*
1	CH_2Cl_2	0.1 equiv **7a**	43%	1.2:1	10.5:1
2	MeOH	0.1 equiv **7a**	58%	4.3:1	> 30:1
3	THF	0.1 equiv **7a**	46%	1.6:1	27:1
4	Acetone	0.1 equiv **7a**	28%	3.0:1	20:1
5	PhMe	0.1 equiv **7a**	76%	1.8:1	20:1
6	PhMe	0.2 equiv **7a**	99%	2.0:1	27:1
7	PhMe	1 equiv **7a**	99%	1.8:1	> 30:1
8	PhMe	0.2 equiv **7b**	54%	1.8:1	7.8:1
9	PhMe	-	64%	1.1:1	5.6:1
10	MeOH	-	43%	> 36:1	5.1:1
11	PhMe	0.1 equiv MeOH	98%	2.6:1	5.1:1
12	PhMe	1 equiv MeOH	100%	**9a** only	17:1

more polar solvents were unsuitable and that toluene was optimal, giving a much higher conversion. Increasing the quantity of boronic acid **7a** to 0.2 equiv led to higher conversion and gave the enone **9a** with a higher *E*:*Z* selectivity (entry 6). However, there was no real benefit in using a stoichiometric quantity of **7a** (entry 7). Phenylboronic acid **7b** was much less effective (entry 8).[13]

In the absence of boronic acid, a lower conversion was observed, suggesting that the boronic acid accelerates the rearrangement reaction (entry 9). Curiously, the use of methanol as solvent, either in the presence (entry 2) or absence of **7a** (entry 10), suppressed the formation of β-hydroxyketone **8a**, with **9a** being obtained as the sole product in the latter case. This led us to examine the use of small quantities of methanol as an additive (Entries 11 and 12). Pleasingly, the use of 1 equiv of methanol, with toluene as the solvent, led to clean rearrangement of **6a** to **9a** with excellent conversion and very high selectivity in favor of the *E* isomer (entry 12).

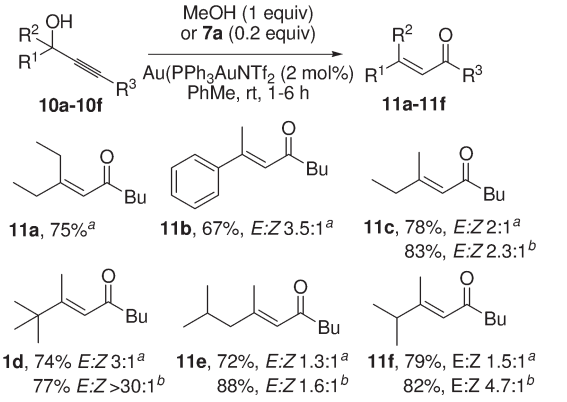
Under the optimized reaction conditions, a number of secondary propargylic alcohols underwent Meyer–Schuster rearrangement to give the corresponding *E*-enones in good to excellent yield and with high *E*:*Z* selectivity (Scheme 3).

SCHEME 3. Gold-Catalyzed Meyer–Schuster Rearrangement of Secondary Propargylic Alcohols



[a]Reaction performed on a 1 g scale with 1 mol % Au catalyst. [b]Sixteen hours reaction time.

SCHEME 4. Gold-Catalyzed Meyer–Schuster Rearrangement of Tertiary Propargylic Alcohols



[a]With 1 equiv MeOH. [b]With 0.2 equiv **7a**.

In combination with the straightforward addition of an alkynyl anion to an aldehyde, this reaction offers a convenient alternative to the Horner–Wadsworth–Emmons olefination or the Wittig reaction of a ketone-stabilized ylide,[1] and avoids the generation of phosphorus waste products. The rearrangement of alcohol **6a** was also performed on a 1 g scale to give the enone **9a** in 83% yield using only 1 mol % Au catalyst.

Tertiary propargylic alcohols also underwent rearrangement in the presence of 1 equiv of methanol to give the corresponding β,β-disubstituted enones (Scheme 4). Higher yields and greater *E*:*Z* selectivities were obtained in the presence of catalytic quantities of boronic acid **7a**, though longer reaction times were required. This method provides access to highly substituted enones in good to excellent yield, and with moderate to excellent *E*:*Z* selectivity. Notably, the sterically crowded enone **11d** was obtained in good yield and

(8) (a) Ramón, R. S.; Gaillard, S.; Slawin, A. M. Z.; Porta, A.; D'Alfonso, A.; Zanoni, G.; Nolan, S. P. *Organometallics* **2010**, *29*, 3665–3668. (b) Lee, S. I.; Baek, J. Y.; Sim, S. H.; Chung, Y. K. *Synthesis* **2007**, 2107–2114. (c) Georgy, M.; Boucard, V.; Debleds, O.; Dal Zotto, C.; Campagne, J.-M. *Tetrahedron* **2009**, *65*, 1758–1766.

(9) (a) Engel, D. A.; Lopez, S. S.; Dudley, G. B. *Tetrahedron* **2008**, *64*, 6988–6996. (b) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027–4029. (c) Lopez, S. S.; Engel, D. A.; Dudley, G. B. *Synlett* **2007**, 949–953.

(10) For examples of other metal catalysts for the Meyer–Schuster rearrangement, see: (a) Tanaka, K.; Shoji, T.; Hirano, M. *Eur. J. Org. Chem.* **2007**, 2687–2699. (b) Stefanoni, M.; Luparia, M.; Porta, A.; Zanoni, G.; Vidari, G. *Chem. – Eur. J.* **2009**, *15*, 3940–3944. (c) Cadierno, V.; Francos, J.; Gimeno, J. *Tetrahedron Lett.* **2009**, *50*, 4773–4776.

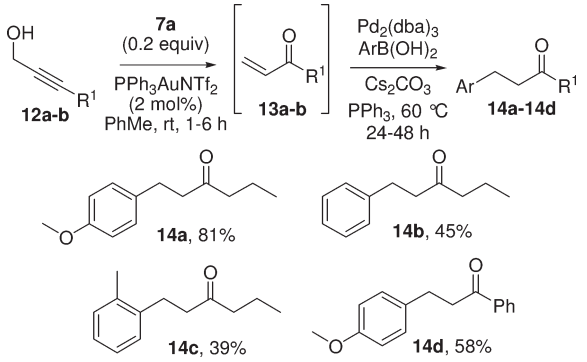
(11) Körner, C. K.; Starkov, P.; Sheppard, T. D. *J. Am. Chem. Soc.* **2010**, *132*, 5968–5969.

(12) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133–4136.

(13) We have observed that commercially available samples of phenylboronic acid often contain large quantities of the trimeric boroxine and this may account for its poor reactivity in this reaction.

(14) (a) Castelani, P.; Comasseto, J. V. *Tetrahedron* **2005**, *61*, 2319–2326. (b) Sparling, B. A.; Moslin, R. M.; Jamison, T. F. *Org. Lett.* **2008**, *10*, 1291–1294. (c) Bunnelle, W. H.; Rafferty, M. A.; Hodges, S. L. *J. Org. Chem.* **1987**, *52*, 1603–1605. See also ref 7a for a synthesis of this compound via a gold-catalyzed Meyer–Schuster rearrangement that proceeds with much lower *E*:*Z* selectivity.

SCHEME 5. One-Pot Meyer−Schuster Rearrangement and Boronic Acid Addition Reactions of Primary Propargylic Alcohols



with excellent selectivity for the *E*-isomer.[14] Even the enone **11c** in which the two alkyl groups are very similar in size was obtained with moderate *E*:*Z* selectivity. These highly hindered enones would be very difficult to access via traditional olefination chemistry.

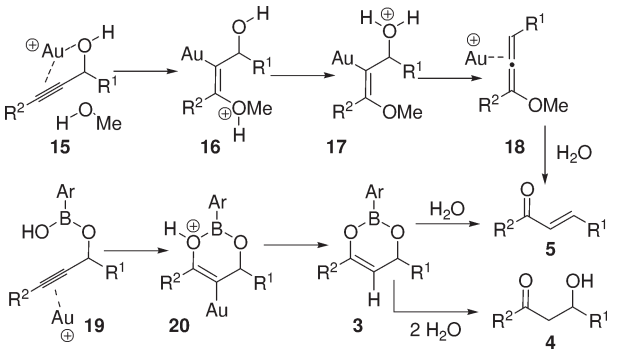
Meyer−Schuster rearrangement of primary propargylic alcohols leads to the formation of highly reactive unsubstituted enones and, even in the presence of the small quantities of methanol used in our reactions, conjugate addition of methanol to the enone was observed.[15] However, in the presence of the boronic-acid additive **7a**, clean rearrangement to the unsubstituted enones could be achieved (Scheme 5). These enone systems are difficult to handle, so we therefore sought to develop practical one-pot procedures for their generation and reaction *in situ*. As an example, gold/boronic acid catalyzed rearrangement could readily be combined with Pd-catalyzed addition of the boronic acid to the enone **13**[16] to give access to β-arylketones **14a**−**14d** in moderate to good yields. The lower yield of **14b** can be attributed to the fact that boronic acid **7b** is less effective in the rearrangement step and this is also likely to be the case for the hindered boronic acid used in the preparation of **14c**.[13]

In the presence of alcohols, the Meyer−Schuster rearrangement has been proposed to proceed via the formation of an allenyl ether (Scheme 6).[2,7−9] This can be generated by addition of methanol (**16**) to the activated alkyne (**15**), followed by proton transfer (**17**) and elimination of water to give the allenyl ether **18**.[5] This then undergoes hydrolysis, possibly via further activation by the gold catalyst, to give the enone **5**. The formation of the enone in the boronic-acid mediated reaction could also proceed via a similar pathway. However, the β-hydroxyketone **4** is also obtained from these reactions and one plausible explanation is that **4** and **5** are produced via a common intermediate such as **3**. This intermediate **3** could be generated via initial formation of the boronate half ester **19**, followed by cyclization (**20**) and protodeauration. The β-hydroxyketone **4** could then be produced via direct hydrolysis of this intermediate and the enone **5** via a concerted (potentially Au-catalyzed) rearrangement. It seems reasonable to assume that the cyclic nature

(15) The addition of methanol to unsubstituted enones during Au(I)-catalyzed Meyer−Schuster rearrangements has been previously observed, see ref 6.

(16) Yamamoto, T.; Iizuka, M.; Takenaka, H.; Ohta, T.; Ito, Y. *J. Organomet. Chem.* **2009**, *694*, 1325–1332.

SCHEME 6. Possible Mechanisms for the Gold-Catalyzed Meyer−Schuster Rearrangement



of the vinyl gold intermediate **20** might help to prevent elimination to form an allenyl boranate analogous to **18**. The possibility that enone **5** may result from boronic acid assisted addition of adventitious water to the alkyne cannot be excluded at this stage however. We have observed that an isolated sample of β-hydroxyketone **8a** was not converted to enone **9a** (and vice versa) under the reaction conditions, so the two products must be produced via divergent reaction pathways, possibly from an intermediate such as **3**. However, we are still not certain exactly what role the protic nucleophile (MeOH or **7a**) plays in the reaction. Further work is underway to obtain a detailed understanding of the mechanism of these rearrangement reactions and to determine the precise role of these additives.

In summary, we have developed convenient and general protocols for gold-catalyzed room temperature Meyer−Schuster rearrangement of secondary and tertiary propargylic alcohols in the presence of small quantities of methanol or 4-methoxyphenylboronic acid. Coupled with the straightforward addition of metalated alkynes to carbonyl compounds, this provides a convenient enone synthesis that is competitive with traditional phosphorus-mediated olefination approaches and proceeds in good to excellent overall yield. Highly reactive terminal enones can also be generated from primary propargylic alcohols, and used directly in one-pot transformations to give β-arylketones via Pd-catalyzed addition of a boronic acid to the resulting enone.

Experimental Section

Dec-6-en-5-one 9a[5c]**.** $[Ph_3PAuNTf_2]_2PhMe$ (8 mg, 1 mol %) and MeOH (0.02 mL, 0.53 mmol) were added to a solution of Dec-5-yn-4-ol **6a** (95 mg, 0.53 mmol) in toluene (0.5 mL) and the solution was stirred at room temperature until the starting material had disappeared (TLC). The solvent was removed *in vacuo* and the crude product was purified by column chromatography to afford Dec-6-en-5-one **9a** as a pale yellow oil: (77 mg, 91%); ν_{max} (film/cm^{-1}) 2933, 2873 (C−H), 1712 (C=O); δ_H (500 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.5), 0.93 (3H, t, *J* 7.4), 1.29−1.37 (2H, sx, *J* 7.5), 1.45−1.53 (2H, sx, J 7.4), 1.55−1.61 (2H, qn, *J* 7.5), 2.16−2.20 (2H, qd, *J* 7.4, 1.4), 2.52 (2H, t, *J* 7.5), 6.08 (1H, dt, *J* 15.8, 1.4), 7.09 (1H, dt, *J* 15.8, 7.0); δ_C (500 MHz, $CDCl_3$) 13.8, 14.0, 21.5, 22.5, 26.4, 34.3, 39.8, 130.7, 147.1, 201.1.

3-Ethyl-non-3-en-5-one 11a. $[Ph_3PAuNTf_2]_2PhMe$ (10 mg, 1 mol %) and MeOH (0.03 mL, 0.65 mmol) or 4-methoxyboronic acid **7a** (21 mg, 0.13 mmol) were added to a solution of 3-ethyl-non-4-yn-3-ol **10a** (100 mg, 0.65 mmol) in toluene (0.5 mL) and

the solution was stirred at room temperature until the starting material had disappeared (TLC). The solvent was removed *in vacuo* and the crude product was purified by column chromatography to afford 3-ethyl-non-3-en-5-one **11a** (75 mg, 75%); ν_{max} (film/cm^{-1}) 2962, 2934, 2875 (C−H), 1686 (C=O); δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.4), 1.03 (3H, t, *J* 7.5), 1.05 (3H, t, *J* 7.5), 1.27−1.34 (2H, sx, *J* 7.4), 1.52−1.57 (2H, qn, *J* 7.5), 2.12−2.17 (2H, qd, *J* 7.4, 1.3), 2.40 (2H, t, *J* 7.4), 2.54 (2H, qd, *J* 7.5, 1.3), 5.97 (1H, s); δ_C (500 MHz, $CDCl_3$) 12.2, 13.1, 14.0, 22.5, 25.9, 26.6, 31.1, 44.3, 121.2, 165.5, 201.4; Found (EI): [M] 168.15087, $C_{11}H_{20}O$ requires 168.15043.

1-(4-Methoxyphenyl)-hexan-3-one 14a[17]**.** $[Ph_3PAuNTf_2]_2PhMe$ (16 mg, 1 mol %) and 4-methoxyphenylboronic acid **7a** (33 mg, 0.20 mmol) were added to a solution of 2-hexyn-1-ol **12a** (100 mg, 1.02 mmol) in toluene (2 mL) under argon and the solution was stirred at room temperature until the starting material had disappeared (TLC). The reaction was then charged with $Pd_2(dba)_3 \cdot CHCl_3$ (27 mg, 2.5 mol %), PPh_3(13 mg, 5 mol %), 4-methoxyphenylboronic acid **7a** (297 mg 1.84 mmol), and cesium carbonate (332 mg 1.02 mmol). The resulting solution was stirred at 60 °C for 24 h. After cooling to room temperature, the reaction was quenched with sat. $NaHCO_3$ solution (5 mL). The organic layer was then extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by column chromatography (ethyl acetate-petrol 1:30) to give **14a** as a colorless oil (170 mg, 81%); ν_{max} (film/cm^{-1}) 2960, 2835 (C−H), 1710 (C=O), 1511 (Ar-OMe); δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.4), 1.58 (2H, sx, *J* 7.4), 2.35 (2H, t, *J* 7.4), 2.68 (2H, t, *J* 7.6), 2.83 (2H, t, *J* 7.6), 3.77 (3H, s), 6.81 (2H, d, *J* 8.5) 7.09 (2H, d, *J* 8.5); δ_C (500 MHz, $CDCl_3$) 13.8, 17.3, 29.1, 44.4, 44.7, 55.4, 114.3, 129.5, 133.4, 158.0, 210.5; Found (EI): [M] 206.13054, $C_{13}H_{18}O_2$ requires 206.13012.

(17) Berthiol, F.; Doucet, H.; Santelli, M. *Appl. Organomet. Chem.* **2006**, *20*, 855–868.

Acknowledgment. We would like to thank the EPSRC (EP/E052789/1: Advanced Research Fellowship to T.D.S., and EP/G040680/1: Organic Synthesis Studentship to M.N.P.), and GlaxoSmithKline for supporting this work.

Supporting Information Available: Experimental procedures, spectral data and copies of ^1H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.