Synthesis M. Seki, Y. Takahashi Paper

Convergent Synthesis of Angiotensin II Receptor Blockers through C–H Arylation of 1-Benzyl-5-phenyl-1*H*-tetrazole with Functionalized Aryl Bromides

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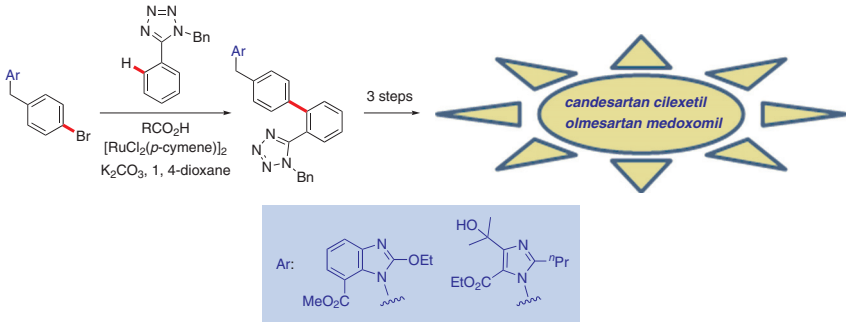

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Abstract Highly convergent synthesis of angiotensin II receptor blockers has been accomplished by means of late-stage C–H arylation using functionalized aryl bromides. C–H arylation of 1-benzyl-5-phenyl-1*H*-tetrazole with aryl bromides carrying methyl 2-ethoxybenzimidazole-7-carboxylate unexpectedly provided coupling products where ethyl group was migrated from oxygen to nitrogen atom. The O-to-N ethyl migration was completely suppressed by the use of *N*-pivaloyl-L-valine rather than the combined use of triphenylphosphine and sodium mesitylenesulfonate to result in the preferential formation of a key intermediate of candesartan cilexetil. In contrast, when an aryl bromide having ethyl 4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate was employed, the C–H arylation proceeded smoothly to provide a late-stage intermediate, which rapidly led to olmesartan medoxomil in 3 steps.

Key words tetrazole, ruthenium, hypertensive drugs

Angiotensin II receptor blockers (ARBs) **1** have gained keen interest as hypertensive drugs due to the high efficacy and safety. Among them, candesartan cilexetil (CAN, **1a**)[1] and olmesartan medoxomil (OLM, **1b**)[2] (Figure 1), have been recognized as the leading contributors to this kind of drugs and extensive process research has been devoted to accomplish a really efficient synthetic method. We have already established a conceptually practical synthesis of **1** by means of C–H arylation.[3] As one of our continuing research projects to establish an efficient synthesis of pharmaceuticals, described herein is an alternative synthetic method employing functionalized aryl bromides as a substrate for C–H arylation to enhance convergency of the methodology.

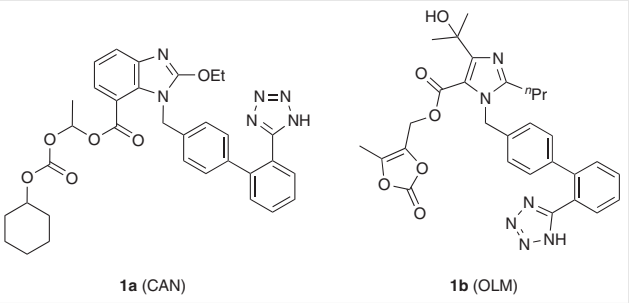

Figure 1 Candesartan cilexetil (**1a**) and olmesartan medoxomil (**1b**)

Previously reported synthetic method of **1a** involves a synthetic route where C–H arylation of 1-benzyl-5-phenyl-1*H*-tetrazole (**2**) with 4-benzoyloxymethylphenyl bromide gave biphenyltetrazole **3**. This was elaborated to chloride **5** in two steps and by alkylation of **5** with benzimidazole derivative **6** to afford an intermediate **7** having candesartan framework.[3f] Even though it is efficient in view of employing preformed benzimidazole **6** and coupling it with **5** in a later stage of the synthesis, it took 5 steps to obtain **7** (Scheme 1, route A).

To further reduce the number of steps and to enhance convergency, an alternative route of synthesis was considered in that alkylation of **6** with commercially available 4-bromobenzyl bromide to provide aryl bromide **8**, which was subjected to C–H arylation with **2** to give **7** just in 2 steps (Scheme 1, route B).[4] Therefore, use of route B would enable a reduction of 3 steps in comparison with route A.

The process development was initiated by the synthesis of aryl bromide **8**, which was accomplished in high yield (72%) by regioselective alkylation of **6** with 4-bromobenzyl

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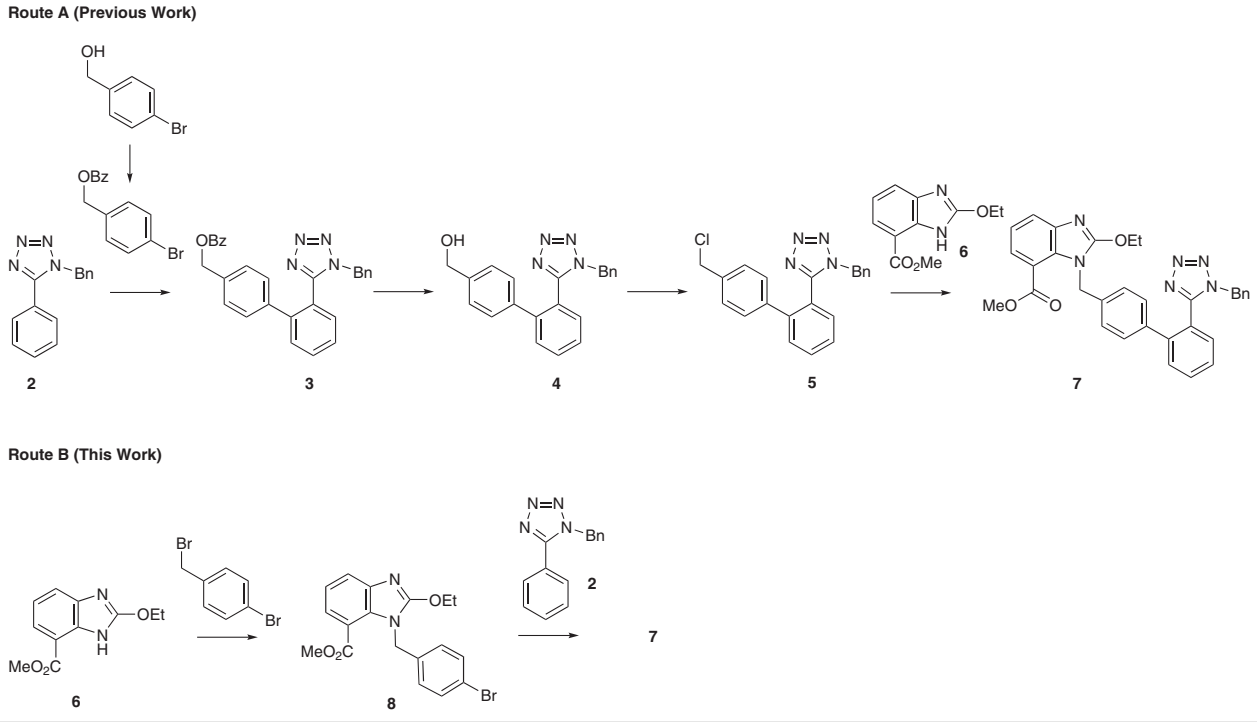
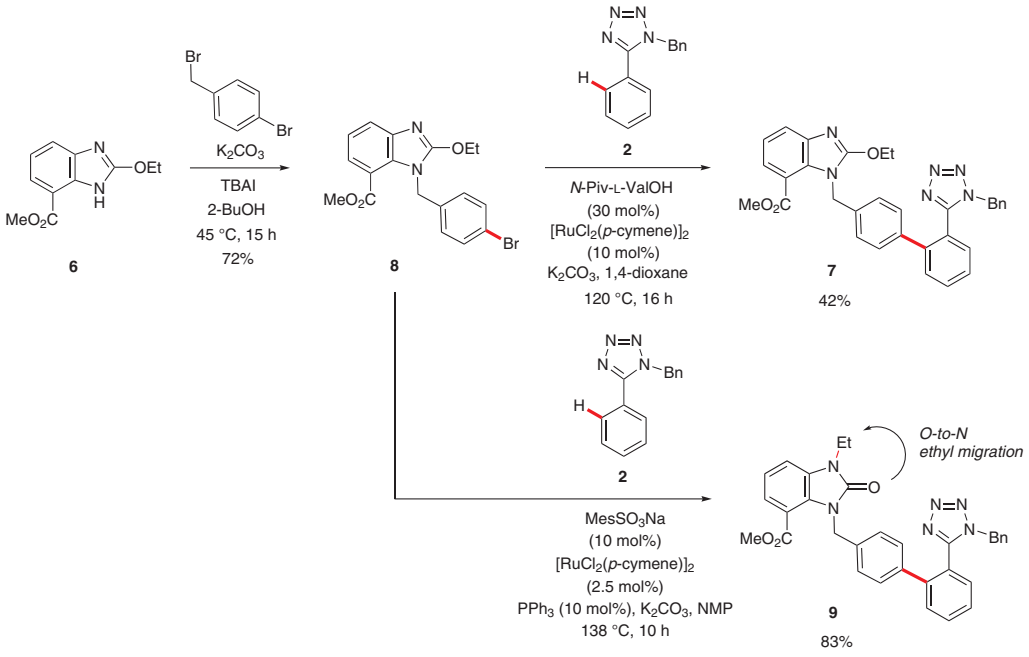


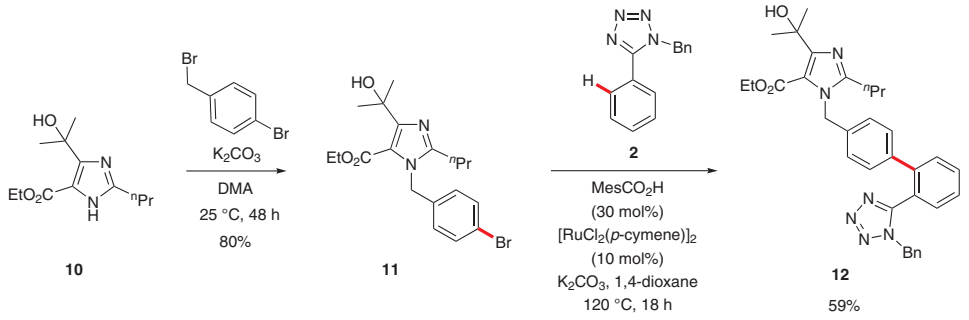
Scheme 1 Strategy for synthesis of CAN key intermediate **7**

bromide in the presence of K_2CO_3 and TBAI in butan-2-ol (Scheme 2). A similar regioselectivity on the alkylation of **6** was observed as well in the reaction employing biphenylmethyl chloride **5**.[3f]

The C–H arylation of **8** with phenyltetrazole **2** was then tested using our previously developed procedure employing $MesSO_3Na$, $[RuCl_2(p\text{-cymene})_2]_2$, PPh_3, and K_2CO_3 in NMP.[3f] The reaction proceeded completely by heating the mixture



Scheme 2 Synthesis of CAN key intermediate **7** through C–H arylation



Scheme 3 Synthesis of OLM key intermediate **12** through C–H arylation

at 138 °C for 10 hours though undesirable O-to-N ethyl migrated compound **9** was formed exclusively. This type of migration was reported by Dong[5] and the presence of PPh_3 was shown to accelerate the transformation.

To avoid the undesirable O-to-N ethyl migration, we initially tested the reaction in the absence of PPh_3. However, it failed to provide **7** under otherwise identical conditions and only **9** was obtained in 60% yield. Finally, to our delight, by treating **8** with **2** at 120 °C for 16 hours in 1,4-dioxane using N-Piv-L-ValOH[4] as an additive, the desired coupling product **7** was obtained without any O-to-N ethyl migration even though the reaction rate was very slow and higher Ru catalyst loading (10 mol%) was required to obtain a moderate yield of **7** (42%). Biphenyltetrazole **7** thus obtained was converted to CAN (**1a**) in 3 steps by simple hydrolysis, prodrug ester formation, and final debenzylation.[3e,f]

Although the overall yield of route B (30%) developed is slightly lower than that of route A (34%),[3f] a significant reduction in the number of reaction steps and need of number of solvents for reaction and work up (i.e., NMP, MTBE, THF, IPE, *n*-heptane, IPA, MeOH, acetone) compensates for this reduction in overall yield. In addition, though much amount of Ru catalyst was required to effect the reaction to reasonable level, the price of Ru ($12/g) is currently very low and affordable when compared with well-employed Pd catalysts (Pd: $92/g).

We then moved to the synthesis of olmesartan medoxomil (OLM, **1b**). The same strategy as that used for the synthesis of **1a** was conducted for the synthesis of **1b** (Scheme 3). To begin with, alkylation of ethyl 4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate (**10**) with 4-bromobenzyl bromide led to the 1-alkylated product **11** in high yield (80%). Aryl bromide **11** obtained was subjected to Ru-catalyzed C–H arylation using $MesCO_2H$[6] as an additive to furnish the desired OLM key intermediate **12**. It is worth noting that the transformation successfully proceeded well with the substrate **11** carrying a free hydroxyl group. From **12**, OLM (**1b**) was obtained just in three steps including ester hydrolysis, prodrug ester formation, and final debenzylation.[3e]

In conclusion, novel and practical syntheses of candesartan cilexetil (**1a**) and olmesartan medoxomil (**1b**) have been worked out by means of C–H arylation of elaborated aryl bromides bearing functional groups. Use of C–H arylation procedure without PPh_3 has avoided the unfavorable side reaction of ethyl group migration in the synthesis of **1a**. Higher convergency combined with the use of readily available reagents, mild reaction conditions of the current process would permit much easier access to ARB drugs.

^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were recorded with TMS as an internal standard. Silica gel column chromatography was performed using Kieselgel 60 (E. Merck). TLC was carried out on E. Merck 0.25 mm pre-coated glass-backed plates (60 F_{254}). Development was accomplished using 5% phosphomolybdic acid in EtOH/heat or visualized by UV light where feasible. All solvents and reagents were used as received.

Methyl 1-(4-Bromobenzyl)-2-ethoxy-1*H*-benzimidazole-7-carboxylate (8)

To a suspension of methyl 2-ethoxy-1*H*-benzimidazol-7-carboxylate (**6**; 10 g, 45.4 mmol) and K_2CO_3 (12.5 g, 90.8 mmol) in butan-2-ol (100 mL) were added 4-bromobenzyl bromide (12 g, 47.9 mmol) and TBAI (0.839 g, 2.27 mmol) at 25 °C. The mixture was stirred at 45 °C for 15 h. After completion of the reaction, the mixture was evaporated. To the residue was added EtOAc (100 mL) and the EtOAc layer was washed with H_2O (3 × 100 mL). The organic phase was separated, dried ($MgSO_4$), and evaporated. The residue was recrystallized from EtOAc to give **8** as a white fine solid; yield: 12.8 g (72%); mp 121 °C (EtOAc).

^{1}H NMR ($CDCl_3$): δ = 7.72 (1 H, dd, *J* = 8.0, 0.8 Hz), 7.57 (1 H, dd, *J* = 8.0, 1.2 Hz), 7.35 (2 H, m), 7.17 (1 H, t, *J* = 8.0 Hz), 6.85 (2 H, d, *J* = 8.4 Hz), 5.57 (2 H, s), 4.64 (2 H, q, *J* = 7.2 Hz), 3.75 (3 H, s), 1.46 (3 H, t, *J* = 7.2 Hz)

^{13}C NMR ($CDCl_3$): δ = 166.8, 158.7, 142.0, 136.6, 131.6, 128.3, 123.9, 122.2, 121.1, 121.0, 115.6, 66.8, 52.3, 46.9, 14.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{18}BrN_2O_3$: 389.0402; found: 389.0499.

Methyl 1-Ethyl-2-oxo-3-({2′-[1-(phenylmethyl)-1*H*-tetrazol-5-yl][1,1′-biphenyl]-4-yl}methyl)-2,3-dihydrobenzimidazole-4-carboxylate (9)

To a mixture of **2** (1.0 g, 4.23 mmol), $[RuCl_2(p\text{-cymene})]_2$ (65 mg, 0.106 mmol, 2.5 mol%), **8** (1.81 g, 4.65 mmol, 1.1 equiv), $MesSO_3Na$ (94 mg, 0.423 mmol, 10 mol%), PPh_3 (111 mg, 0.423 mmol, 10 mol%), and K_2CO_3 (585 mg, 4.23 mmol, 1.0 equiv) was added NMP (5 mL) under N_2 atmosphere. The mixture was stirred under N_2 atmosphere at 138 °C for 10 h. After completion of the reaction, the mixture was diluted with EtOAc and filtered through Celite. The solids were washed with EtOAc. The filtrate and washings were combined and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc 2:1) to provide **9** as a colorless oil; yield: 1.9 g (83%).

^{1}H NMR ($CDCl_3$): δ = 7.60 (1 H, ddd, *J* = 7.6, 1.6 Hz), 7.50 (1 H, dd, *J* = 7.6, 0.8 Hz), 7.42–7.33 (3 H, m), 7.19–7.09 (5 H, m), 7.02–6.95 (4 H, m), 6.72 (2 H, d, *J* = 7.2 Hz), 5.46 (2 H, s), 4.62 (2 H, s), 4.06 (2 H, q, *J* = 7.2 Hz), 3.70 (3 H, s), 1.40 (3 H, s).

^{13}C NMR ($CDCl_3$): δ = 166.5, 154.8, 154.5, 141.0, 137.8, 137.2, 133.2, 131.6, 131.4, 130.6, 130.2, 128.7, 128.5, 127.9, 127.8, 127.6, 127.4, 122.8, 122.7, 120.7, 115.5, 110.8, 52.6, 50.7, 45.8, 36.4, 13.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{29}N_6O_3$: 545.2256; found: 545.2301.

Methyl 2-Ethoxy-1-({2′-[1-(phenylmethyl)-1*H*-tetrazol-5-yl][1,1′-biphenyl]-4-yl}methyl)-1*H*-benzimidazole-7-carboxylate (7)[3f]

A mixture of 1-benzyl-5-phenyl-1*H*-tetrazole (**2**; 0.5 g, 2.12 mmol), **8** (0.907 g, 2.33 mmol, 1.1 equiv), $[RuCl_2(p\text{-cymene})]_2$ (0.13 g, 0.212 mmol, 10 mol%), *N*-Piv-L-ValOH (0.128 g, 0.636 mmol, 0.3 equiv), and K_2CO_3 (0.879 g, 6.36 mmol, 3.0 equiv) in 1,4-dioxane (3 mL) was stirred at 120 °C for 16 h under N_2 atmosphere. To the mixture was added activated carbon (0.13 g) and EtOAc (2 mL) and filtered through Celite. The solid materials were washed thoroughly with EtOAc. The filtrate and washings were combined and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc 2:1) to give **7** as white prisms; yield: 0.485 g (42%); mp 146 °C (EtOAc/*n*-hexane).

^{1}H NMR ($CDCl_3$): δ = 7.73 (1 H, d, *J* = 7.6 Hz), 7.57–6.89 (13 H, m), 6.71 (2 H, d, *J* = 7.2 Hz), 5.59 (2 H, s), 4.68 (4 H, m), 3.76 (3 H, s), 1.50 (3 H, t, *J* = 7.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 166.8, 158.8, 154.6, 142.1, 141.2, 137.9, 137.4, 133.2, 131.6, 131.5, 131.4, 130.2, 128.8, 128.7, 128.6, 128.0, 127.8, 127.4, 123.8, 122.8, 122.1, 121.1, 115.8, 66.9, 52.5, 50.8, 46.9, 14.8.

MS: *m*/*z* = 545.40 [M + H]$^+$.

Ethyl 1-(4-Bromobenzyl)-4-(1-hydroxy-1-methylethyl)-2-propyl-1*H*-imidazole-5-carboxylate (11)

A mixture of ethyl 5-(1-hydroxy-1-methylethyl)-2-propyl-3*H*-imidazol-4-carboxylate (**10**; 10 g, 41.7 mmol), K_2CO_3 (7.1 g, 51.6 mmol), and 4-bromobenzyl bromide (10.8 g, 43 mmol) in DMA (40 mL) was stirred at 25 °C for 48 h. After completion of the reaction, H_2O (120 mL) was added to the reaction mixture. The solids formed were collected and recrystallized from EtOAc/*n*-hexane to give **11** as a white fine solid; 13.6 g (80%); mp 86 °C (EtOAc/*n*-hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (2 H, d, *J* = 8.4 Hz), 6.81 (2 H, d, *J* = 8.0 Hz), 5.75 (1 H, br s), 5.41 (2 H, s), 4.22 (2 H, q, *J* = 7.2 Hz), 2.61 (2 H, t, *J* = 7.6 Hz), 1.70 (2 H, m), 1.64 (6 H, s), 1.16 (3 H, t, *J* = 7.2 Hz), 0.94 (3 H, t, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 159.0, 151.4, 136.3, 132.0, 127.2, 121.3, 116.9, 70.4, 61.3, 48.6, 29.4, 29.3, 21.4, 14.0, 13.9.

HRMS: *m*/*z* [M + 1]$^+$ calcd for $C_{19}H_{26}BrN_2O_3$: 411.1062; found: 411.1110.

Ethyl 4-(1-Hydroxy-1-methylethyl)-1-({2′-[1-(phenylmethyl)-1*H*-tetrazol-5-yl][1,1′-biphenyl]-4-yl}methyl)-2-propyl-1*H*-imidazole-5-carboxylate (12)[3d]

A mixture of 1-benzyl-5-phenyl-1*H*-tetrazole (**2**; 0.945 g, 4 mmol), **11** (1.80 g, 4.4 mmol, 1.1 equiv), $[RuCl_2(p\text{-cymene})]_2$ (0.245 g, 0.4 mmol, 10 mol%), mesitylenecarboxylic acid (0.197 g, 1.2 mmol, 0.3 equiv), and K_2CO_3 (1.7 g, 12 mmol, 3 equiv) in 1,4-dioxane (4 mL) was stirred at 120 °C for 18 h under N_2 atmosphere. To the mixture was added activated carbon (0.25 g) and EtOAc (3 mL) and filtered through Celite. The solid materials were washed thoroughly with EtOAc. The filtrate and washings were combined and evaporated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc 1:1) to give **12** as a white fine solid; yield: 1.33 g (59%); mp 88–91 °C (EtOAc/*n*-hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (1 H, ddd, *J* = 8.0, 7.8, 1.2 Hz), 7.53 (1 H, dd, *J* = 7.8, 1.2 Hz), 7.43 (1 H, ddd, *J* = 7.8, 7.4, 1.6 Hz), 7.31 (1 H, dd, *J* = 7.6, 0.8 Hz), 7.23–7.13 (3 H, m), 7.07 (2 H, d, *J* = 8.8 Hz), 6.84 (2 H, d, *J* = 8.0 Hz), 6.78 (2 H, d, *J* = 6.8 Hz), 5.76 (1 H, br s), 5.42 (2 H, s), 4.82 (2 H, s), 4.21 (2 H, q, *J* = 7.2 Hz), 2.63 (2 H, t, *J* = 8.0 Hz), 1.72 (2 H, m), 1.64 (6 H, s), 1.16 (3 H, t, *J* = 7.6 Hz), 0.97 (3 H, t, *J* = 7.6 Hz).

MS: *m*/*z* = 565 [M + H]$^+$.

Conflict of Interest

The authors declare no conflict of interest.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1472-0925.

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