Highly Regioselective Palladium-Catalyzed *β*-Arylation of *N,N*-Dialkylallylamines

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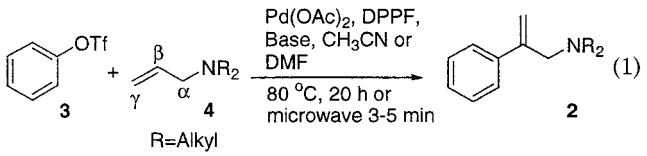
The arylethylamine fragment **1** is common in many bioactive compounds and molecules with this structural unit are of importance in the search for effective therapeutics. Arylethylamines possessing an exomethylene group **2** (R═H or alkyl) are similarly often of interest in medicinal chemistry and serve as building blocks of more advanced chemical entities (Chart 1). We needed access to a method for the preparation of structures encompassing **2** in an ongoing medicinal chemistry program.[1] A direct synthesis of **2** by a regiocontrolled Heck-reaction,[2] resulting in the addition of an aryl group at the internal (*β*-carbon) of *N,N*-dialkylallylamines, appeared to be an attractive alternative to the previously reported methods[3,4] due to the simplicity of the experimental procedure and the easily available starting materials.

We are here reporting a highly regioselective, one-pot, palladium-catalyzed synthesis of the 2-aryl-3-(*N,N*-dialkylamino)-1-propenes **2**. The long reaction times required for full conversion of the aryl triflates **3** with standard, thermal heating could in many cases be shortened considerably with retained, high regioselectivity under single-mode microwave irradiation[5,6] (Eq 1). In addition, performing the standard Heck-coupling reaction under a carbon monoxide atmosphere allowed for the synthesis of *N,N*-dimethylbenzamide.



Results

The aryl triflates **3a**−**j** were in the standard, thermal, experiments mixed with *N,N*-dimethylallylamine **4a**,

Chart 1

palladium acetate, DPPF,[7] base (triethylamine, potassium carbonate or pentamethylpiperidine (PMP)) in acetonitrile as solvent.[8] The reactions were conducted at 80 °C and completed after 20 h with more than 99.5% conversion of **3a**−**j**. The preparative results are summarized in Table 1. For the majority of the couplings, the internally, *β*-arylated product **2** was strongly predominant and isolated in moderate to good yields (35−81%).[9] One notable side-reaction was the deoxygenation of the triflate to the corresponding arene.[10] Large amounts of arene were produced in some cases in the presence of triethylamine as base, for example with the naphthalene triflate **3g** and the electron-poor triflates **3h**−**j**. This side-reaction could be reduced upon changing triethylamine to the inorganic potassium carbonate, which proved to be the generally most applicable base, even though triethylamine (Method C, entries 5 and 6) and PMP (Method D, entries 8 and 10) were found to deliver higher yields in a few cases, see Table 1 and Experimental Section. Increasing the amount of catalyst was also effective in improving the yields (Method B, entries 4, 7 and 9, Table 1), even though phenyl migration[11,12] became more of a problem with the accompanying larger amounts

(1) (a) Alterman, M.; Andersson, H. O.; Garg, N.; Ahlsén, G.; Lövgren, S.; Classon, B.; Danielsson, U. H.; Kvarnström, I.; Vrang, L.; Unge, T.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1999**, *42*, 3835−3844. (b) Hultén, J.; Andersson, H. O.; Schaal, W.; Danielson, H. U.; Classon, B.; Kvarnström, I.; Karlén, A.; Unge, T.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1999**, *42*, 4054−4061.

(2) (a) Heck, R. F. *Org. React.* **1982**, *27*, 345−390. (b) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379−2411. (c) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Chichester 1995; pp 125−168. (d) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2−7. (e) Jeffery, T. *Advances in Metal-Organic Chemistry*; Liebeskind, L. S. Ed.; Jai Press Inc: Greenwich 1996, *vol 5*, pp 153−258. (f) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427−436. (g) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254−278. (h) Larhed, M.; Hallberg, A. *Handbook of Organo-Palladium Chemistry for Organic Synthesis*; Negishi, E.-I. Ed.; Wiley-Interscience. In press.

(3) For examples of preparations of **2**, see: (a) Gupton, J. T.; Andrew, S. S.; Lizzi, M. J. *Synth. Commun.* **1982**, *12*, 361−371. (b) Schwan, A. L.; Warkentin, J. *Can. J. Chem.* **1988**, *66*, 1686−1694.

(4) For the use of **2** in organometallic displacement reactions, see (a) Gupton, J. T.; Layman, W. J.; Forman, J. T. *Synth. Commun.* **1986**, *16*, 1393−1400. (b) Gupton, J. T.; Layman, W. J. *J. Org. Chem.* **1987**, *52*, 3683−3686.

(5) (a) Neas, E. D.; Collins, M. J. *Introduction to Microwave Sample Preparation*; Kingston, H. M.; Jassie, L. B. Eds.; American Chemical Society: Washington, DC 1988, 7−31. (b) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665−1692. (c) Majetich, G.; Wheless, K. In *Microwave-Enhanced Chemistry*; Kingston, H. M.; Haswell, S. J., Eds; American Chemical Society: Washington, DC, 1997; 455−505. (d) Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 233−238. (e) Langa, F.; de la Cruz, P.; de la Hoc, A.; Díaz Ortiz, A.; Díez Barra, E. *Contemp. Org. Synth.* **1997**, 373−386. (f) Hájek, M. *Collect. Czech. Chem. Commun.* **1997**, *62*, 347−354. (g) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213−223. For a discussion on the influence of pressure in microwave-heated closed vessels, see: (h) Gedye, R. N.; Wei, J. B.; *Can. J. Chem.* **1998**, *76*, 525−532.

(6) For examples of microwave irradiation in palladium-catalysed reactions, see: (a) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582−9584. (b) Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 5583−5587. (c) Olofsson, K.; Kim, S.-Y.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1999**, *64*, 4539−4541. See also ref 1a.

(7) DPPF = 1,1'-bis(diphenylphosphino)ferrocene. Although several other bidentate ligands, including DPPP (1,3-bis(diphenylphosphino)-propane), have been tried, only DPPF yields high regioselectivities under the present reaction conditions. (a) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158−163. (b) Butler, I. R.; Cullen, W. R.; Kim, T. J.; Rettig, S. J.; Trotter, J. *Organometallics* **1985**, *4*, 972−980. (c) Gan, K. S.; Hor, T. S. A. *Ferrocenes*; Togni, A.; Hayashi, T., Eds.; VCH: Weinheim 1995; pp 3−104.

(8) DMF and acetonitrile were both found to be suitable solvents, giving substantially identical yields and regioselectivities.

(9) Couplings with the *para*-nitro triflate resulted in no notable product formation and couplings with the *meta*-aldehyde triflate only in 13% isolated yield. The 2-pyridyl triflate, which should be capable of strong palladium coordination, resulted in only trace amounts of product.

(10) (a) Cabri, W.; DeBernardinis, S.; Francalanci, F.; Penco, S.; Santi, R. *J. Org. Chem.* **1990**, *55*, 350−353. (b) Jutand, A.; Mosleh, A. *J. Org. Chem.* **1997**, *62*, 261−274. Deoxygenation of the triflates has been suggested to be partially brought about through donation of hydride from organic bases, such as triethylamine, although several mechanisms may be at hand as deoxygenation occurs in the presence of inorganic bases without hydrogens as well. (c) Saá, J. M.; Dopico, M.; Martorell, G.; García-Raso, A. *J. Org. Chem.* **1990**, *55*, 991−995.

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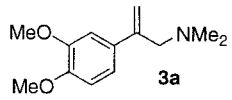
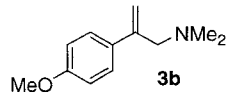
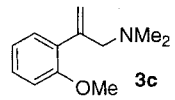
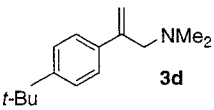
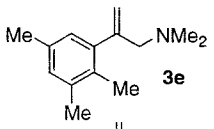
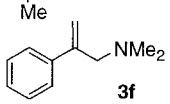
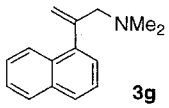
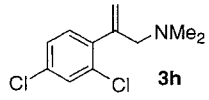
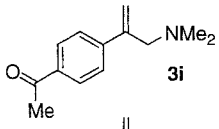
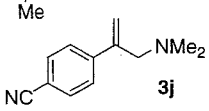
Table 1. Internal Arylation of Allylamine 4a

		Thermal Heating[a]				Microwave Heating[b]		
Entry	Product	Base	β/γ[c]	Method	Isolated Yield **2** (%)[d]	Time (min)/ Effect (W)	β/γ[c]	Isolated Yield **2** (%)[d]
1	 **3a**	K_2CO_3	92/8	A	41	3/20	92/8	35
2	 **3b**	K_2CO_3	94/6	A	40	5/20	95/5	30
3	 **3c**	K_2CO_3	99/1	A	49	5/20	>99.5/0.5[e]	46
4	 **3d**	K_2CO_3	93/7	B	35	5/15	84/16	21
5	 **3e**	Et_3N	>99.5/0.5	C	81	5/15	96/4	48
6	 **3f**	Et_3N	>99.5/0.5[e]	C	42	5/15	88/12	24
7	 **3g**	K_2CO_3	>99.5/0.5[e]	B	71	5/15	>99.5/0.5[e]	42
8	 **3h**	PMP	>99.5/0.5[e]	D	38			[f]
9	 **3i**	K_2CO_3	>99.5/0.5[e]	B	48			[f]
10	 **3j**	PMP	>99.5/0.5[e]	D	50			[f]

[a] The thermal reactions were run in 2.5 mmol scale under nitrogen atmosphere at 80 °C with 1 equiv of **3a**−**j**; $Pd(OAc)_2$, see Methods below; DPPF, see Methods below; 5 equiv of *N*,*N*-dimethylallylamine **4a**; base, see Methods below; and 10 mL of acetonitrile. Method A (entries 1−3): 0.03 equiv of $Pd(OAc)_2$, 0.132 mmol of DPPF, 1.5 equiv of K_2CO_3. Method B (entries 4, 7, 9): 0.06 equiv of $Pd(OAc)_2$, 0.264 equiv of DPPF, 1.5 equiv of K_2CO_3. Method C (entries 5−6): As Method A but with 2 equiv of triethylamine instead of K_2CO_3. Method D (entries 8, 10); As Method A but with 2 equiv of PMP instead of K_2CO_3. All reactions were completed after 20 h. [b]Continuous irradiation at 2450 MHz. The microwave heated reactions were run in 1.0 mmol scale in septum-sealed Pyrex tubes with 1 equiv of **3a**−**j**, 3 equiv of **4a**, 0.03 equiv of $Pd(OAc)_2$, 0.132 equiv of DPPF and 1.2 equiv of K_2CO_3 in 1.0 mL of DMF. [c]Selectivity internal β-arylation/terminal γ-arylation. Determined by GC-MS and ^{1}H NMR.[d]>95% by GC-MS. [e]Only one product detected by GC-MS. [f]Not isolated.

of DPPF. No traces of arylpropanal or the corresponding enamides were detected in the reaction mixture in any of the reactions. It was not possible to extend the high regioselectivities with aryl triflates to vinyl triflates. When cyclohexenyl triflate was coupled under the standard reaction conditions, a mixture of products was formed.

Reactions with **3f** and the allylamines 3-piperidino-1-propene **4b** and 3-morpholino-1-propene **4c** as olefins provided the expected internally arylated products **2k** and **2l**, which were isolated in moderate yields; 50% and 56%, respectively (Chart 2). An excellent, internal β-regioselectivity was achieved with **4b** (β/γ >99.5/0.5) but

(11) (a) Andersson, C.-M.; Hallberg, A., Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 3529−3536. (b) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Beller, M.; Fischer, H. *J. Organomet. Chem.* **1995**, *491*, C1−C4. For two different mechanisms see: (c) Morita, D. K.; Stille J. K.; Norton, J. R. *J. Am. Chem. Soc.* **1995**, *117*, 8576−8581. (d) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441−12453. It has been demonstrated that phenyl migration does not take place in the GC-MS, see: (e) Kong, K.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6313−6315.

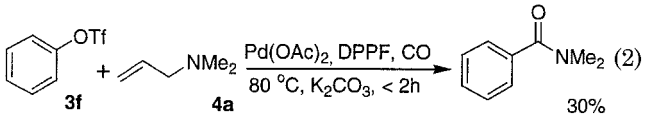
(12) Couplings with triflate **3d** were found to give a substantial degree of phenyl migration (**2d**/**2f** = 5, GC-MS integration). In fact, this was the only case where trisubstituted phosphines P(*p*−*t*-BuPh)$_3$ were detected by GC-MS. The disubstituted $PPhAr_2$ (Ar = arene from triflates **3**) were formed in several couplings. Electron rich aromatic rings have been reported to migrate more easily, see ref 11b.

Chart 2

not with the morpholine containing **4c**, where a considerably lower degree of regiocontrol was encountered (β/γ = 88/12).

A series of single-mode microwave-heated couplings was conducted in DMF.[13] Potassium carbonate was chosen as the base due to the good results documented in the thermal reactions and the recognized ability of ions to absorb microwave irradiation efficiently.[5g] The results are summarized in Table 1. The reaction times were shortened to 3−5 min for the electron rich and -neutral triflates with selectivities comparable to the thermal reactions (with the exceptions of entries 4 and 6, Table 1) despite the faster heating rate and higher temperatures (up to approximately 190 °C).[14] The yields, on the other hand, were markedly lower[15] with microwave heating. Even though several combinations of reaction time and microwave effect were tried it was difficult to prevent the development of tar[16] in several of the high temperature microwave experiments (tar was produced in the thermal experiments as well but not as extensively). The electron-poor triflates did not couple efficiently under microwave irradiation and although subjected to numerous attempts resulted in low yields with poor reproducibility (entries 8−10). More temperature stable palladium catalysts such as the chiral ligands 1,2-diaminocyclohexane-*N*,*N*'-bis(2'-diphenylphosphinobenzoyl) and 4-*tert*-butyl-2-(2-diphenylphosphinophenyl)-4,5-dihydro-oxazole were tested under microwave irradiation[17,18] but failed to yield any product.

A somewhat unexpected result was encountered when phenyl triflate **3f** and **4a** were coupled at 80 °C on oil bath under a carbon monoxide atmosphere (1 atm)[19] yielding 30% of *N*,*N*-dimethylbenzamide (Eq 2). As it was not clear if the *N*,*N*-dimethylamide group originated from a carbonylative coupling with **4a** and a subsequent deallylation[19] or from the solvent (DMF), two variations of the coupling conditions were designed. A coupling in the absence of olefin **4a** resulted in no product formation and a coupling with acetonitrile as solvent instead of DMF (with **4a**) did yield product, albeit less than what was the case in DMF. This should indicate that the dimethylamine group is not derived from DMF.



(2)

Discussion

Cabri et al. introduced the use of bidentate ligands in Heck-couplings to achieve a high selectivity for arylation at the internal carbon of acyclic, electron rich olefins.[2d,20] With bidentate ligands bound to the palladium and with organotriflates used instead of halocompounds, a weakly coordinated triflate anion is assumed to dissociate from the palladium complex[21] and favor a cationic rather than a neutral reaction pathway. The regiochemical outcome of the insertion process is believed to be more influenced by electronic than by steric effects in the cationic mechanism.[20]

The previously reported regioselectivities for internal arylation with 4-methyl-1-pentene and allyltrimethylsilane[22] as olefins are lower than the herein reported regioselectivities with *N*,*N*-dialkylallylamines. This finding suggests that additional factors are affecting the regiochemical outcome of the insertion in the case of *N*,*N*-dialkylallylamines. A coordination of the amine[23] moiety to the metal center through an energetically favored five-membered intermediate[24−26] is plausible (Scheme 1). A pentacoordinated palladium π-complex[27−29] **5** should give rise to a five-membered σ-intermediate **6**, which results

(13) DMF was chosen in favour of acetonitrile as solvent since DMF absorbs microwave irradiation better than acetonitrile, see Baghurst, D. R.; Mingos, D. M. P. **1992**, *J. Chem. Soc., Dalton Trans.* 1151−1155 and ref 5g. The microwave-heated reactions were run on a smaller scale than the thermal due to the limited space in the microwave cavity and the reaction tubes. The amount of olefin was reduced as 3 equiv of olefin did not result in lower yields than 5 equiv. A lower yield was associated with 2 equiv of olefin.

(14) Temperature profiles were measured on several microwave heated experiments, see Supporting Information, including entries 5 and 6, showing that the temperature reached the boiling point of DMF and sometimes surpassed it with 10−50 °C. The boiling point elevation due to pressure in a closed Pyrex tube allows higher temperatures than is ordinarily feasible.

(15) Running 1.0 and 2.5 mmol reactions under otherwise identical conditions resulted in 3−6% lower isolated yield for the 1.0 mmol reactions.

(16) Tar (polymers) has been reported in Heck-couplings with allylamine: Malek, N. J.; Moorman, A. E. *J. Org. Chem.* **1982**, *47*, 5395−5397.

(17) Bremberg, U.; Lutsenko, S.; Kaiser, N.-F.; Larhed, M.; Hallberg, A.; Moberg, C. *Synthesis* In press.

(18) Kaiser, N.-F.; Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *J. Organomet. Chem.* In press.

(19) A similar deallylation has been reported previously. Mori, M.; Ban, Y. *Chem. Pharm. Bull.* **1976**, *24*, 1992−1999.

(20) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1992**, *57*, 3558−3563.

(21) Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810−1817.

(22) Olofsson, K.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 5076−5079.

(23) Examples of palladium-chelating σ- and π-complex intermediates with nitrogen have been reported on many occasions: (a) Cope, A. C.; Kliegman, J. M.; Friedrich, E. C. *J. Am. Chem. Soc.* **1967**, *89*, 287−291. (b) Holton, R. A.; Kjonaas, R. A. *J. Am. Chem. Soc.* **1977**, *99*, 4177−4179. (c) McCrindle, R.; McAlees, A. J. *J. Chem. Soc., Dalton Trans.* **1983**, 127−131. (d) Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 2464−2470. (e) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1993**, *58*, 7421−7426. (f) Filippini, L.; Gusmeroli, M.; Riva, R. *Tetrahedron Lett.* **1993**, *34*, 1643−1646. (g) Larhed, M.; Andersson, C.-M.; Hallberg, A. *Tetrahedron* **1994**, *50*, 285−304. (h) Crisp, G. T.; Gebauer, M. G. *Tetrahedron Lett.* **1995**, *36*, 3389−3392.

(24) Five-membered intermediates are known to play an important part in metal-catalysed chemistry. Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metallic Chemistry;* University Science Books: 1987; pp 825−859.

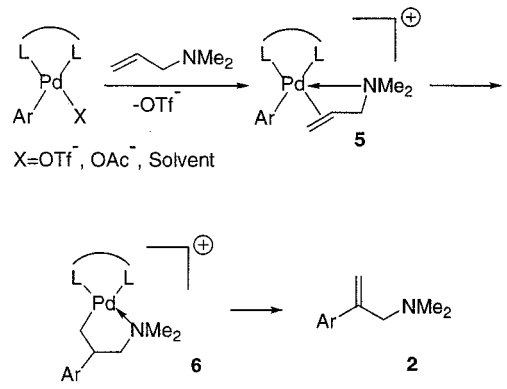
(25) (a) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488−6499. The five-membered intermediate has been demonstrated to be more stable than the six-membered intermediate in the case of chelation between palladium and homoallylmercaptan. (b) Albéniz, A. C.; Espinet, P.; Lin, Y.-S. *Organometallics* **1996**, *15*, 5010−5017.

(26) A similar mechanism has been proposed by Blart and Ricci et al. in the discussion of regioselectivities with arylation of (*E*)-*N*-(*tert*-butoxycarbonyl)-3-trimethylsilylallylamine. Alvisi, D.; Blart, E.; Bonini, B. F.; Mazzanti, G.; Ricci, A.; Zani, P. *J. Org. Chem.* **1996**, *61*, 7139−7146.

(27) Pentacoordinated palladium complexes have been suggested in the Heck-mechanism, see refs 2g, 23e and 25a. Pentacoordinated palladium complexes have also been isolated: Vila, J.; Pereira, M. T.; Ortigueira, J. M.; Fernández, J. J.; Fem, A.; López-Torres, M.; Adams, H. *Organometallics* **1999**, *18*, 5484−5487.

(28) The possibility of a temporary dissociation of one of the arms of the bidentate ligand cannot be neglected, although the fact that monodentate ligands (PPh_3, $P(o\text{-tol})_3$) give poor regioselectivities would contradict this theory (unpublished results from our laboratory). See also ref 25a. DPPF is known to be more flexible and more loosely coordinated to the metal than many other bidentate ligands, see ref 7c.

Scheme 1



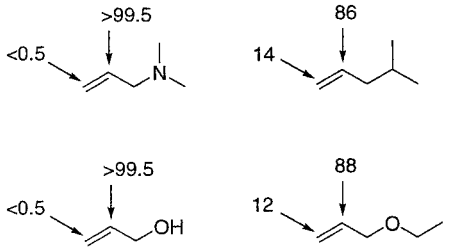
in the internally arylated product **2**. The fact that electron poor triflates usually give better regioselectivities than electron rich under thermal heating with *N*,*N*-dialkylallylamines as olefins also supports a chelation-controlled insertion.[23g] Furthermore, the inferior selectivity registered with the *N*-allylmorpholine compound **4c** (Chart 2) could possibly be attributed to a competitive chelation effect of the oxygen of the morpholine moiety.

One result of coordination between nitrogen and palladium should be that the electropositive character of the metal center in **5** and **6** decreases as a result of electron donation from the amine moiety.[23e,30−31] In a competitive experiment with phenyl triflate **3f** as arylating agent and 4-methyl-1-pentene and *N*,*N*-dimethylallylamine **4a** as olefins (5 equiv of each olefin was added), a 65/35 ratio of arylated 4-methyl-1-pentene to arylated **4a** was encountered. A similar competitive experiment with allyltrimethylsilane instead of 4-methyl-1-pentene resulted in an even higher ratio of 92/8 of arylated allyltrimethylsilane to arylated **4a**. It is thus possible to assume that the lower reactivity of **4a** is attributed to a slower, rate limiting, insertion step due to electron donation from the nitrogen to palladium.

The involvement of a pentacoordinated palladium π-complex could also account for the very high β-selectivity that was reported by Cabri with allyl alcohol as olefin.[20] Using the same reaction conditions as was used in the arylation of the dialkylamines we encountered a β/γ ratio of >99.5/0.5 with allyl alcohol[20] (65% isolated yield) while arylation of allyl ethyl ether resulted in a poorer selectivity with a β/γ ratio of 88/12 (62% isolated yield) (Scheme 2). These results suggest that a strong coordination between palladium and oxygen[32] occurs in the regiocontrol-determining step when allyl alcohol is employed as olefin.

Apart from the electronic effects can the influence of the steric bulk of the aryl-palladium precursors on the regioselectivity not be neglected. The *ortho*-methoxy substituted triflate **3c** coupled with better selectivity than

Scheme 2. Regioselectivity in the DPPF-controlled Heck Reaction with Phenyl Triflate (3f)



the *para*- **3b** and *meta*, *para*-disubstituted **3a** analogues, but with only a slight difference in yield (entries 1−3, Table 1). To further investigate the effect of steric hindrance we coupled the *ortho*, *ortho*-substituted 2,3,6-trimethyl triflate, which should make an interesting comparison with the 2,3,5-trimethyl triflate **3e**. The *ortho*, *ortho* substituted compound produced only trace amounts of products with poor regioselectivity, in stark contrast to **3e**, demonstrating that too much steric congestion can be disadvantageous and effectively inhibit the reaction.

In conclusion, internally arylated *N*,*N*-dialkylallylamines **2** have been provided by a short and convenient synthetic route in good to moderate yields. The regioselectivies are high and a wide range of functionalities is tolerated. The reaction times can be reduced to a few minutes with single-mode microwave irradiation for electron rich and -neutral triflates, although a concurrent reduction in yield is also noted. We suggest that the very high regioselectivity observed in the arylation of allylamines as well as in the arylation of allyl alcohol is attributed to palladium−nitrogen and palladium−oxygen coordination, respectively. Allyl ethyl ether can in a new Heck-procedure be arylated with moderate regioselectivity on the internal, β-position. Furthermore, an unexpected formation of *N*,*N*-dimethylbenzamide from phenyl triflate and *N*,*N*-dimethylallylamine under a carbon monoxide atmosphere was observed. Although only a limited number of examples are given herein, we believe that the regiocontrolled arylation of dialkylamines should provide an attractive complement to the existing methods.

Experimental Section

Procedures. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 270 and 67.8 MHz, respectively. Chemical shifts were reported as δ values (ppm) indirectly referenced to TMS by the solvent signal ($CHCl_3$) δ 7.26 and ($CDCl_3$) δ 77.0. Low resolution mass spectra were recorded on a GC-MS instrument equipped with a HP-1 capillary column (25 m × 0.22 mm) operating at an ionization potential of 70 eV. The β-arylated products were assumed to have the same response factor as the γ-arylated products. The oven temperature was 70−305 °C (gradient 30 °C/min). Microwave heating was carried out with a MicroWell 10 single-mode microwave cavity,[33] producing continuous irradiation at 2450 MHz. All microwave reactions were performed under nitrogen in Pyrex tubes[34] with a perforated stopcock with septa. In the event of overpressurization, the septum should burst. The inner diameter of the lower part of the tubes (to the height of 3 cm) was 8 mm. The upper part was slightly wider

(29) Four-coordinated Pd-complexes are believed to be favoured over five-coordinated complexes in the insertion process. (a) Thorn, D. L.; Hoffmann, R. *J. Am. Chem. Soc.* **1978**, *100*, 2079−2090. (b) Samsel, E. G.; Norton, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 5505−5512.

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(inner diameter 11 mm) to increase the expansion volume. Great care should be taken when performing pressurized reactions using microwave heating.[35] The microwave-heated reactions were performed without stirring. Temperature profiles were recorded using a NoEMI-TS Reflex (Nortech Fibronic, Inc. Québec, Canada), utilizing temperature sensitive fluoroptic probes (TPP-01-M2.5-A; Nortech Fibronic). The probe was positioned approximately 1 cm from the bottom of the reaction tube. Sampling rate was 3 Hz. Elemental analyses were performed by Mikro Kemi AB; Uppsala, Sweden.

Materials. Aluminum oxide (150 mesh, 58 Å, Aldrich no 19,-997−4, deactivated with 6% water) was used for chromatography. All reagents except the aryl triflates were commercially available. The aryl triflates were prepared from the corresponding phenols.[10c,36] Products **2b**, **2f**,[3a,37] 2-phenyl allyl alcohol[38] and 3-ethoxy-2-phenyl-1-propene[39] were previously characterized.

General Procedure for the Thermal Internal Arylation of *N,N*-Dimethylallylamine 4a (Table 1). A mixture of 2.50 mmol of aryl triflate **3a**−**j**; $Pd(OAc)_2$, see Methods below; DPPF, see Methods below; 12.5 mmol (1.06 g) of *N,N*-dimethylallylamine **4a**; base, see Methods below; and 10 mL of acetonitrile was heated at 80 °C on oil bath under nitrogen in oven-dried, heavy-walled and thin-necked Pyrex tubes, sealed with a Teflon stopcock. Method A (entries 1−3): 0.075 mmol (16.8 mg) of $Pd(OAc)_2$, 0.330 mmol (183 mg) of DPPF, 3.75 mmol (518 mg) of K_2CO_3. Method B (entries 4, 7, 9): 0.15 mmol (33.7 mg) of $Pd(OAc)_2$, 0.660 mmol (366 mg) of DPPF, 3.75 mmol (518 mg) of K_2CO_3. Method C (entries 5−6): As Method A but with 5 mmol (506 mg) of triethylamine instead of K_2CO_3. Method D (entries 8, 10); As Method A but with 5 mmol (777 mg) of PMP instead of K_2CO_3. Samples were periodically taken and partitioned between diethyl ether and 0.1 M NaOH. The organic layers were dried over potassium carbonate before analyses by GC-MS. All reactions were completed in 20 h (>99.5% conversion of the aryl triflate). All reactions were worked up by extraction between diethyl ether and 0.1 M NaOH and subsequent chromatography on aluminum oxide. Eluents: isohexanes−ethyl acetate 2:1 (**2a**−**c**, **i**−**j**), isohexanes−ethyl acetate 19:1 (**2d**−**h**). The eluents were removed under reduced pressure and purified (>95% purity), where indicated, by bulb-to-bulb distillation. **2d** (entry 4) was purified of contaminating **2f** by being set under reduced pressure.

Microwave Heated Internal Arylation of *N,N*-Dimethylallylamine 4a (Table 1). To a heavy-walled, oven-dried Pyrex tube were added: 1.00 mmol of aryl triflate **3a**−**j**; 0.03 mmol (6.7 mg) of $Pd(OAc)_2$, 0.132 mmol (73 mg) of DPPF, 3.0 mmol (0.26 g) of **4a**, 1.2 mmol (173 mg) of K_2CO_3 and 1.0 mL of DMF. The height of the reaction mixture in the tube was 3 cm. The reaction mixture was flushed with nitrogen and the screw cap tightened thoroughly (finger-tight) before mixing with a Whirlimixer. Heating was then applied by means of microwave irradiation. The reaction tube was allowed to cool in the microwave cavity for a couple of minutes before any handling of the reaction mixture took place and was thereafter purified by extraction between diethyl ether and 0.1 M NaOH. The products were further purified as described under General Procedure for the Thermal Internal Arylation of *N,N*-Dimethylallylamine **4a**.

Thermal Internal Arylation of *N,N*-Dialkylallylamines 4b−c (Chart 2). A mixture of 2.50 mmol (0.5650 g) of phenyl triflate **3f**; 0.075 mmol (16.8 mg) of $Pd(OAc)_2$; 0.330 mmol (183 mg) of DPPF; 7.5 mmol of allylamine **4b**−**c**; 5 mmol (0.51 g) of Et_3N and 10 mL of acetonitrile was heated at 80 °C on oil bath under nitrogen in oven-dried, heavy-walled and thin-necked Pyrex tubes, sealed with a Teflon stopcock. The reactions were completed after 20 h. The reactions were purified as described under General Procedure for the Thermal Internal Arylation of *N,N*-Dimethylallylamine **4a**. Eluents: **2k**, isohexanes−ethyl acetate 19:1; **2l**, isohexanes−ethyl acetate 5:1.

Synthesis of *N,N*-dimethylbenzamide (Eq 2).[40] A mixture of 2.50 mmol (0.5650 g) of phenyl triflate **3f**; 0.075 mmol (16.8 mg) of $Pd(OAc)_2$; 0.330 mmol (183 mg) of DPPF; 7.5 mmol (0.64 g) of allylamine **4a**; 3.75 mmol (0.52 g) of K_2CO_3 and 10 mL of DMF was mixed in an oven-dried three-necked round-bottomed flask equipped with a reflux condenser and bubbled with carbon monoxide through a needle and rubber septum for 5 min before the reaction mixture was heated at 80 °C on oil bath with a continuous flow of carbon monoxide for 2 h. The reaction was purified as described under General Procedure for the Thermal Internal Arylation of *N,N*-Dimethylallylamine **4a**. Eluents for chromatography: isohexanes−ethyl acetate 4:1 to 1:1.

Competitive Phenylations of *N,N*-Dimethylamine 4a, 4-Methyl-1-pentene and Allyltrimethylsilane. The competitive experiments were performed with 1.00 mmol (0.226 g) of **3f**, 5.0 mmol of **4a**, and 5.0 mmol of allyltrimethylsilane or 4-methyl-1-pentene, 0.030 mmol (6.7 mg) of $Pd(OAc)_2$, 0.132 mmol (73.2 mg) of DPPF and 2.0 mmol (0.20 g) of Et_3N in 4 mL acetonitrile. The reactions were performed at 80 °C and the product ratios were analyzed by GC-MS integration and subsequently with ^1H NMR to confirm that the GC-MS response factors for the different products were comparable.

Thermal Internal Arylation of Allyl Alcohol and Allyl Ethyl ether (Scheme 2). A mixture of 2.50 mmol (0.565 g) of phenyl triflate **3f**; 0.075 mmol (16.8 mg) of $Pd(OAc)_2$; 0.330 mmol (183 mg) of DPPF; 7.5 mmol of allyl alcohol or allyl ethyl ether; 5 mmol (0.51 g) of K_2CO_3 and 10 mL of acetonitrile was heated at 80 °C on oil bath under nitrogen in oven-dried, heavy-walled and thin-necked Pyrex tubes, sealed with a Teflon stopcock. The reactions were completed after 20 h. The reactions were purified as described under General Procedure for the Thermal Internal Arylation of *N,N*-Dimethylallylamine **4a**. Eluents:, isohexanes−ethyl acetate 19:1.

3-*N,N*-Dimethylamino-2-(1-naphthyl)-1-propene (2g). Compound **2g** was isolated in 71% yield at 80 °C and 42% yield after microwave irradiation (5 min/15 W). The boiling point at bulb-to-bulb distillation was ∼110 °C at 8 mmHg. ^1H NMR (270 MHz, $CDCl_3$) δ 8.1 (m, 1H), 7.8 (m, 2H), 7.5 (m, 4H), 5.66 (m, 1H), 5.31 (m, 1H), 3.33 (s, 2H), 2.32 (s, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 145.3, 140.0, 133.8, 131.3, 128.4, 127.3, 125.7, 125.5, 125.2, 117.9, 66.5, 45.7. MS *m/z* (relative intensity 70 eV) 211 (M^+, 34), 165 (15), 152 (17), 58 (100). Anal. Calcd for $C_{15}H_{17}N$: C, 85.3; H, 8.11; N, 6.63. Found: C, 85.6; H, 7.9; N, 6.6.

3-Morpholino-2-phenyl-1-propene (2l). Compound **2l** was isolated in 56% yield at 80 °C. The boiling point at bulb-to-bulb distillation was ∼90 °C at 1 mmHg.^1H NMR (270 MHz, $CDCl_3$) δ 7.56−7.51 (m, 2H), 7.37−7.28 (m, 3H), 5.50 (d, J = 2 Hz, 1H), 5.25 (q, J = 1 Hz, 1H), 3.69 (m, 4H), 3.34 (d, J = 1 Hz, 2H), 2.48 (m, 4H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 143.6, 140.2, 128.1, 127.5, 126.2, 115.6, 67.1, 63.5, 53.5. MS *m/z* (relative intensity 70 eV) 203 (M^+, 9), 172 (2), 144 (7), 118 (23), 100 (100). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.8; H, 8.4; N, 6.9. Found: C, 76.9; H, 8.5; N, 6.7.

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Supporting Information Available: ^1H-, ^{13}C- and MS-spectra for all new compounds. Temperature profiles for two microwave heated reactions. This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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