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4-Aryl-2-quinolones through a Pseudo-Domino Heck/Buchwald–Hartwig Reaction in a Molten Tetrabutylammonium Acetate/Tetrabutylammonium Bromide Mixture

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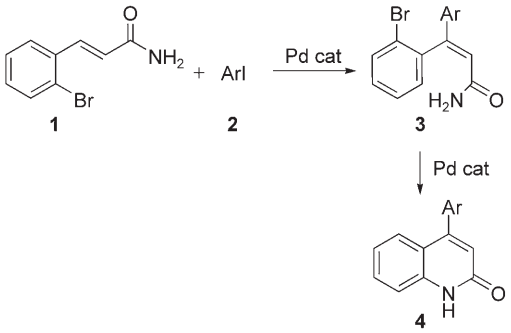
Abstract: 4-Aryl-2-quinolones can be prepared from readily available *o*-bromocinnamamide and aryl iodides using phosphine-free palladium(II) acetate as the precatalyst and a molten tetra(*n*-butyl)ammonium acetate/tetra(*n*-butyl)ammonium bromide mixture as the reaction medium. The reaction proceeds through a pseudo-domino process involving two mechanistically independent, sequential catalytic cycles: a Heck reaction followed by an intramolecular Buchwald–Hartwig C–N bond forming reaction.

Keywords: aryl iodides; cyclization; domino reactions; palladium

The construction of heterocyclic rings based upon the concept of the domino Heck reaction/cyclization process is a useful synthetic methodology.[1] We have developed this chemistry into new versatile and efficient procedures for the preparation of butyrolactones,[2] cardenolides,[3] butenolides,[4] quinolines,[5] and coumarins.[5,6] In all these processes, an α,β-unsaturated carbonyl compound bearing a nucleophile on the β substituent undergoes an initial palladium-catalyzed vinylic substitution followed, in some cases *in situ*, by an intramolecular nucleophilic attack of an oxygen or nitrogen nucleophile to the carbonyl group. Recent developments in the palladium-catalyzed *N*- and *O*-arylation process,[7] pioneered and extensively investigated by Buchwald[8] and Hartwig,[9] prompted us to explore a different strategy, in which the Heck reaction of an olefinic system, bearing an *ortho* C–Br bond on the β aryl substituent, could be followed by a palladium-catalyzed $C_{(aryl)}$-heteroatom bond forming reaction *in situ*.

In particular, we decided to develop a new approach to the *de novo* 2-quinolone system construction using the readily available 3-(*o*-bromophenyl)-acrylamide **1** as the building block according to the domino process[10] outlined in Scheme 1. The initial



Scheme 1.

Heck reaction should produce the vinylic substitution product **3** which, under the same conditions, should undergo an intramolecular palladium-catalyzed *N*-arylation to give the desired 2-quinolone product **4**.

Although palladium catalysis proved to be a powerful tool for the construction of heterocyclic rings,[11] very few examples of palladium-catalyzed synthesis of 2-quinolones have been reported. Internal alkynes have been recently described by Larock et al.[12] to give 2-quinolones *via* carbonylative annulation by *N*-substituted *o*-iodoanilines. Olefinic systems have also been used as precursors. (*Z*)-2-Acetamido-α-bromostyrene was converted into 2-quinolone *via* a carbonylation/cyclization process.[13] β-Substituted acrylic acid derivatives and methyl acrylate were used to prepare

2-quinolones through a Heck reaction/cyclization process with, respectively, *o*-iodoanilines[1] and *o*-bromonitrobenzenes.[14] The utility of the olefinic-based methods, however, appears to be severely limited.

On the other hand, the 2-quinolone motif is abundant in many biologically active compounds and this appears to justify efforts to develop new and versatile synthetic procedures. For example, 2-quinolone derivatives have been evaluated as inhibitors of HIV-1 reverse transcriptase,[15] gonadotropin-releasing hormone antagonists,[16] NMDA and AMPA antagonists,[17] anti-infectives,[18] antiviral and antihypertensive agents.[19] The 4-aryl-2-quinolone derivative tipifarnib exhibits anticancer activity.[20,21] 2-Quinolones are also useful synthetic intermediates. For example, they can be readily converted into 2-chloroquinoline derivatives[22] and quinoline 2-triflates[23] and then into 2-aminoquinoline derivatives. 2-Chloroquinolines[24] and quinoline 2-triflates[25] can also be involved in palladium-catalyzed reactions to afford a wide range of quinoline products.

Herein, we report the results of this study.

Initial attempts focused on exploring the feasibility of the domino process outlined in Scheme 1. Particularly, we decided to develop reaction conditions in which a single palladium-based catalytic system would share two mechanistically unrelated sequential catalytic cycles.[26,27] The successful execution of this type of domino processes – a palladium-catalyzed pseudo-domino (Pd-PDOM) *type I* process according to the definition given by Poli et al.[26f] – is not a trivial task. Possible and often unpredictable incompatibilities among the different catalytic cycles can in fact make this synthetically useful chemistry not viable. In the present case, it is also necessary to avoid the intermolecular *N*-arylation of the starting amide, a reaction which might be expected to be competitive.[28a–e] Furthermore, the formation of the *Z* isomer **3** in the Heck reaction is a vital prerequisite for the success of the cyclization step.[29]

p-Iodoanisole and **1** were used as the model system and the following reaction variables were examined: the bases, the additives, the nature of phosphine ligands, and the reaction temperature. Under a variety of conditions typical for the Heck reaction, using 5 mol% of $Pd(OAc)_2$ as the source of Pd(0), Et_3N (3 equivs.) as the base, PPh_3 (10 mol%) and DMF as the solvent at 100 °C the starting olefin was recovered in 80–90% yield. The use of the Herrmann catalyst[30] under the same conditions produced the vinylic substitution product **3a** in 58% yield along with minor amounts of **4a** (18%). The starting material was recovered in 18%. Increasing temperature to 120 °C gave **3a** in 38% yield and the starting olefin was recovered in 38% yield. Neither the vinylic substitution derivative nor the quinolone product was formed at 100–120 °C under the conditions developed by Buchwald et al. for the intramolecular aryl amidation[28g] (toluene, MOP[31] or Xantphos,[32] K_2CO_3). Attempts to combine some typical elements of the intramolecular *N*-arylation of amides with those of the vinylic substitution met with failure. For example, treatment of **1** with 1.5 equivs. of *p*-iodoanisole, 2 equivs. of Cs_2CO_3, 0.05 equivs. of $Pd(OAc)_2$, 0.05 equivs. of Xantphos in DMF at 100 °C for 48 h, led to the isolation of **3a** and **4a** in 40 and 11% yields, respectively. Omitting phosphine ligands led again to the formation of **3a** as the main reaction product under a variety of reaction conditions (Table 1, entries 1–6).

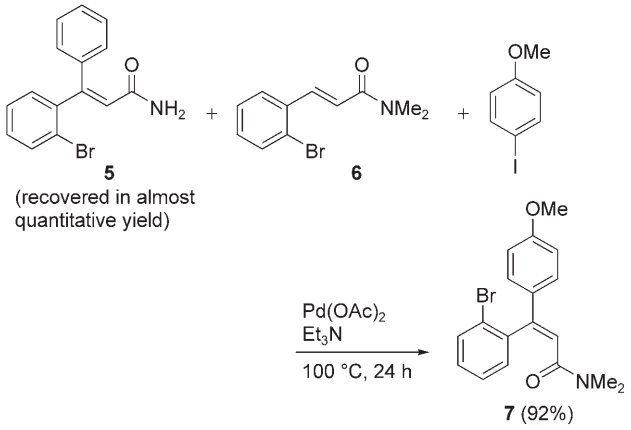
Noteworthy, although formation of *E/Z* mixtures has been reported in previous vinylic substitution reactions of β-substituted acrylamides,[29] only the Heck product containing the amide group on the same side of the carbon-carbon double bond as the preexisting β-substituent was formed, most probably as the result of a diastereoselective Heck reaction. The involve-

Table 1. Bases, additives and temperature in the palladium-catalyzed synthesis of **4a** from **1** and *p*-iodoanisole.[a]

Entry	Reaction conditions	°C/h	Yield [%] of **3a**[b]	Yield [%] of **4a**[b]
1	DMF,[c] Et_3N (3 equivs.)	100/48	56	-
2	DMF,[c] Et_3N (3 equivs.), LiCl (5 equivs.)	100/48	46	-
3	DMF,[c] Cs_2CO_3 (2 equivs.), LiCl (5 equivs.)	100/48	40	-
4	DMF,[c] Na_2CO_3 (2 equivs.), LiCl (5 equivs.)	100/48	40	-
5	DMF,[c] *n*-Bu_4NOAc (2 equivs.)	100/48	53	22
6	Et_3N (5 equivs.)	100/12	87	-
7	DMF,[c] *n*-Bu_4NOAc (2 equivs.)	120/48	12	33
8	*n*-Bu_4NOAc (1 equiv), *n*-Bu_4NBr (3 equivs.)	120/48	50	25
9	*n*-Bu_4NOAc (2 equivs.), *n*-Bu_4NBr (2 equivs.)	120/48	35	35
10	*n*-Bu_4NOAc (2.5 equivs.), *n*-Bu_4NBr (4 equivs.)	120/48	23	52
11	*n*-Bu_4NOAc (3 equivs.), *n*-Bu_4NBr (3 equivs.)	120/48	-	73

[a] Reactions were carried out on a 0.5 mmol scale under argon using 1 equiv. of **1**, 1.5 equivs. of *p*-iodoanisole, and 0.05 equivs. of $Pd(OAc)_2$.
[b] Yields are given for isolated products.
[c] 2 mL.

ment of an *E/Z* equilibrium following the *syn*-β-elimination step was ruled out on the basis of the following experiment. A pure sample of **5** (the stereoisomer of **3a**), prepared *via* the reaction of cinnamamide with *o*-iodobromobenzene, was subjected to the best conditions producing vinylic substitution products (Table 1, entry 6) in the presence of **6** (the *N,N*-dimethyl derivative was used to make separation of the reaction mixture easier) and *p*-iodoanisole (Scheme 2). The



Scheme 2.

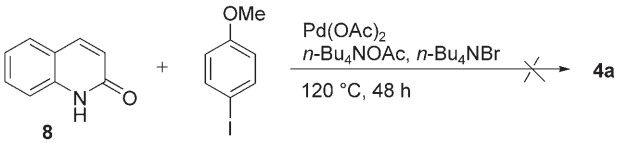
3,3-diarylacrylamide **7**, formed *via* the reaction of **6** with *p*-iodoanisole, was isolated in 92% yield. Compound **5** was recovered in almost quantitative yield and its stereochemistry was maintained, even on prolonging the reaction time to 24 h.

Only after switching to *n*-Bu_4NOAc as the base in DMF at 120 °C did the mixture contain predominantly the desired **4a** (Table 1, entry 7). Although the yield was unsatisfactory from a synthetic standpoint, the very high selectivity in favor of the intramolecular C–N bond forming reaction compared with the intermolecular reaction was rewarding. Indeed, formation of the *N*-arylation product generated *via* intermolecular palladium-catalyzed reaction of the amide group of **1** with *p*-iodoanisole, expected as a possible side-reaction, was observed only in trace amounts.

We next explored the use of a molten *n*-Bu_4NOAc/*n*-Bu_4NBr mixture as the reaction medium. This molten salt mixture was recently shown by us to be particularly suited for performing highly stereoselective Heck reactions on cinnamate esters[33] and domino Heck reaction/cyclization processes producing coumarins.[6] Initial attempts were discouraging since **3a** was still the main reaction product (Table 1, entry 8). However, the reaction outcome was found to depend on the *n*-Bu_4NOAc/*n*-Bu_4NBr molar ratio and, after some experimentation (the results of a couple of the runs we carried out are shown in Table 1, entries 9 and 10), we arrived at the optimal combination (3 equivs. of *n*-Bu_4NOAc and 3 equivs. of *n*-Bu_4NBr) which produced **4a** in 73% yield (Table 1, entry 11).

This result is particularly interesting because phosphine ligands are known to play a pivotal role in Buchwald–Hartwig *N*-arylation of amides[28] and, to the best of our knowledge, no examples of this type of chemistry have been reported so far with phosphine-free palladium catalysts. Most probably, under our conditions the reaction involves tetraalkylammonium-stabilized palladium nanoparticles[34] and this may have an influence on the reaction outcome. The intramolecular nature of the C–N bond forming process must also favor the reaction.

No evidence of the vinylic substitution intermediate **3a** was attained by monitoring the reaction mixture by TLC or HPLC. However, subjecting a pure sample of **3a** to the conditions shown in Table 1, entry 11 produced **4a** in 80% yield (no starting material was detected by HPLC when we monitored the reaction mixture after 45 min). In addition, the reaction under the same conditions of *p*-iodoanisole with the parent quinolone **8** – which might form *via* an *E/Z* isomerization of **1** followed by a cyclization step – did not afford the quinolone derivative **4a**[35] (Scheme 3).



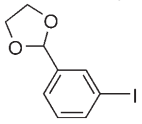
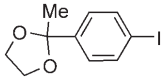
Scheme 3.

Compound **8** was recovered in almost quantitative yield. Taken together, these results support the view that **3a** is the precursor of **4a** and that a fast cyclization step follows the Heck reaction under these conditions.

We have also repeated the experiment described in Scheme 2 using the reaction conditions shown in Table 1 entry 11. The 3,3-diarylacrylamide **7** was isolated in 87% yield, compound **5** was recovered in 70% yield and quinolone **4n** was obtained in 15% yield (no evidence of its stereoisomer **3a** was obtained). This result suggests that under these conditions an *E/Z* isomerization process might follow the vinylic substitution step.

The best conditions found with the model reaction [*n*-Bu_4NOAc (3 equivs.), *n*-Bu_4NBr (3 equivs.), $Pd(OAc)_2$ (0.05 equivs.), 120 °C] were then used when the pseudo-domino reaction was extended to other aryl iodides in order to examine the scope and limitations of this process. The results are summarized in Table 2. 4-Aryl-2-quinolones were isolated in acceptable to good yields in many cases with a variety of aryl iodides including those with ether, amide, and ester functionalities. Unfortunately, *m*-iodobenzaldehyde

Table 2. Synthesis of 2-quinolones **4** through a domino Heck/Buchwald–Hartwig process.[a]

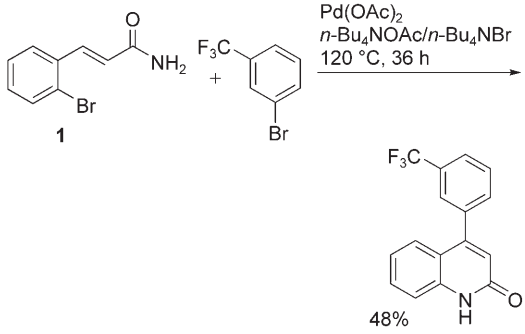
Entry	Aryl iodide **2**		*t* [h]	Yield [%] of **4**[b]	
1	*p*-MeO-C_6H_4-I	**2a**	24	73	**4a**
2	*p*-Me-C_6H_4-I	**2b**	36	65	**4b**
3	*m*-MeO-C_6H_4-I	**2c**	36	65	**4c**
4	*m*-F-C_6H_4-I	**2d**	36	62	**4d**
5	*m*-CF_3-C_6H_4-I	**2e**	36	50	**4e**
6	*p*-CO_2Et-C_6H_4-I	**2f**	36	40	**4f**
7	*o*-F-C_6H_4-I	**2g**	48	40	**4g**
8	*m*-HCO-C_6H_4-I	**2h**	48	20[c]	**4h**
9		**2i**	24	60	**4i**
10	*p*-MeCO-C_6H_4-I	**2j**	48	-	**4j**
11		**2k**	24	80	**4k**
12	*p*-MeCON(Me)-C_6H_4-I	**2l**	48	65	**4l**
13	*m*-MeCON(Me)-C_6H_4-I	**2m**	48	54	**4m**
14	PhI	**2n**	24	75	**4n**

[a] Unless otherwise stated, reactions were carried out on a 0.5 mmol scale at 120 °C under argon using 1 equiv of **1**, 1.5 equivs. of **2**, 3 equivs. of *n*-Bu_4NOAc, 3 equivs. of *n*-Bu_4NBr and 0.05 equivs. of $Pd(OAc)_2$.
[b] Yields are given for isolated products.
[c] Calculated by NMR analysis.

gave the corresponding 2-quinolone product in low yield (Table 2, entry 8) and when *p*-iodoacetophenone was subjected to our standard conditions the corresponding quinolone derivative was not obtained at all (Table 2, entry 10). However, appropriately protected aldehydic and ketonic aryl iodides afforded the desired products in good to high yield. (Table 2, entries 9 and 11).

Attempts to extend the reaction to aryl bromides were also made. However, aryl bromides such as *N,N*-dimethyl-*p*-bromoaniline, *p*-bromoanisole, *o*-fluorobromobenzene, and *p*-bromobenzonitrile failed to give quinolone products, generating instead complex reaction mixtures that we have not further investigated. Very likely, oxidative addition of the aryl bromide fragment of **1** to Pd(0) may be a significant competitive reaction in these cases. Nevertheless, *m*-trifluoromethylbromobenzene produced the corresponding 2-quinolone derivative in satisfactory yield (Scheme 4), comparable to that obtained with *m*-trifluoromethyliodobenzene (Table 2, entry 5).

To conclude, we have developed a straightforward new approach to 4-aryl-2-quinolones from readily available starting materials using $Pd(OAc)_2$ as the precatalyst and a molten *n*-Bu_4NOAc/*n*-Bu_4NBr mixture as the reaction medium. The phosphine-free catalyst system works well even in the intramolecular C–N bond forming step. Although isolated yields are moderate to good, they refer to a multistep palladium-catalyzed pseudo-domino process involving two



Scheme 4.

mechanistically independent, sequential catalytic cycles. On the whole, the present procedure may represent a convenient alternative to the known, olefinic-based[1,13,14] palladium-catalyzed syntheses of this class of compounds.

Experimental Section

Melting points were determined with a Büchi B-545 apparatus and are uncorrected. The acetal **2i** and the ketal **2k** were prepared according to standard methods from the corresponding carbonyl derivative. Compounds **2l** and **2m** were prepared *via* *N*-methylation of the corresponding acetamides. All the other reagents, catalysts, and solvents are

commercially available and were used as purchased, without further purification. Reaction products were purified on axially compressed columns, packed with SiO_2 25–40 μm (Macherey–Nagel), connected to a Jasco RI-031 Plus solvent delivery system and to a Jasco PU-2087 Plus refractive index detector, and eluting with *n*-hexane/ethyl acetate mixtures. ^{1}H NMR (400 MHz), ^{13}C NMR (100.6 MHz) and ^{19}F NMR (376.5 MHz) spectra were recorded with a Bruker Avance 400 spectrometer. IR spectra were recorded with a Jasco FT/IR-430 spectrometer. Mass spectra were recorded with a Shimadzu GCMS-QP2010S.

Synthesis of 3-(*o*-Bromophenyl)acrylamide (1)

To a stirred solution of acrylamide (74.5 mg, 1.05 mmol), 1-bromo-2-iodobenzene (128 μL, 1 mmol) and Et_3N (418 μL, 3 mmol) in CH_3CN (1 mL), Hermann catalyst (9.36 mg, 0.01 mmol) was added. The reaction mixture was stirred for 12 h at 100 °C. After cooling, the reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; 40/60 v/v *n*-hexane/ethyl acetate) to give **1**; yield: 180 mg; mp 171–173 °C; IR (KBr): ν = 3340, 3153, 1671 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 7.70–7.63 (m, 4H), 7.44 (m, 1H), 7.32 (m, 1H), 7.24 (bs, 1H), 6.63 (d, J = 15.64 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ = 166.6, 137.7, 135.0, 133.7, 131.6, 128.8, 128.2, 126.0, 124.7; MS: *m/z* (relative intensity) = 226.90 (4.25 %), 225.95(0.78 %), 224.90 (M^+, 4.29 %),146.10 (100.00 %), 102.10 (34.45 %), 44 (41.00 %).

Typical Procedure for the Preparation of 4-Aryl-2-quinolones (4)

To a mixture of **1** (0.113 g, 0.50 mmol), *p*-iodoanisole (0.093 mL, 0.75 mmol), *n*-BuN_4OAc (0.452 g, 1.5 mmol) and *n*-BuN_4Br (0.483 g, 1.5 mmol), $Pd(OAc)_2$ (0.006 g, 0.025 mmol) was added. The mixture was stirred for 48 h at 120 °C. After cooling, the reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; 25/75 v/v *n*-hexane/ethyl acetate) to give **4a**; yield: 0.092 g (73 %); mp 196–198 °C; IR (KBr): ν = 3131, 1672 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 11.82 (bs, 1H), 7.51 (t, J = 8 Hz, 1H), 7.44–7.36 (m, 4H), 7.13–7.07 (m, 3H), 6.35 (s, 1H), 3.82 (s, 3H); ^{13}C NMR (DMSO-d_6): δ = 161.3, 159.6, 151.1, 139.3, 130.4, 130.1, 128.8, 126.2, 121.7, 120.9, 118.5, 115.8, 114.1, 55.2; MS: *m/z* (relative intensity) = 251 (M^+, 100 %), 252 (40 %), 236 (30 %) 208 (50 %).

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References

[1] N. A. Cortese, C. B. Ziegler Jr., B. J. Hrnjez, R. F. Heck, *J. Org. Chem.* **1978**, *43*, 2952.
[2] A. Arcadi, E. Bernocchi, S. Cacchi, F. Marinelli, *Tetrahedron* **1991**, *47*, 1525.
[3] A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, P. Pace, *Tetrahedron* **1996**, *52*, 6983.
[4] S. Cacchi, P. G. Ciattini, E. Morera, P. Pace, *Synlett* **1996**, 545.
[5] A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, P. Pace, *Synlett* **1996**, 568.
[6] G. Battistuzzi, S. Cacchi, I. De Salve, G. Fabrizi, L. M. Parisi, *Adv. Synth. Catal.* **2005**, *347*, 308.
[7] For some reviews, see: a) J. F. Hartwig, *Synlett* **1997**, 329; b) D. Baranano, G. Mann, J. F. Hartwig, *Curr. Org. Chem.* **1997**, *1*, 287; c) J. F. Hartwig, *Acc. Chem. Res.* **1998**, *31*, 852; d) J. P. Wolfe, S. Wagaw, J.-F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805; e) J. F. Hartwig, *Angew. Chem. Int. Edit.* **1998**, *37*, 2046; f) J. F. Hartwig, *Pure Appl. Chem.* **1999**, *71*, 1417; g) B. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, *576*, 125; h) D. Prim, J. M. Campagne, D. Joseph, B. Andrioletti, *Tetrahedron* **2002**, *58*, 2041; i) B. Shlummer, U. Sholz *Adv. Synth. Catal.* **2004**, *346*, 1599.
[8] A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem. Int. Ed.* **1995**, *34*, 1348.
[9] J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609.
[10] For a general review on domino processes, see: L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115.
[11] J. J. Li, G. W. Gribble, *Palladium in Heterocyclic Chemistry*, Pergamon, New York, **2000**.
[12] D. V. Kadnikov, R. C. Larock, *J. Org. Chem.* **2004**, *69*, 6772.
[13] M. Mori, K. Chiba, N. Ohta, Y. Ban, *Heterocycles* **1979**, *13*, 329.
[14] C. W. Holzapfel, C. Dwyer, *Heterocycles* **1998**, *48*, 215.
[15] G. A. Freeman, C. W. Andrews III, A. L. Hopkins, G. S. Lowell, L. T. Schaller, J. R. Cowan, S. S. Gonzales, G. W. Koszalka, R. J. Hazen, L. R. Boone, G. Rob, R. G. Ferris, K. L. Creech, G. B. Roberts, S. A. Short, K. Weaver, J. David, D. J. Reynolds, J. Milton, J. Ren, D. I. Stuart, D. K. Stammers, J. H. Chan, *J. Med. Chem.* **2004**, *47*, 5923.
[16] M. Goulet, E. E. Allen, R. J. DeVita, J. Jiang, T. F. Walsh, J. R. Young, M. J. Wyvratt, Jr., R. B. Toupence, F. Ujjainwalla, *World Patent* WO 9744339, **1997**; *Chem. Abstr.* **1997**, *128*, 48236.
[17] J. J. Kulagowski, M. Rowley, P. D. Leeson, I. M. Mawer, *European Patent* EP 481676, **1992**; *Chem. Abstr.* **1992**, *117*, 131086.
[18] D. Dhanak, A. C. Kaura, A. Shaw, *World Patent* WO 2001085172, **2001**; *Chem. Abstr.* **2001**, *135*, 371990.
[19] A. Afonso, J. Weinstein, M. J. Gentles, *World Patent* WO 9204326, **1992**; *Chem. Abstr.* **1992**, *117*, 26358.
[20] a) P. Norman, *Curr. Opin. Invest. Drugs* **2002**, *3*, 313; b) M. Venet, D. End, P. Angibaud *Curr. Top. Med. Chem.* **2003**, *3*, 1095; c) E. van Cutsem, H. van de Velde, P. Karasek, H. Oettle, W. L. Vervenne, A. Szawlowski, P. Schoffski, S. Post, C. Verslype, H. Neumann, H. Safran, Y. Humblet, J. P. Ruixo, Y. Ma, D. von Hoff, *J. Clin. Oncol.* **2004**, *22*, 1430.

[21] For a recent study using tipifarnib as a template, see: Q. Li, K. W. Woods, W. Wang, N.-H. Lin, A. Claiborne, W.-z. Gu, J. Cohen, V. S. Stoll, C. Hutchins, D. Frost, S. H. Rosenberg, H. L. Sham, *Bioorg. Med. Chem. Lett.* **2005**, *15,* 2033.
[22] M. Anzini, A. Cappelli, S. Vomero, *J. Heterocycl. Chem.* **1991**, *28*, 1809.
[23] S. Cacchi, A. Carangio, G. Fabrizi, L. Moro, P. Pace, *Synlett* **1997**, 1400.
[24] A. Godard, J. M. Fourquez, R. Tamion, F. Marsais, G. Quéguiner, *Synlett* **1994**, 235.
[25] A. Arcadi, S. Cacchi, G. Fabrizi, F. Manna, P. Pace, *Synlett* **1998**, 446.
[26] For a review on palladium-catalyzed domino processes, see: G. Poli, G. Giambastiani, A. Heumann, *Tetrahedron* **2000**, *56*, 5959.
[27] For some recent leading examples of palladium-catalyzed processes featuring mechanistically independent, sequential catalytic cycles, see the following. Heck/Tsuji–Trost (and *vice versa*) processes: a) J.-M. Gaudijn, *Tetrahedron Lett.* **1991**, *32*, 6113; b) D. Flubacher, G. Helmchen, *Tetrahedron Lett.* **1999**, *40*, 3867; c) I. Shimizu, Y. Lee, Y. Fujiwara, *Synlett* **2000**, 1285; d) L. F. Tietze, G. Nordmann, *Eur. J. Org. Chem.* **2001**, 3247; e) G. Poli, G. Giambastaini, B Pacini, *Tetrahedron Lett.* **2001**, *42*, 5179; f) G. Poli, G. Giambastiani, *J. Org. Chem.* **2002**, *67*, 9456; g) S. Lemiare, G. Prestat, G. Giambastiani, D. Madec, B. Pacini, G. Poli, *J. Organomet. Chem.* **2003**, *687*, 291; Heck reaction/reductive N-heteroannulation: h) B. C. Sőderberg, S. R. Rector, S. N. O'Neil, *Tetrahedron Lett.* **1999**, *40*, 3657; Tsuji–Trost reaction/Pauson–Khand type reaction: i) N. Jeong, S. D. Seo, J. Y. Shin, *J. Am. Chem. Soc.* **2000**, *122*, 10220; Suzuki/Buchwald-Hartwig processes: j) M. Watanabe, T. Yamamoto, M. Nishiyama, *Angew. Chem. Int. Ed.* **2000**, *39*, 2501; k) S. Thielges, E. Meddah, P. Bisseret, J. Eustache, *Tetrahedron Lett.* **2004**, *45*, 907.
[28] For intermolecular *N*-arylations of amides, see for example: a) W. Shakespeare, *Tetrahedron Lett.* **1999**, *40*, 2035; b) S. D. Edmondson, A. Mastracchio, E. R. Parmee, *Org. Lett.* **2000**, *2*, 1109; c) J. Yin, S. L. Buchwald, *Org. Lett.* **2000**, *2*, 1101; d) P. J. Manley, M. T. Bilodeau, *Org. Lett.* **2004**, *6*, 2433; e) A. S. Dallas, K. V. Gothelf, *J. Org. Chem.* **2005**, *70*, 3321; for intramolecular *N*-arylations of amides, see for example: f) J. P. Wolfe, R. A. Rennels, S. L. Buchwald, *Tetrahedron* **1996**, 52, 7525; g) B. H. Yang, S. L. Buchwald, *Org. Lett.* **1999**, *1*, 35.
[29] Previous studies on the Heck reaction of β-arylacrylamides reported the formation of mixtures of diastereoisomers; see, for example: L. Botella, C. Nájera, *J. Org. Chem.* **2005**, *70*, 4360.
[30] W. A. Herrmann, C. Brossmer, K. Öfele, C.-P. Reisenger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem. Int. Ed.* **1995**, *34*, 1844.
[31] Y. Uozumi, T. Hayashi, *J. Am. Chem. Soc.* **1991**. *113*; 9887.
[32] a) M. Kranenburg, Y. E. M. van der Burgt, P. C. J. Kramer, P. W. N. M. van Leeuwen, K. Goubitz, J. Fraanje, *Organometallics* **1995**, *14*, 3081; for recent reviews on the use of Xantphos ligands in transition metal-catalyzed reactions, see: b) P. W. N. M. van Leeuwen, P. C. J. Kramer, J. N. H. Reek, P. Dierkes, *Chem. Rev.* **2000**, *100*, 2741; c) P. C. J. Kramer, P. W. N. M. van Leeuwen, J. N. H. Reek, *Acc. Chem. Res.* **2001**, *34*, 895.
[33] G. Battistuzzi, S. Cacchi, G. Fabrizi, *Synlett* **2002**, 439.
[34] For some leading references on tetraalkylammonium-stabilized palladium nanoparticles, see: a) M. T. Reetz, R. Breinbauer, K. Wanninger, *Tetrahedron Lett.* **1996**, *37*, 4499; b) M. Beller, H. Fischer, K. Kühlein, C.-P. Reisinger, W. A. Herrmann, *J. Organomet. Chem.* **1996**, *520,* 257; c) M. T. Reetz, M. Maase, *Adv. Mater.* **1999**, *11*, 773; d) M. T. Reetz, E. Westermann, *Angew. Chem. Int. Ed.* **2000**, *39*, 165; e) V. Caló, A. Nacci, A. Monopoli, A. Detomaso, P. Iliade, *Organometallics* **2003**, *22*, 4193; f) V. Caló, A. Nacci, A. Monopoli, S. Laera, N. Cioffi, *J. Org. Chem.* **2003**, *68*, 2929; for a recent review on transition-metal nanoparticles, see: g) M. Moreno-Mañas, R. Pleixats, *Acc. Chem. Res.* **2003**, *36*, 638.
[35] For the formation of vinylic substitution products from cyclic derivatives, see for example: a) J. P. Genet, E. Blart, M. Savignac, *Synlett* **1992**, 715; b) S. Cacchi, G. Fabrizi, F. Gasparrini, P. Pace, C. Villani, *Synlett* **2000**, 650.

