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Cascade Palladium-Catalyzed Alkenyl Aminocarbonylation/ Intramolecular Aryl Amidation: An Annulative Synthesis of 2-Quinolones

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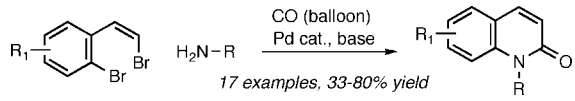
ABSTRACT



Palladium-catalyzed intermolecular aminocarbonylation/intramolecular amidation cascade sequences can be used to convert a range of 2-(2-haloalkenyl)aryl halide substrates efficiently and selectively to the corresponding 2-quinolones. Delaying the introduction of the CO atmosphere allows an amination/carbonylation sequence and the preparation of an isoquinolone.

The development of efficient palladium-[1] and, more recently, copper-catalyzed[2] methods for the amination of aryl halides has revolutionized the synthesis of aromatic C−N bonds. These reactions have been exploited in the synthesis in a number of heterocyclic systems,[1−3] most often when combined with a second transformation.[4] Less common are processes in which a catalytic amination reaction is combined with a second metal-catalyzed step to construct the heterocycle core.[5] Given the variety of C−C and C−X bond forming reactions that are catalyzed by palladium,[6] such approaches have the potential to deliver powerful new routes to heteocyclic structures.

We recently demonstrated that 2-(2-haloalkenyl)aryl halides can undergo two sequential palladium-catalyzed amination reactions, the first intermolecular, the second intramolecular, to provide efficient routes to a range of *N*-functionalized indoles (**1** → **2**, Scheme 1).[7] We reasoned that if a catalyst capable of promoting both amination and

(1) Reviews: (a) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, p 1051. (b) Jiang, L.; Buchwald, S. L. In *Metal-Catalysed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; p 699.

(2) Reviews: (a) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3096. (b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

(3) Selected recent examples: (a) Nodwell, M.; Riffell, J. L.; Roberge, M.; Andersen, R. J. *Org. Lett.* **2008**, *10*, 1051. (b) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3311. (c) Venkatesh, C.; Sundaram, G. S. M.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2006**, *71*, 1280. (d) Wrona, I. E.; Gabarda, A. E.; Evano, G.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 15026. (e) van den Hoogenband, A.; den Hartog, J. A. J.; Lange, J. H. M.; Terpstra, J. W. *Tetrahedron Lett.* **2004**, *45*, 8535.

(4) Selected examples: (a) Huang, J.; Chen, Y.; King, A. O.; Dilmeghani, M.; Larsen, R. D.; Faul, M. M. *Org. Lett.* **2008**, *10*, 2609. (b) Minatti, A.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2721. (c) Zheng, N.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 4749. (d) Zou, B.; Yuan, Q.; Ma, D. *Org. Lett.* **2007**, *9*, 4291. (e) Martín, R.; Rodríguez Rivero, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079. (f) Willis, M. C.; Snell, R. H.; Fletcher, A. J.; Woodward, R. L. *Org. Lett.* **2006**, *8*, 5089. (g) Scott, J. P. *Synlett* **2006**, 2083. (h) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2004**, *6*, 2433.

(5) Selected examples: (a) Viirre, R. D.; Evindar, G.; Batey, R. A. *J. Org. Chem.* **2008**, *73*, 3452. (b) Jensen, T.; Pedersen, H.; Bang-Andersen, B.; Madsen, R.; Jørgensen, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 888. (c) Battistuzzi, G.; Bernini, R.; Cacchi, S.; Salve, I. D.; Fabrizi, G. *Adv. Synth. Catal.* **2007**, *349*, 297. (d) Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett.* **2007**, *9*, 5255. (e) Loones, K. T. J.; Maes, B. U. W.; Meyers, C.; Deruytter, J. *J. Org. Chem.* **2006**, *71*, 260. (f) Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2005**, *7*, 3549.

(6) (a) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, 2nd ed.; Wiley: Chichester, 2004. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley-Interscience: New York, 2002.

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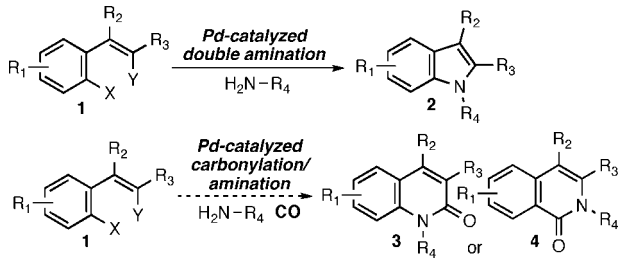
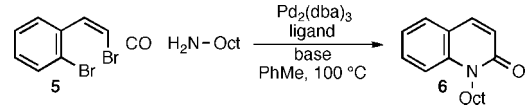
Scheme 1. Pd-Catalyzed Indole, Quinolone, and Isoquinolone Synthesis



carbonylation processes could be identified, then combination of the same precursors with an *N*-nucleophile under an atmosphere of carbon monoxide should allow access to the corresponding quinolone or isoquinolone derivatives (**1** → **3** or **4**, Scheme 1).[8] In this paper, we detail the realization of this goal, with an efficient and selective synthesis of 2-quinolones from 2-(2-haloalkenyl)aryl halides. We also show that using modified reaction conditions allows the same substrates to deliver an isoquinolone.

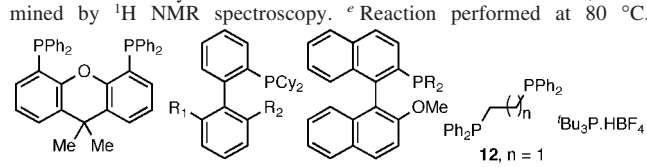
Both quinolones and isoquinolones are important heterocycles, featuring in a number of natural products and designed medicinal agents, and also serve as useful precursors to the corresponding quinoline and isoquinolines, respectively.[9] The ability to access both systems from a single precursor was an attractive prospect. However, for synthetic utility, it was important that reactions selective for the specific isomers be achieved. Which isomer was obtained would be dependent on the site of initial reaction—aryl halide versus alkenyl halide—and on which of the two catalytic reactions occurred first—amination or carbonylation. Based on our own earlier studies on indole synthesis using the same class of substrates,[7] and on related literature examples,[10] we expected the alkenyl halide to be the site of first reaction. Literature precedent suggested that carbonylation should be the faster of the two processes.[6b,11] These two predictions would lead to the formation of 2-quinolones from the 2-(2-haloalkenyl)aryl halide substrates. To test this hypothesis, we explored the coupling of dibromo styrene **5** and octylamine under a balloon pressure of carbon monoxide (Table 1). Guided by recent aminocarbonylation examples, we evaluated a variety of phosphines in combination with $Pd_2(dba)_3$ using Cs_2CO_3 as base.[11]

Table 1. Reaction Evaluation for the Formation of Quinolone **6**[a]



entry	base	ligand	yield[b] (%)
1	Cs_2CO_3	**7**	48
2	Cs_2CO_3	**8**	62
3	Cs_2CO_3	**9**	61
4	Cs_2CO_3	**10**	53
5	Cs_2CO_3	**11**	77
6	Cs_2CO_3	**12**	22
7	Cs_2CO_3	**13**	74
8	Cs_2CO_3	**14**	47
9	Cs_2CO_3	**15**	66
10	Na_2CO_3	**13**	<5
11	K_3PO_4	**13**	<5
12	NaO^{t}Bu	**13**	0
13[c]	Cs_2CO_3	**13**	12[d]
14[e]	Cs_2CO_3	**13**	14[d]

[a] Reaction conditions: dibromide (1.0 equiv), octylamine (2.0 equiv), $Pd_2(dba)_3$ (3 mol %), ligand (6 mol %), base (3.0 equiv), CO (balloon pressure), toluene, 100 °C, 16 h. Alkene used as a 12.1 mixture of *Z*/*E* isomers. [b] Isolated yields. [c] Dioxane used as solvent. [d] Conversion, determined by ^{1}H NMR spectroscopy. [e] Reaction performed at 80 °C.



7

8, $R_1 = R_2 = OMe$
9, $R_1 = NMe_2$, $R_2 = H$

10, R = Ph
11, R = ^{i}Pr

12, n = 1
13, n = 2
14, n = 3

15

Pleasingly, a number of structurally varied ligands delivered reasonable yields of the expected quinolone product **6** (entries 1−9). For example, the ^{i}Pr-phosphine derivative of MOP (**11**), the simple diphosphine dppp (**13**), and the bulky electron-rich monodentate phosphine P^{t}Bu$_3$ (**15**) all delivered >65% yields of *N*-octylquinolone. Formation of the corresponding isoquinolone was not observed. Use of the alternative bases Na_2CO_3, K_3PO_4, or NaO^{t}Bu, in combination with the ligand dppp (**13**), resulted in inefficient reactions (entries 10−12). Finally, exchanging the solvent to dioxane (from toluene), or performing the reactions at 80 °C instead of 100 °C, also resulted in poor yields of product (entries 13 and 14).

(7) (a) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403. (b) Willis, M. C.; Brace, G. N.; Findlay, T. J. K.; Holmes, I. P. *Adv. Synth. Catal.* **2006**, *348*, 851. (c) Fletcher, A. J.; Bax, M. N.; Willis, M. C. *Chem. Commun.* **2007**, 4764.

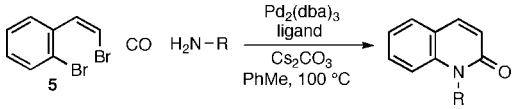
(8) For examples of carbonylation used in combination with alternative palladium-catalyzed reactions, see: (a) Worlikar, S. A.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 7175. (b) Chouhan, G.; Alper, H. *Org. Lett.* **2008**, *10*, 4987. (c) Zheng, H.; Alper, H. *Org. Lett.* **2008**, *10*, 4903. (d) Tang, S.; Yu, Q.-F.; Peng, P.; Li, J.-H.; Zhong, P.; Tang, R.-Y. *Org. Lett.* **2007**, *9*, 3413. (e) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 6772. (f) Kaliinin, V. N.; Shostakovsky, M. V.; Poonomaryov, A. B. *Tetrahedron Lett.* **1992**, *33*, 373. (g) Mori, M.; Chiba, K.; Ohta, N.; Ban, Y. *Heterocycles* **1979**, *13*, 329.

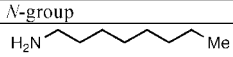
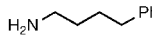
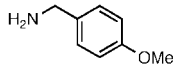
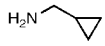
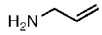
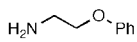
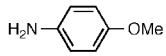
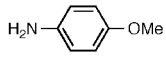
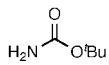
(9) (a) González, M. C.; Zafia-Polo, M. C.; Blázquez, M. A.; Serrano, A.; Cortes, D. *J. Nat. Prod.* **1997**, *60*, 108. (b) Chen, C.-Y.; Chang, F.-R.; Pan, W.-B.; Wu, Y.-C. *Phytochemistry* **2001**, *56*, 753. (c) Ruchelman, A. L.; Houghton, P. J.; Zhou, N.; Liu, A.; Liu, L. F.; LaVoie, E. J. *J. Med. Chem.* **2005**, *48*, 792. (d) Nagarajan, M.; Moreell, A.; Fort, B. C.; Rae Meckley, M.; Anthony, S.; Kohlhagen, G.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2004**, *47*, 5651. (e) Wang, S.-W.; Pan, S.-L.; Huang, Y.-C.; Guh, J.-H.; Chiang, P.-C.; Hunag, D.-Y.; Kuo, S.-C.; Lee, K.-H.; Teng, C.-M. *Mol. Cancer Ther.* **2008**, *7*, 350.

(10) Barluenga, J.; Fernández, M. A.; Aznar, F.; Valdés, C. *Chem.—Eur. J.* **2004**, *10*, 494.

(11) Examples of palladium catalyzed aminocarbonylation: (a) Deagostino, A.; Larini, P.; Occhiato, E. G.; Pizzuto, L.; Prandi, C.; Venturello, P. *J. Org. Chem.* **2008**, *73*, 1941. (b) Doi, T.; Kamioka, S.; Shimazu, S.; Takahashi, T. *Org. Lett.* **2008**, *10*, 817. (c) Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8460. (d) Martinelli, J. R.; Freckmann, D. M. M.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 4843. (e) Trost, B. M.; Ameriks, M. A. *Org. Lett.* **2004**, *6*, 1745.

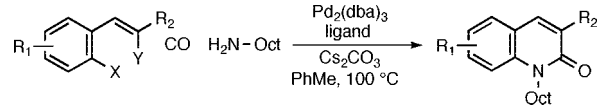
Table 2. Variation of the *N*-Nucleophile[a]

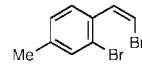
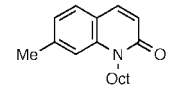
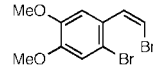
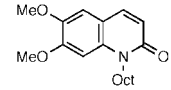
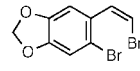
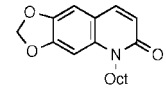
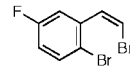
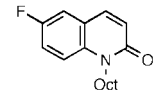
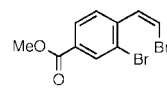
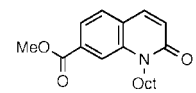
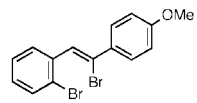
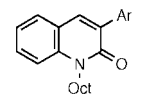
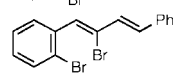
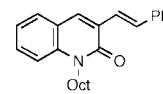
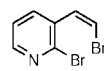
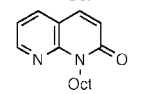


entry	*N*-group	ligand	yield (%)[b]
1		**11**	77
2		**11**	68
3		**11**	72
4		**13**	80
5		**15**	56
6[c]		**15**	74
7[d]		**13**	77
8		**7**	33
9[e]		**7**	65
10		**11**	0

[a] Reaction conditions: dibromide (1.0 equiv), *N*-nucleophile (2.0 equiv), $Pd_2(dba)_3$ (3 mol %), ligand (6 mol %), Cs_2CO_3 (3.0 equiv), CO (balloon pressure), toluene, 100 °C, 16 h. Alkene used as a 12.1 mixture of *Z*:*E* isomers. [b] Isolated yields. [c] 3.0 equiv of amine used. Heated at 50 °C for 2 h and then 100 °C for 16 h. [d] CO balloon removed after 3 h, purged with N_2, and heated at 100 °C for a further 16 h. [e] Reaction performed in two stages with isolation of amide intermediate. See main text and the Supporting Information for further details.

Table 3. Variation of Dibromide Alkenylarenes[a]



entry	substrate	(*Z*:*E*)	ligand	product	yield (%)[b]
1		9:1	**11**		66
2		11:1	**11**		79
3		14:1	**13**		69
4		14:1	**13**		74
5		12:1	**13**		65
6		>15:1	**15**		76
7		>15:1	**15**		71
8		>15:1	**13**		73

[a] Reaction conditions: (i) dibromide (1.0 equiv), octylamine (2.0 equiv), $Pd_2(dba)_3$ (3 mol %), ligand (6 mol %), Cs_2CO_3 (3.0 equiv), CO (balloon pressure), toluene, 100 °C, 3 h; (ii) purge with N_2, 100 °C, 16 h. [b] Isolated yields.

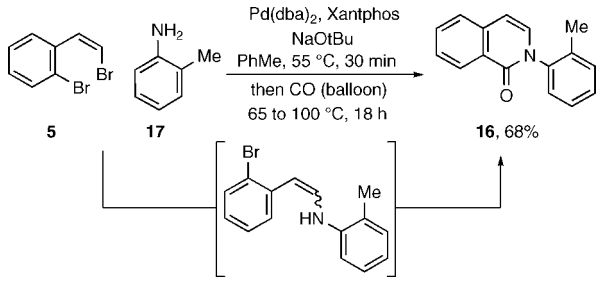
We next explored the variety of *N*-nucleophiles that could be incorporated in the process. In all examples, Cs_2CO_3 was used as base, along with $Pd_2(dba)_3$ as the Pd source. However, some variation of the ligand was used to achieve optimum yields. The three simple alkyl amines, together with *p*-methoxybenzylamine, used in Table 2, entries 1−4, all delivered the expected quinolones in good yield. The same procedure allowed access to a cyclopropylmethyl-substituted quinolone by simply employing cyclopropylmethylamine as the nucleophile (entry 5). Despite its volatility, allylamine could also be successfully introduced; the reaction was performed at the lower temperature of 50 °C for 2 h before heating at 100 °C (entry 6). The use of *O*-phenylethanolamine initially proved problematic, with only low yields of product being obtained with a variety of ligands. A convenient solution was to start the reaction using the standard conditions and then remove the CO atmosphere after 3 h had elapsed. Using this protocol, the expected quinolone was isolated in 77% yield (entry 7). *p*-Anisidine was also a problematic substrate; reactions under the standard conditions, using Xantphos as ligand, delivered only 33% of the *N*-arylquinolone (entry 8). Closer inspection of the products of these reactions showed that efficient conversion to the intermediate amide was being achieved; however, the final ring closure to deliver the quinolone was extremely sluggish. Removing the CO atmosphere at an intermediate time, as used in entry 6, failed to improve the process. Access to the *N*-aryl product could be achieved. However, it required a discrete two-step process involving isolation of the intermediate *N*-arylamide, and then resubjection of the amide to ring-closure conditions. Xantphos was employed as the ligand for both steps of the process and allowed the quinolone to be isolated in 65% yield for the two steps (entry 9).[12] The final entry demonstrates that carbamate nucleophiles could not be successfully employed.

Table 3 presents the scope of the process with respect to variation of the dihalide substrates; *N*-octylamine was used as the coupling partner in all cases and to achieve the most coherent results the reactions were all performed with the CO atmosphere being removed after 3 h. Entries 1−3 establish that a range of electron-donating substituents can be tolerated on the aryl ring, while entries 4 and 5 demonstrate that both inductive and resonance electron-withdrawing groups can also be introduced. Entries 6 and 7 establish the successful incorporation of alkenyl substitution. The final entry illustrates the use of a pyridyl substrate to generate the corresponding azaquinolone product in good yield.

Having established that a variety of 2-(2-haloalkenyl)aryl halides can be selectively and efficiently converted to

(12) See the Supporting Information for further details.

Scheme 2. Pd-Catalyzed Isoquinolone Synthesis



quinolones, we turned our attention to transforming the same substrates into the corresponding isoquinolones. Although it was not possible to access isoquinolones in a cascade sequence analogous to the quinolone synthesis, variation of the order of reagent addition provided a successful route. For example, *N*-arylisoquinolone **16** could be prepared using the two-step one-pot procedure shown in Scheme 2. Dibromo styrene **5** and *o*-Me-aniline (**17**) were combined using a Xantphos-derived catalyst and NaO^{t}Bu as base at 55 °C under an N_2 atmosphere to generate the corresponding *N*-arylenamine.[13] After 30 min reaction time, the vessel was opened to a CO atmosphere and the temperature increased to 100 °C, triggering carbonylation of the aryl bromide, followed by ring closure, to deliver the isoquinolone in 68% yield. A limitation of this approach is the requirement to employ a sterically demanding *N*-nucleophile, as the use of less hindered coupling partners results in competitive indole formation.[14]

In summary, we have demonstrated that a number of Pd catalysts can be used to promote intermolecular aminocarbonylation/intramolecular amidation cascade sequences to convert 2-(2-haloalkenyl)aryl halide substrates efficiently and selectively to the corresponding 2-quinolones. Significant variation of both the *N*-nucleophile and the styryl-backbone is possible, allowing access to a range of structurally varied quinolones, including an azaquinolone. We have also established that when starting from the same initial substrate, an amination/carbonylation sequence, achieved by delaying the introduction of the carbon monoxide atmosphere, allows a corresponding isoquinolone derivative to be prepared. The conversion of 2-(2-haloalkenyl)aryl halides to quinolone and isoquinolone systems, together with their earlier use in the preparation of indoles, begins to establish this group of substrates as a general class of precursors for heterocycle syntheses;[15] further applications in this direction are underway in our laboratory.

Acknowledgment. We thank the EPSRC and AstraZeneca for their support of this study.

Supporting Information Available: Experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For example, reaction of styrene **5** with *p*-anisidine results in the formation of 58% of the expected isoquinolone, together with 17% of the corresponding indole.

(15) For an example of the related alkenyl triflate-aryl halide substrates used in benzofuran synthesis, see: Tadd, A. C.; Fielding, M. R.; Willis, M. C. *Tetrahedron Lett.* **2007**, *48*, 7578.