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Palladium-Catalyzed Intramolecular Amidation of C(sp^2)−H Bonds: Synthesis of 4-Aryl-2-quinolinones

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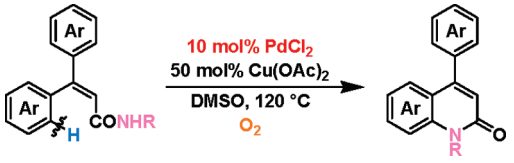

A catalytic synthetic approach for the synthesis of 2-quinolinone compounds through a Pd-catalyzed C(sp^2)−H functionalization/intramolecular amidation sequence is described. The cyclization process efficiently proceeds in the presence of a catalytic amount of $PdCl_2$ and $Cu(OAc)_2$ under an O_2 atmosphere, providing practical access to a range of variously substituted 4-aryl-2-quinolinones.

2-Quinolinones are subunits of a range of pharmaceuticals and natural products with unique biological activities, constituting an important class of heterocycles. In particular, 4-aryl-2-quinolinone derivatives, including several natural products[1] and compounds that are currently in clinical trials,[2] have attracted much attention in recent years.[1−4] Moreover, 2-quinolinones serve as valuable synthetic intermediates because they can be easily transformed into 2-(pseudo)haloquinolines (e.g., 2-Cl, 2-OTf), which can undergo further functionalization, such as nucleophilic aromatic substitutions and Pd-catalyzed coupling reactions.[5] Although many strategies for the construction of the 2-quinolinone ring rely on cyclization approaches,[6,7] including classic base-catalyzed Friedländer[6a] and acid-catalyzed Knorr synthesis,[6b] few synthetic methods based on transition-metal catalysis exist. However, such methods would provide a more facile, versatile, and practical route.

Several research groups recently demonstrated the successful use of a palladium catalyst in 2-quinolinone synthesis.[8−10] Larock et al. reported the carbonylative annulation of alkynes with 2-iodoanilines and CO in the presence of $Pd(OAc)_2$, leading to 3,4-disubstituted 2-quinolinones.[8e] More recently, Cacchi, Fabrizi, and co-workers developed a protocol for preparing 4-aryl-2-quinolinones from 2-bromocinnamamides and aryl iodides through a tandem-type Heck reaction/Buchwald−Hartwig amination sequence.[8c] Willis' group also reported a one-pot formation of 2-quinolinones from 2-(2-haloalkenyl)aryl halides and

(1) (a) Kobayashi, Y.; Harayama, T. *Org. Lett.* **2009**, *11*, 1603–1606. and references cited therein.. (b) Kitahara, Y.; Shimizu, M.; Kubo, A. *Heterocycles* **1990**, *31*, 2085–2090. and references cited therein..

(2) (a) Kraus, J. M.; Verlinde, C. L. M. J.; Karimi, M.; Lepesheva, G. I.; Gelb, M. H.; Buckner, F. S. *J. Med. Chem.* **2009**, *52*, 1639–1647. (b) Hong, D. S.; Sebti, S. M.; Newman, R. A.; Blaskovich, M. A.; Ye, L.; Gagel, R. F.; Moulder, S.; Wheler, J. J.; Naing, A.; Tannir, N. M.; Ng, C. S.; Sherman, S. I.; Naggar, A. K. E.; Khan, R.; Trent, J.; Wright, J. J.; Kurzrock, R. *Clin. Cancer Res.* **2009**, *15*, 7061–7068. (c) Capell, B. C.; Olive, M.; Erdos, M. R.; Cao, K.; Faddah, D. A.; Tavarez, U. L.; Conneely, K. N.; Qu, X.; San, H.; Ganesh, S. K.; Chen, X.; Avallone, H.; Kolodgie, F. D.; Virmani, R.; Nabel, E. G.; Collins, F. S. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 15902–15907. (d) Andresen, B. M.; Couturier, M.; Cronin, B.; D'Occhio, M.; Ewing, M. D.; Guinn, M.; Hawkins, J. M.; Jasys, V. J.; LaGreca, S. D.; Lyssikatos, J. P.; Moraski, G.; Ng, K.; Raggon, J. W.; Stewart, A. M.; Tickner, D. L.; Tucker, J. L.; Urban, F. J.; Vazquez, E.; Wei, L. *Org. Process Res. Dev.* **2004**, *8*, 643–650. (e) Venet, M.; End, D.; Angibaud, P. *Curr. Top. Med. Chem.* **2003**, *3*, 1095–1102.

(3) (a) Boy, K. M.; Guernon, J. M.; Sit, S.-Y.; Xie, K.; Hewawasam, P.; Boissard, C. G.; Dworetzky, S. I.; Natale, J.; Gribkoff, V. K.; Lodge, N.; Starrett, J. E., Jr. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5089–5093. (b) Hewawasam, P.; Fan, W.; Cook, D. A.; Newberry, K. S.; Boissard, C. G.; Gribkoff, V. K.; Starret, J.; Lodge, N. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4479–4482. (c) Hewawasam, P.; Fan, W.; Ding, M.; Flint, K.; Cook, D.; Goggings, G. D.; Myers, R. A.; Gribkoff, V. K.; Boissard, C. G.; Dworetzky, S. I.; Starret, J. E., Jr.; Lodge, N. J. *J. Med. Chem.* **2003**, *46*, 2819–2822. (d) Hewawasam, P.; Fan, W.; Knipe, J.; Moon, S. J.; Boissard, C. G.; Gribkoff, V. K.; Starret, J. E., Jr. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1779–1783.

(4) (a) Cheng, P.; Zhang, Q.; Ma, Y.-B.; Jiang, Z.-Y.; Zhang, X.-M.; Zhang, F.-X.; Chen, J.-J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3787–3789. (b) Wall, M. J.; Chen, J.; Meegalla, S.; Ballentine, S. K.; Wilson, K. J.; DesJarlais, R. L.; Schubert, C.; Chaikin, M. A.; Crysler, C.; Petrounia, I. P.; Donatelli, R. R.; Yurkow, E. J.; Boczon, L.; Mazzulla, M.; Player, M. R.; Patch, R. J.; Manthey, C. L.; Molloy, C.; Tomczuk, B.; Illig, C. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2097–2102. (c) Peifer, C.; Urich, R.; Schattel, V.; Abadleh, M.; Röttig, M.; Kohlbacher, O.; Laufer, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1431–1435. (d) Mederski, W. W. K. R.; Osswald, M.; Dorsch, D.; Christadler, M.; Schmitges, C.-J.; Wilm, C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1883–1886. (e) Beier, N.; Labitzke, E.; Mederski, W. W. K. R.; Radunz, H.-E.; Rauschenbach-Ruess, K.; Schneider, B. *Heterocycles* **1994**, *39*, 117–131.

(5) For selected recent examples, see: (a) Goodell, J. R.; Puig-Basagoiti, F.; Forshey, B. M.; Shi, P.-Y.; Ferguson, D. M. *J. Med. Chem.* **2006**, *49*, 2127–2137. (b) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Manna, F.; Pace, P. *Synlett* **1998**, 446–448. (c) Godard, A.; Fourquez, J. M.; Tamion, R.; Marsais, F.; Quéguiner, G. *Synlett* **1994**, 235–236. (d) Anzini, M.; Cappelli, A.; Vomero, S. *J. Heterocycl. Chem.* **1991**, *28*, 1809–1812.

(6) (a) Domínguez-Fernández, F; López-Sanz, J.; Pérez-Mayoral, E.; Bek, D.; Martín-Aranda, R. M.; López-Peinado, A. J.; Čejka, J. *Chem. Cat. Chem.* **2009**, *1*, 241–243. and references cited therein.. (b) Marull, M.; Lefebvre, O.; Schlosser, M. *Eur. J. Org. Chem.* **2004**, 54–63. and references cited therein..

(7) For selected recent examples, see: (a) Minville, J.; Poulin, J.; Dufresne, C.; Sturino, C. F. *Tetrahedron Lett.* **2008**, *49*, 3677–3681. (b) Ryabukhin, D. S.; Vasil'ev, A. V. *Russ. J. Org. Chem.* **2008**, *44*, 1849–1851. (c) Park, K. K.; Lee, J. J. *Tetrahedron* **2004**, *60*, 2993–2999. (d) Wang, J.; Discordia, R. P.; Crispino, G. A.; Li, J.; Grosso, J. A.; Polniaszek, R.; Truc, V. C. *Tetrahedron Lett.* **2003**, *44*, 4271–4273.

(8) (a) Tadd, A. C.; Matsuno, A.; Fielding, M. R.; Willis, M. C. *Org. Lett.* **2009**, *11*, 583–586. (b) Liu, Z.; Shi, C.; Chen, Y. *Synlett* **2008**, 1734–1736. (c) Battistuzzi, G.; Bernini, R.; Cacchi, S.; De Salve, I.; Fabrizi, G. *Adv. Synth. Catal.* **2007**, *349*, 297–302. (d) Bernini, R.; Cacchi, S.; Fabrizi, G.; Sferrazza, A. *Heterocycles* **2006**, *69*, 99–105. (e) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 6772–6780.

(9) (a) Mori, M.; Chiba, K.; Ohta, N.; Ban, Y. *Heterocycles* **1979**, *13*, 329–332. (b) Cortese, N. A.; Ziegler, C. B., Jr.; Hrnjez, B. J.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2952–2958.

(10) Pd-catalyzed functionalizations of 2-quinolinones were also reported; see, for example: (a) Wang, A.; Wang, B.; Wu, J. *J. Comb. Chem.* **2007**, *9*, 811–817. (b) Glasnov, T. N.; Stadlbauer, W.; Kappe, C. O. *J. Org. Chem.* **2005**, *70*, 3864–3870.

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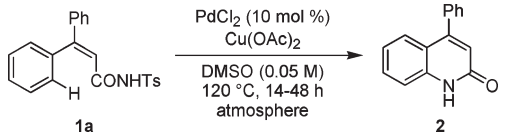
TABLE 1. Pd-Catalyzed 2-Quinolinone Synthesis: Effect of Reaction Parameters



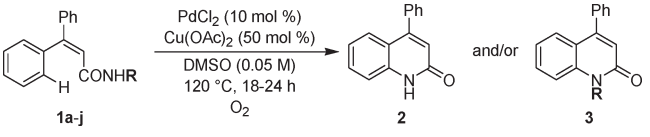
entry	$Cu(OAc)_2$ (mol %)	atmosphere	yield[a] (%)
1	100	Ar	53 (45)[b]
2	100	O_2	82
3	50	O_2	85
4	30	O_2	88
5	15	O_2	47 (53)[b]
6	0	O_2	0 (96)[b]
7	50	air	97
8	30	air	65 (25)[b]

[a]Yield of isolated product from reaction on a 0.13 mmol scale. [b]Recovered yield of starting material in parentheses.

amines in the presence of CO by means of a Pd-catalyzed intermolecular aminocarbonylation/intramolecular amidation sequence.[8a]

During the past several years, Pd-catalyzed functional group-directed C−H functionalization has been intensively studied, with most investigations focused on carbon−carbon, carbon−oxygen, and carbon−halogen bond formation.[11] Carbon−nitrogen bond formation through Pd-catalyzed C−H functionalization (C−H amination) has so far been less studied,[12−14] but it would be a complementary approach to the Buchwald−Hartwig (C−X, X = halogen atom) amination reaction.[15]

TABLE 2. Pd-Catalyzed 2-Quinolinone Synthesis: Effect of Substituent on Nitrogen Atom



		yield[a] (%)		
entry	R	**2**	**3**	recovered **1**
1	Ts (**1a**)	85	0	0
2	Ac (**1b**)	53	0	0
3	Boc (**1c**)	36	0	0
4	H (**1d**)	25		23 (**1d**)
5	Me (**1e**)	0	24 (**3e**)	68 (**1e**)
6	^{i}Pr (**1f**)	0	0 (**3f**)	78 (**1f**)
7	OMe (**1g**)	0	99 (**3g**)	0
8[b]	Ph (**1h**)	0	62 (**3h**)	21 (**1h**)
9[b]	4-$OMeC_6H_4$ (**1i**)	0	58 (**3i**)	trace (**1i**)
10[b]	4-$NO_2C_6H_4$ (**1j**)	0	82 (**3j**)	0

[a]Yield of isolated product from reaction on a 0.13 mmol scale. [b]100 mol % of $Cu(OAc)_2$.

Several reports have shown the potential of Pd-catalyzed C−H amination for the synthesis of nitrogen atom-based heterocycles that makes use of the intramolecular variant of the process.[16] In 2005, Buchwald's group reported that an intramolecular C−H amination of 2-acetaminobiphenyl compounds can be realized in the presence of a catalytic amount of $Pd(OAc)_2$, leading to an efficient formation of carbazoles.[12k] After this pioneering work, several groups, including ours, successfully expanded the method for synthesizing some nitrogen atom-based heterocycles, such as indolines,[12a,b] oxindoles,[12c,e] indoles,[12h] indazoles,[12i] and carbazoles.[12d,f,g] Yu et al. recently developed an efficient method for the synthesis of lactams via intramolecular C−H amination.[12e] In light of these successful precedents for Pd-catalyzed intramolecular C−H amination, we anticipated that the cyclization of 3-arylacrylamides through a C−H amination process would lead to an efficient protocol for the synthesis of 2-quinolinone compounds. Herein, we address the details of this subject.

Initial studies were performed using *N*-tosyl-3,3-diphenylacrylamide (**1a**) to determine the optimal reaction conditions (Table 1). On the basis of our recent reports about Pd-catalyzed C−H amination,[12h,i] we examined various combinations of a catalytic palladium and a copper salt as a stoichiometric reoxidant in DMSO solvent. The use of 10 mol % of $PdCl_2$ and 100 mol % of $Cu(OAc)_2$ resulted in the formation of the cyclized product. Unexpectedly, detosylation of 2-quinolinone also occurred during the course of the reaction, generating 4-phenyl-2-quinolinone (**2**) in fairly good yield (53%, entry 1).[17,18]

Unfortunately, further optimization of this initial lead using a range of solvents, palladium sources, and reoxidants did not improve the yield. Various metal salts, aryliodonium

(11) For recent reviews on transition-metal-catalyzed C−H functionalization, see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (b) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, *39*, 540–548. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677–685. (d) Ackermann, L.; Vincente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826. (e) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (f) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (g) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335–344. (h) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447–2464. (i) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417–424. (j) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949–957. (k) Kakkiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013–3039. (l) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179. (m) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35–41.

(12) (a) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806–10807. (b) Neumann, J. J.; Rakshit, S.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892–6895. (c) Miura, T.; Ito, Y.; Murakami, M. *Chem. Lett.* **2009**, *38*, 328–329. (d) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184–16186. (e) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058–14059. (f) Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7603–7610. (g) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115–1118. (h) Inamoto, K.; Saito, T.; Hiroya, K.; Doi, T. *Synlett* **2008**, 3157–3162. (i) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931–2934. (j) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048–9049. (k) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560–14561.

(13) (a) For a recent review on catalytic C−H amination, see: Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061–5074. (b) For Pd-catalyzed allylic C−H amination, see: Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11707–11711. (c) For Pd-catalyzed dehydrogenative diamination of terminal alkenes, see: Wang, B.; Du, H.; Shi, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8224–8227.

(14) Examples of C−S bond formation via catalytic C−H functionalization are much rarer in the literature; see: (a) Zhao, X.; Dimitrijević, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466–3467. (b) Joyce, L. L.; Batey, R. A. *Org. Lett.* **2009**, *11*, 2792–2795. (c) Inamoto, K; Hasegawa, C.; Hiroya, K.; Doi, T. *Org. Lett.* **2008**, *10*, 5147–5150. (d) Inamoto, K.; Arai, Y.; Hiroya, K.; Doi, T. *Chem. Commun.* **2008**, 5529–5531.

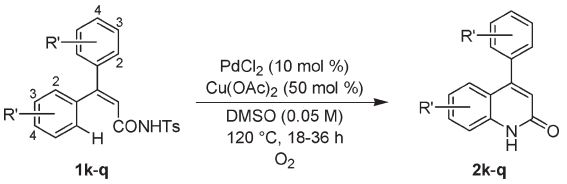
(15) Janey, J. M. In *Name Reactions for Functional Group Transformations*; Li, J. J., Corey, E. J., Eds.; Wiley: New York, 2007; pp 564−604.

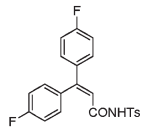
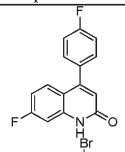
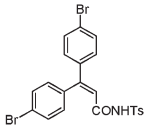
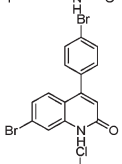
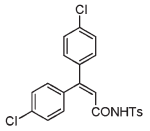
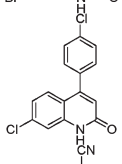
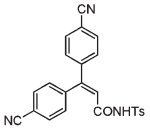
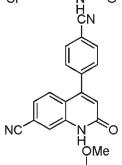
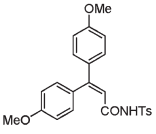
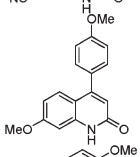
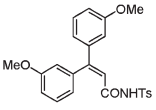
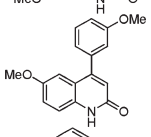
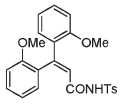
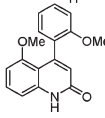
(16) For recent reviews on the construction of heterocyclic compounds via C−H functionalization, see: (a) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874–5883. (b) Zhang, M. *Adv. Synth. Catal.* **2009**, *351*, 2243–2270.

(17) Heating independently prepared 1-tosyl-4-phenyl-2-quinolinone at 120 °C in DMSO in the absence of palladium and copper salts resulted in the detosylation, producing compound **2** in quantitative yield. Similar detosylation has been previously reported; see ref 8e.

(18) For detailed results of screening, see the Supporting Information.

TABLE 3. Pd-Catalyzed 2-Quinolinone Synthesis: Substrate Scope



entry	substrate		product		yield (%)[a]
1		**1k**		**2k**	79
2		**1l**		**2l**	87
3		**1m**		**2m**	61
4		**1n**		**2n**	38 (38)[b]
5		**1o**		**2o**	85
6[c]		**1p**		**2p**	86
7[e]		**1q**		**2q**	98

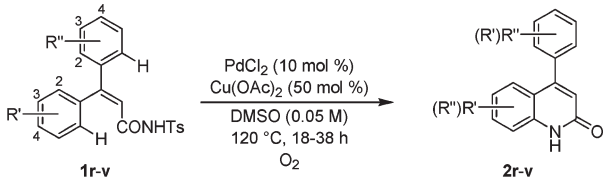
[a]Yield of isolated product from reaction on a 0.13 mmol scale. [b]Recovered yield of starting material in parentheses. [c]140 °C.

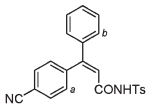
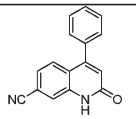
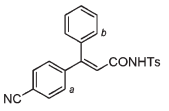
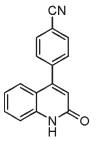
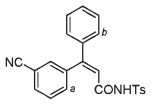
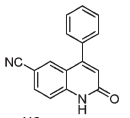
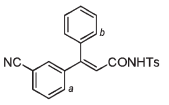
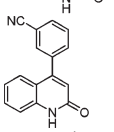
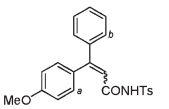
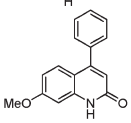
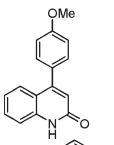
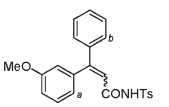
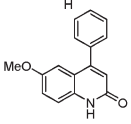
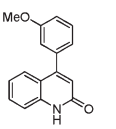
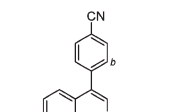
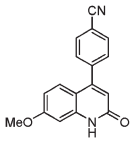
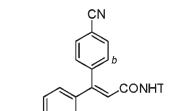
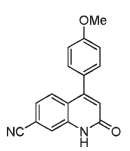
salts, benzoquinone, and Oxone were used as a reoxidant, but none of them yielded better results. However, we were pleased to find that the use of an O_2 atmosphere greatly enhanced the process (entry 1 vs 2)[19,20] and reduced the amount of $Cu(OAc)_2$ to 30 mol % (entry 4). From a practical point of view, it is noteworthy that the catalytic activity of the

(19) Molecular oxygen (O_2), because of its nontoxic, readily available, and easy-to-handle character, can be considered as one of the most ideal reoxidants and has often been employed as a terminal co-reoxidant for similar catalytic C−H functionalization processes; see ref 12c,12f,12g,12k. For other selected recent examples, see: (a) Ueda, S.; Nagasawa, H. *J. Org. Chem.* **2009**, *74*, 4272–4277. (b) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932–1934. (c) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207–2210. (d) Ferreira, E. M.; Zhang, H.; Stoltz, B. M. *Tetrahedron* **2008**, *64*, 5987–6001. (e) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137–3139. (f) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790–6791.

(20) For selected reviews on Pd-catalyzed oxidation reactions using molecular oxygen, see: (a) Gligorich, K. M.; Sigman, M. S. *Chem. Commun.* **2009**, 3854–3867. (b) Muzart, J. *Chem. Asian J.* **2006**, *1*, 508–515. (c) Stahl, S. S. *Science* **2005**, *309*, 1824–1826. (d) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329–2363. (e) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (f) Nishimura, T.; Uemura, S. *Synlett* **2004**, 201–216.

TABLE 4. Pd-Catalyzed 2-Quinolinone Synthesis: Unsymmetrical Substrates



entry	substrate		product		yield (%)[a]
1[b,c]		**1r**-*Z*		**2r**-*a*	74
2[b,c]		**1r**-*E*		**2r**-*b*	69
3[b]		**1s**-*Z*		**2s**-*a*	18 (61)[d,e]
4		**1s**-*E*		**2s**-*b*	> 99
5		**1t**[f]		**2t**-*a*	43
				**2t**-*b*	51
6		**1u**[g]		**2u**-*a*	21
				**2u**-*b*	59
7[b]		**1v**-*Z*		**2v**-*a*	86
8		**1v**-*E*		**2v**-*b*	80

[a]Yield of isolated product from reaction on a 0.13 mmol scale. [b]140 °C. [c]15 mol % of $PdCl_2$ was used. [d]Recovered yield of starting material in parentheses. [e]Obtained as a 1:2.7 mixture of *E*-/*Z*-isomers. [f]A 1.4:1 mixture of *E*-/*Z*-isomers was used. [g]A 2.6:1 mixture of *E*-/*Z*-isomers was used.

system was also found in the reaction conducted under an air atmosphere (entry 7).

We next explored the effect of the substituent on the nitrogen atom of an amide moiety (Table 2). As the tosyl group described above (entry 1), cyclization of the substrate possessing an electron-withdrawing acetyl (Ac) or a *tert*-butoxycarbonyl (Boc) group proceeded with concomitant loss of an Ac or a Boc group, thereby producing deprotected 2-quinolinone (**2**) (entries 2 and 3). The use of free amide (**1d**, entry 4) or alkyl amides (**1e** and **1f**, entries 5 and 6) resulted in poor yields, whereas a methoxy substituent significantly enhanced this process (entry 7). The benzene ring was also found to be a suitable substituent on a nitrogen atom (entries 8−10). Interestingly, the yield increased as the electron density of the benzene ring on the nitrogen atom diminished, suggesting that the nucleophilicity of the nitrogen atom plays an important role in the process.

This new method for 2-quinolinone synthesis can be applied to cyclization of a range of substrates possessing various functional groups on the benzene ring (Table 3). Halogen atoms, including bromine, are well tolerated under the reaction conditions employed (entries 1−3). The substrate **1n**, which contains two electron-withdrawing cyano groups at the *para*-position, was not suitable for this process (entry 4), whereas amides **1o**−**q**, which have two electron-donating methoxy groups at the *ortho*-, *meta*-, or *para*-position, produced the corresponding 2-quinolinone compounds **2o**−**q** in high yields (entries 5−7).

The scope of the catalytic conditions developed above was further investigated using several unsymmetrical substrates (Table 4). The reaction of the *Z*-isomer of the substrate **1r**, which had one cyano group at the *para*-position, gave 2-quinolinone **2r**-*a* as a sole product in high yield (entry 1). Similarly, the use of its *E*-isomer (**1r**-*E*) resulted in the successful formation of **2r**-*b* (entry 2). The *E*-isomer is much more reactive than the *Z*-isomer in the case of the *m*-cyano-substituted compound **1s** (entries 3 and 4). From the former (**1s**-*E*), quinolinone **2s**-*b* was produced in quantitative yield (entry 4), whereas the cyclization of the latter (**1s**-*Z*) provided **2s**-*a* in only 18% yield along with the recovery of **1s** as a 1:2.7 mixture of *E*-/*Z*-isomers (61%, entry 3). Although the reason for the difference in the reactivity is unknown at present, a plausible rationale for these results might involve the relatively slow rate of isomerization compared to that of cyclization and deactivation of the catalyst system employed during the reaction course.[21] Due to the difficulty of separation, a mixture of isomers was used for the reactions of **1t** and **1u**. Both compounds smoothly underwent the cyclization, affording a mixture of regioisomers that included **2t**-*a* and **2t**-*b* and **2u**-*a* and **2u**-*b*, respectively (entries 5 and 6). Reactions of **1v**-*Z* and **1v**-*E* proceeded efficiently without isomerization, providing **2v**-*a* and **2v**-*b* as sole products in high yields (entries 7 and 8).[22,23]

In summary, we have demonstrated that the cyclization of 3,3-diarylacrylamides through intramolecular C−H amination can be performed in the presence of a palladium catalyst to produce variously substituted 2-quinolinones generally in high yields. The use of an O_2 atmosphere along with a semicatalytic amount of $Cu(OAc)_2$ as a reoxidation system proved to be crucial for the process. The method provides a novel and efficient protocol to construct a pharmaceutically important 2-quinolinone nucleus, and this technique should be a valuable tool in the fields of medicinal chemistry as well as organic synthesis. Further studies of the application of the Pd-catalyzed intramolecular C−H amination process for the synthesis of other nitrogen atom-based heterocycles are currently underway.

Experimental Section

Representative Procedure for Pd-Catalyzed 2-Quinolinone Synthesis (Table 1, Entry 4). Compound **1a** (50.0 mg, 0.13 mmol), $PdCl_2$ (2.3 mg, 0.013 mmol), and $Cu(OAc)_2$ (7.2 mg, 0.040 mmol) were weighed in a pear-shaped flask. The flask was evacuated and refilled with Ar. Under a positive Ar pressure, DMSO (2.6 mL) was added via syringe. The flask was again evacuated and refilled with O_2. The reaction mixture was then stirred at 120 °C for 14 h under an O_2 atmosphere (balloon). After being cooled to room temperature, the reaction mixture was extracted with ethyl acetate (10 mL × 3), and the combined organic layer was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by silica gel column chromatography [hexane−ethyl acetate (4:1)] to give **2** (25.8 mg, 88%) as a colorless solid.

4-Phenyl-1*H*-quinolin-2-one (2): mp 259−260 °C (white needles from EtOH, lit.[8c] mp 252−254 °C); IR ν (film, cm^{-1}) 2849, 1659; ^1H NMR (400 MHz, $CDCl_3$) δ 6.70 (1H, s), 7.14−7.18 (1H, m), 7.46−7.56 (8H, m), 12.56 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.7, 119.5, 120.7, 122.5, 126.6, 128.5, 128.7, 128.8, 130.6, 137.0, 138.8, 153.3, 164.1; MS *m*/*z* 221 (M^+, 100); HRMS calcd for $C_{15}H_{11}NO$ 221.0841, found 221.0831. Anal. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.16; H, 5.23; N, 6.33.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Young Scientists (B) from the Japan Society for the Promotion of Science (JSPS).

Supporting Information Available: Experimental details and spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) *E*-/*Z*-Isomerization of **1s** was observed when either **1s**-*Z* or **1s**-*E* was heated in DMSO at 120 °C for 8 h, resulting in the formation of a 1:1.9 mixture of *E*-/*Z*-isomers from both isomers.

(22) Although extensive mechanistic studies have yet to be conducted, experiments with the isotopically labeled substrates revealed primary kinetic isotope effects (k_H/k_D) of 3.5 (intramolecular) and 2.7 (intermolecular), indicating that cleavage of the C−H bond is involved in the rate-determining step. Similar KIE values (intramolecular: 3.5, intremolecular: 2.6) were previously observed in a related aromatic palladation process; see: Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 5636–5637. For experimental details, see the Supporting Information.

(23) Compared with an air atmosphere, the use of an O_2 atmosphere for the reactions of **1k**−**v** gives better results in terms of the yield and the reaction time.