ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 3227

Received 2nd January 2014,
Accepted 3rd February 2014

DOI: 10.1039/c4cc00027g

www.rsc.org/chemcomm

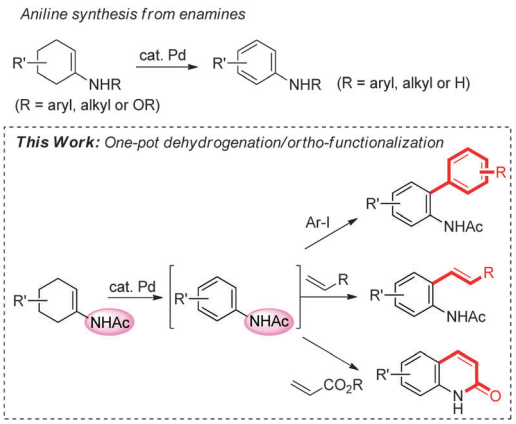
A Pd-Catalyzed one-pot dehydrogenative aromatization and *ortho*-functionalization sequence of *N*-acetyl enamides†

Jinhee Kim, Youngtaek Moon, Suhyun Lee and Sungwoo Hong*

The one-pot dehydrogenation and *ortho*-functionalization sequence provides access to highly functionalized arylamine-containing derivatives from readily accessible cyclic *N*-acetyl enamides.

Aniline derivatives are common and important structural motifs in numerous natural products and pharmaceuticals.[1] The introduction of functional groups at the *meta* position of anilines represents a key challenge because electrophilic aromatic substitutions of anilines are generally limited to *ortho*- and *para*-positions because of strong electron directing effects. Recently, the Pd(II)-catalyzed dehydrogenation of imines or enamines has been demonstrated to be an attractive alternative synthetic approach for generating various aniline derivatives because *meta*-substituted cyclohexanone precursors can be readily prepared starting from cyclohexenones.[2] Furthermore, Stahl and co-workers identified the Pd(II)-catalyzed aromatization of cyclohexenone oximes to yield primary arylamines.[3] Despite advances in this area, substituents of the enamine (imine) moiety have been mostly confined to aryl or alkyl groups, thereby limiting the potential for further functionalization or one-pot sequential reactions of the resulting anilines.

We speculated that the appropriately substituted anilines[4] generated *in situ* from the Pd(II)-catalyzed dehydrogenation reactions could be utilized for further cross-coupling with suitable alkenes, or arylating agents *via* a Pd–Ar complex to afford diversely functionalized anilines (Scheme 1). In this study, the *N*-acetyl enamide group[5,6] was selected with a view to developing a one-pot sequential transformation. *N*-Acetyl enamides are easily prepared *via* condensation of cyclohexanones and acetamides. Herein, we describe the first example of Pd(II)-catalyzed dehydrogenative aromatization of cyclic *N*-acetyl enamides and reaction conditions compatible with the sequential cross-coupling.



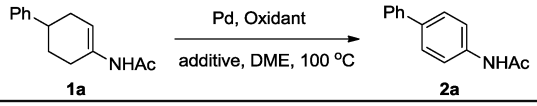
Scheme 1 Strategy for the synthesis of functionalized arylamines through a one-pot dehydrogenation/*ortho*-functionalization sequence.

We initially focused on the dehydrogenation reaction of *N*-acetyl enamide **1a**; representative catalyst screening data for the conversion are listed in Table 1. The catalytic system consisting of $Pd(OAc)_2$, O_2, Bu_4NBr, and molecular sieves in a toluene–DMSO co-solvent, which was employed previously in the dehydrogenation of imines,[2] allowed the isolation of acetanilide **2a** but only in 22% yield (Table 1, entry 1). Addition of an acid such as pivalic acid, TFA or TsOH resulted in lower yields, presumably due to the sensitivity of the *N*-acetyl enamide group to acidic conditions. Among the palladium sources tested, $Pd(OAc)_2$ displayed the best catalytic reactivity. After screening a variety of (co)solvents, we found that DME gave improved results with minimal by-product formation. A variety of oxidizing agents, including Cu(II), $K_2S_2O_8$, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), $PhCO_3{}^tBu$ and (2,2,6,6-tetramethyl-piperidin-1-yl)oxy (TEMPO), were evaluated, and $PhCO_3{}^tBu$ was found to be the most effective and economical oxidant. No beneficial effects were observed in the presence of ligands such as PPh_3, Xanphos, pyridine, or 4,5-diazafluorenone, which have been used in other Pd-catalyzed reactions (entry 6). Further screening studies revealed that the optimal result could be obtained with the addition of a catalytic amount of iPr_2S[7]

Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, 305-701, Korea. E-mail: hongorg@kaist.ac.kr; Fax: +82 42-350-2810; Tel: +82 42-350-2811

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc00027g

Table 1 Optimization of dehydrogenative aromatization of *N*-cyclohexenylacetamide **1a**[a]



Entry	Pd	Oxidant (equiv.)	Additive (equiv.)	Yield[b] (%)
1[c]	$Pd(OAc)_2$	O_2	Bu_4NBr (2)	22
2	$Pd(OAc)_2$	$K_2S_2O_8$ (2)	—	10
3	$Pd(OAc)_2$	$PhCO_3{}^tBu$ (2)	—	55
4	$Pd(OPiv)_2$	$PhCO_3{}^tBu$ (2)	—	53
5	$Pd_2(dba)_3$	$PhCO_3{}^tBu$ (2)	—	53
6	$Pd(OAc)_2$	$PhCO_3{}^tBu$ (2)	Xanphos (0.2)	53
7	$Pd(OAc)_2$	$PhCO_3{}^tBu$ (2)	DMSO (14)	80
8	$Pd(OAc)_2$	$PhCO_3{}^tBu$ (2)	iPr_2S (0.05)	81
9	$Pd(OAc)_2$	$PhCO_3{}^tBu$ (2)	iPr_2S (0.025)	82
10	$Pd(OAc)_2$	AgOAc (4)	—	63
11	$Pd(OAc)_2$	AgOAc (4)	iPr_2S (0.025)	78

[a] Condition A: reactions were conducted with *N*-cyclohexenylacetamide, $Pd(OAc)_2$ (0.2 equiv.), iPr_2S (2.5 mol%) and oxidant in DME (0.1 M) at 100 °C for 3.5 h. [b] Isolated yields. [c] Reaction was conducted in a toluene–DMSO co-solvent. DME = 1,2-dimethoxyethane.

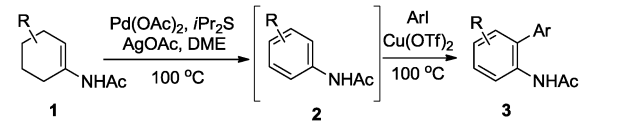
(entries 8 and 9) by minimizing the precipitation of palladium black. Under the optimized reaction conditions, the dehydrogenative aromatization of **1a** (1 equiv.) in the presence of $Pd(OAc)_2$ (0.2 equiv.), $PhCO_3{}^tBu$ (2 equiv.), and iPr_2S (0.025 equiv.) in DME at 100 °C, afforded the product **2a** in the highest yield (82%). When $Pd(OAc)_2$ (0.1 equiv.) was employed, 73% yield of **2a** was obtained after prolonged reaction time (16 h, Table S1, ESI†).

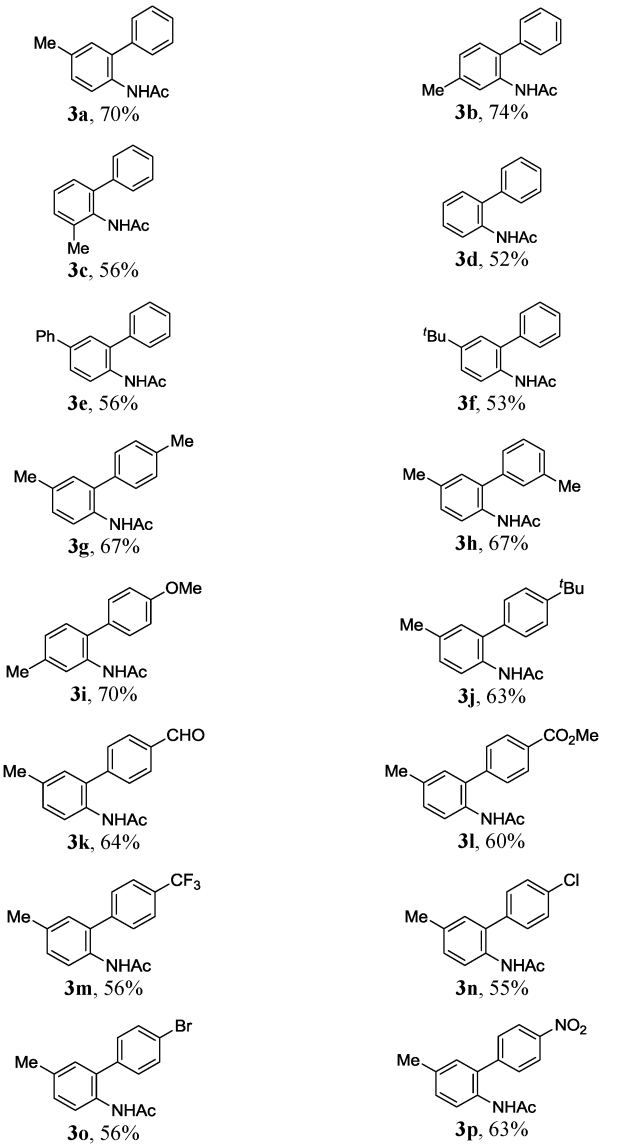
It was found that when the dehydrogenation reaction was conducted using AgOAc as the oxidant instead of $PhCO_3{}^tBu$, the desired acetanilide **2a** was produced in comparable yield (78%, entry 11). The ability to convert cyclohexenylacetamide into the corresponding acetanilide by using either $PhCO_3{}^tBu$[6] (entry 10) or AgOAc (entry 11) as the oxidant prompted us to explore the feasibility of further sequential catalytic cross-coupling.

We next evaluated the potential of the proposed one-pot dehydrogenation/arylation sequence by investigating the reactivity of 4-phenylcyclohexenylacetamide (**1a**) and phenyl iodide (**2a**) as substrates. Unfortunately, however, we did not detect any trace of the coupling product resulting from cross-coupling under the optimized reaction conditions for the dehydrogenative aromatization step. Through screening experiments, we found that the *in situ* addition of $Cu(OTf)_2$ was crucial in arylating the resulting acetanilide, thus demonstrating that the sequential process was indeed operating.[8] When $PhCO_3{}^tBu$ was used as the oxidant instead of AgOAc in this sequence, no *ortho*-arlyation product was isolated. The optimal conditions were then applied to a variety of substituted substrates (Table 2).

We next investigated the Pd-catalyzed sequential dehydrogenation–alkenylation[9] process. Under slightly altered reaction conditions in which $PhCO_3{}^tBu$ was employed instead of AgOAc, the one-pot process could be utilized to produce the desired product **4**, albeit in only 10% yield. Optimization studies disclosed that a variety of substrates underwent rapid alkenylation with the *in situ* addition of an acid such as $TsOH{\cdot}H_2O$.[6] Having identified suitable reaction conditions, a variety of alkenes were tested and shown to react well, as illustrated in Table 3. For example, alkene

Table 2 One-pot dehydrogenation/arylation sequence of *N*-cyclohexenylacetamides[a]



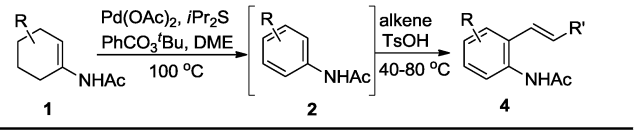


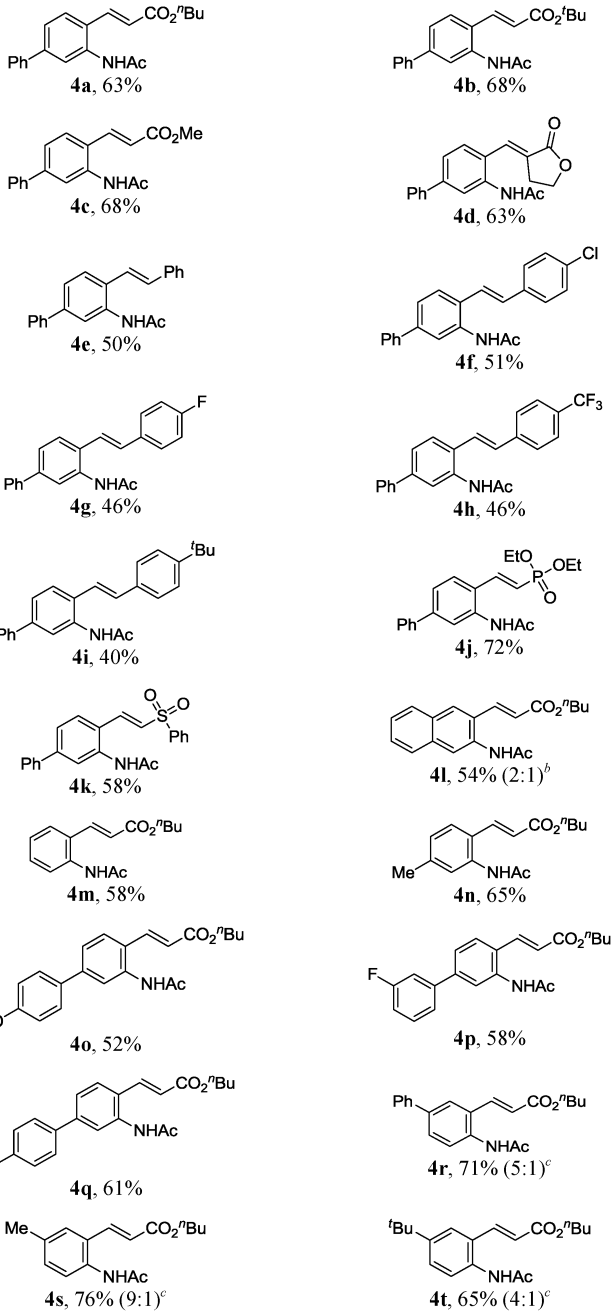
[a] Condition B: reactions were conducted with *N*-cyclohexenylacetamide, $Pd(OAc)_2$ (0.2 equiv.), AgOAc (4 + 1 equiv.) and iPr_2S (2.5 mol%) in DME (0.1 M) at 100 °C for 3.5 h and then ArI (3–5 equiv.) and $Cu(OTf)_2$ (2.0 equiv.) for 12–18 h.

substrates conjugated with ester, lactone, phosphonate or sulfone groups all coupled smoothly. Moreover, a variety of styrene substrates were compatible with the sequential reaction conditions. The substrate scope of cyclohexenylacetamides was subsequently examined, and a relatively broad range of functional groups (*e.g.*, alkyl, fluoro, methoxy, phenyl, and acetyl) were found to be compatible with the reaction conditions.

The synthetic utility of the one-pot sequence was further demonstrated by our finding that it provides convenient access

Table 3 Sequential dehydrogenative aromatization/alkenylation sequence of *N*-cyclohexenylacetamides[a]

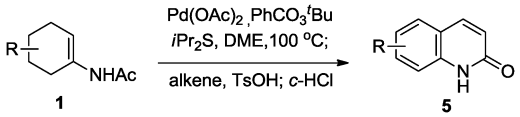


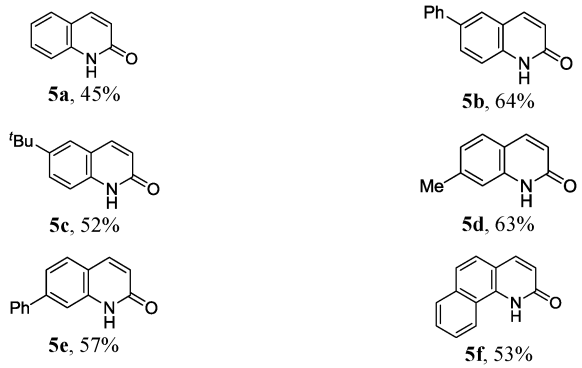


[a] Condition C: *N*-cyclohexenylacetamide, $Pd(OAc)_2$ (0.2 + 0.1 equiv.), $PhCO_3{}^tBu$ (2 + 1 equiv.) and iPr_2S (2.5 mol%) in DME (0.1 M) at 100 °C; alkenes (1.2-1.5 equiv.), and $TsOH{\cdot}H_2O$ (0.4 equiv.) at 40–80 °C. [b] Ratio of positional isomers. [c] Ratio of mono- and di-olefinated products.

to the quinolinone moiety, which constitutes the core of a wide variety of naturally occurring compounds and privileged medicinal scaffolds.[10] Indeed, the sequential dehydrogenation–alkenylation process followed by *in situ* acid-mediated

Table 4 Sequential dehydrogenative aromatization/alkenylation sequence of *N*-cyclohexenylacetamides[a]





[a] Condition D: reactions were conducted with *N*-cyclohexenylacetamide, $Pd(OAc)_2$ (0.2 + 0.1 equiv.), $PhCO_3{}^tBu$ (2 + 1 equiv.) and iPr_2S (2.5 mol%) in DME (0.1 M) at 100 °C; alkenes (1.2 equiv.), and $TsOH{\cdot}H_2O$ (0.4 equiv.) at 40–80 °C; *c*-HCl (0.2 mL).

cyclization allows the rapid generation of the corresponding quinolinones (Table 4).

In summary, we have developed a Pd(II)-catalyzed dehydrogenative aromatization of cyclic *N*-acetyl enamides and a sequential cross-coupling process. This simple and efficient approach offers an unprecedented one-pot route to highly functionalized arylamines and their derivatives. The synthetic utility of the one-pot sequence was further demonstrated by its ability to provide convenient access to quinolinone derivatives.

This research was supported by the National Research Foundation of Korea (NRF) through general research grants (NRF-2011-0016436) and the Institute for Basic Science (IBS).

Notes and references

1 (*a*) *The Chemistry of Anilines, Parts 1 and 2*, ed. Z. Rappoport, John Wiley & Sons, New York, 2007; (*b*) M. Negwer, *Organic Chemical Drugs and their Synonyms*, Akademie Verlag GmbH, Berlin, 7th edn, 1994.

2 For selected examples: (*a*) S. A. Girard, X. Hu, T. Knauber, F. Zhou, M. O. Simon, G. J. Deng and C. J. Li, *Org. Lett.*, 2012, **14**, 5606; (*b*) A. Hajra, Y. Wei and N. Yoshikai, *Org. Lett.*, 2012, **14**, 5488; (*c*) Y. Wei, I. Deb and N. Yoshikai, *J. Am. Chem. Soc.*, 2012, **134**, 9098; (*d*) P. Horrillo-Martinez, M.-A. Virolleaud and C. Jaekel, *ChemCatChem*, 2010, **2**, 175; (*e*) H. Neumann, A. J. Wangelin, S. Klaus, D. S. Bing, D. Grdes and M. Beller, *Angew. Chem., Int. Ed.*, 2003, **42**, 4503; (*f*) M. Sutter, M.-C. Duclos, B. Guicheret, Y. Raoul, E. Métay and M. Lemaire, *ACS Sustainable Chem. Eng.*, 2013, **1**, 1463; (*g*) Y. Izawa, D. Pun and S. S. Stahl, *Science*, 2011, **333**, 209; (*h*) T. Diao and S. S. Stahl, *J. Am. Chem. Soc.*, 2011, **133**, 14566; (*i*) T. Diao, T. J. Wadzinski and S. S. Stahl, *Chem. Sci.*, 2012, **3**, 887; (*j*) D. Pun, T. Diao and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 8213.

3 W. P. Hong, A. V. Iosub and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 13664.

4 (*a*) M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries and P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.*, 2002, **124**, 1586; (*b*) F. W. Patureau and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 9982; (*c*) Y. Aihara and N. Chatani, *J. Am. Chem. Soc.*, 2013, **135**, 5308.

5 (*a*) G. Z. Zhang, C. Q. Chen, X. H. Feng and G. S. Huang, *J. Chem. Sci.*, 2010, **122**, 149; (*b*) Z. Shi, B. Li, X. Wan, J. Cheng, Z. Fang, B. Cao, C. Qin and Y. Wang, *Angew. Chem., Int. Ed.*, 2007, **46**, 5554; (*c*) S. Yang, B. Li, X. Wan and Z. Shi, *J. Am. Chem. Soc.*, 2007, **129**, 6066; (*d*) N. R. Deprez and M. S. Sanford, *J. Am. Chem. Soc.*, 2009, **131**, 11234.

6 (*a*) T. Nishikata and B. H. Lipshutz, *Org. Lett.*, 2010, **12**, 1972; (*b*) B. S. Kim, C. Jang, D. J. Lee and S. W. Youn, *Chem.–Asian J.*, 2010, **5**, 2336; (*c*) X. Liu and K. K. Hii, *J. Org. Chem.*, 2011, **76**, 8022; (*d*) B. Schmidt and N. Elizarov, *Chem. Commun.*, 2012, **48**, 4350.

7 (*a*) C.-Y. He, S. Fan and X. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 12850; (*b*) Y. Fuchita, K. Hiraki, Y. Kamogawa and M. Suenaga, *Chem. Commun.*, 1987, 941; (*c*) F. Chen, Z. Feng, C.-Y. He, H.-Y. Wang, Y.-L. Guo and X. Zhang, *Org. Lett.*, 2012, **14**, 1176.

8 When $Pd(OAc)_2$ (0.1 equiv.) was employed, about 8% lower yields were obtained.

9 For selected examples for alkenylation: (*a*) Y.-Y. Yu, M. J. Niphakis and G. I. Georg, *Org. Lett.*, 2011, **13**, 5932; (*b*) D. Cheng and T. Gallagher, *Org. Lett.*, 2009, **11**, 2639; (*c*) Y. Moon, D. Kwon and S. Hong, *Angew. Chem., Int. Ed.*, 2012, **51**, 11333; (*d*) Y.-H. Xu, Y. K. Chok and T.-P. Loh, *Chem. Sci.*, 2011, **2**, 1822; (*e*) N. P. Grimster, C. Gauntlett, C. R. A. Godfrey and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2005, **44**, 3125; (*f*) D. Kim and S. Hong, *Org. Lett.*, 2011, **13**, 4466; (*g*) H. Geo, M. J. Niphakis and G. I. Georg, *J. Am. Chem. Soc.*, 2008, **130**, 3708; (*h*) D. Kim, M. Min and S. Hong, *Chem. Commun.*, 2013, **49**, 4021.

10 M. Venet, D. End and P. Angibaud, *Curr. Top. Med. Chem.*, 2003, **3**, 1095.

