ChemComm

This article was published as part of the

2009 'Catalysis in Organic Synthesis' web theme issue

Showcasing high quality research in organic chemistry

Please see our website
(http://www.rsc.org/chemcomm/organicwebtheme2009)
to access the other papers in this issue.

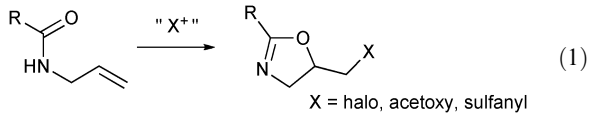
Palladium-catalysed arylative cyclisation of *N*-allylacetamides with aryl halides yielding benzyl-substituted oxazolines†‡

Daishi Fujino, Sayuri Hayashi, Hideki Yorimitsu* and Koichiro Oshima*

Received (in Cambridge, UK) 30th June 2009, Accepted 21st August 2009
First published as an Advance Article on the web 3rd September 2009
DOI: 10.1039/b912895f

Treatment of *N*-allylacetamide with aryl halide in the presence of sodium *t*-butoxide and a palladium catalyst leads to arylative cyclisation to provide the corresponding benzyl-substituted oxazoline in high yield.

Oxazoline is an important skeleton often found in biologically interesting molecules,[1] synthetic intermediates,[2] and ligands for transition metal complexes.[3] Oxazolines are usually prepared from carboxylic acid derivatives and β-aminoalcohols.[2a,b] Oxidative cyclisation of *N*-allylamides is also a useful route to oxazolines since the oxazolines thus formed can possess a functionalised side chain at the 5-position (eqn (1)).[4]



(1)

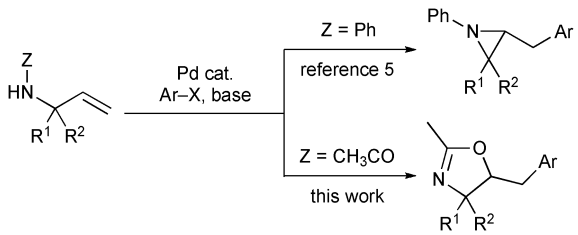
We have developed palladium-catalysed intramolecular arylative cyclisation reactions of *N*-allylanilines with aryl halides to yield aziridines (Scheme 1, Z = Ph).[5] During the course of the study, we found that a similar reaction of *N*-allylacetamides resulted in the selective formation of 5-benzyl-substituted oxazolines without contamination by the corresponding aziridines (Scheme 1, Z = CH_3CO). Here we report the preliminary results of the arylative cyclisation for the synthesis of oxazolines.[6,7] This is regarded as a new variant of the carboetherification reactions that Wolfe and others recently developed to construct tetrahydrofuran derivatives.[8]

Treatment of *N*-allylacetamide **1a** with bromobenzene under the same conditions as reported previously[5] afforded benzyl-substituted oxazoline **2a** in 75% yield (Table 1, entry 1). The cyclisation reaction inevitably competed with the Mizoroki–Heck reaction, which yielded **3a** as the only identifiable byproduct. Several ligands were screened (Fig. 1), and bulky ligands are generally effective for the cyclisation. SPhos and RuPhos are excellent (entries 1 and 2), while larger XPhos showed no activity for the cyclisation (entry 3). Other biphenylyl phosphines are less effective (entries 4 and 5). Xantphos and tri-*t*-butylphosphine were inferior in terms of **2a**/**3a** selectivity (entries 6 and 7). After further fine tuning, the use of SPhos with smaller amounts of *t*-BuONa, PhBr, and toluene proved to be the best conditions in terms of both yield of **2a** and **2a**/**3a** ratio (entry 8).[9] The choice of sodium *t*-butoxide is crucial. The use of sodium methoxide, sodium hydroxide, potassium *t*-butoxide, potassium carbonate, or caesium carbonate resulted in exclusive formation of **3a**.[10,11] Although other amides such as benzamide could undergo similar transformations, yields of the corresponding oxazolines were much lower, up to 30%.

The scope of aryl halides is summarised in Table 2. Aryl chlorides as well as aryl bromides participated in the reaction (entries 1, 7, and 8). Sterically demanding aryl bromides reacted smoothly (entries 2, 3, and 10). Electron-deficient fluorinated aryl bromides were also reactive (entries 4 and 5). Aryl halides bearing a *t*-butoxycarbonyl, diethylaminocarbonyl, or cyano group underwent the arylative cyclisation to yield the corresponding products in good yields (entries 6–8). The reaction of **1a** with electron-rich 4-bromoanisole resulted in a modest yield of **2i** and formation of a significant amount of Mizoroki–Heck byproduct (entry 9). On the other hand, the steric hindrance of 2-bromoanisole is likely to retard the side reaction (entry 10). It is worth noting that separation of **2** from **3** was readily performed on silica gel in each case.[9]

Several *N*-allylacetamides that bear a stereogenic center at the allylic position were prepared and subjected to the arylative cyclisation reaction (Table 3). The reactions proceeded smoothly with good diastereoselectivity. The major isomers have the larger R group and the newly formed benzyl group in a trans relationship. The relative stereochemistries of **4** and **5** were determined by NOE analysis.

Based on the previous results,[5,8] a plausible reaction mechanism is outlined in Scheme 2. Oxidative addition is followed by exchange between the bromide and amide **1a** to yield **7**. Intermediate **7** would undergo intramolecular



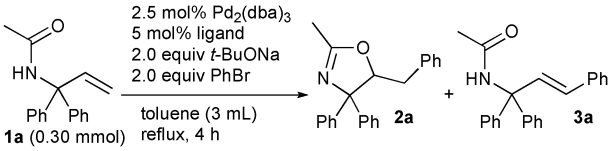
Scheme 1 Palladium-catalysed reactions of allylamine derivatives with aryl halides.

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto-daigaku Katsura, Nishikyo-ku, Kyoto 615-8510, Japan.
E-mail: yori@orgrxn.mbox.media.kyoto-u.ac.jp; oshima@orgrxn.mbox.media.kyoto-u.ac.jp; Fax: +81-75-383-2438; Tel: +81-75-383-2437

† This article is part of a ChemComm 'Catalysis in Organic Synthesis' web-theme issue showcasing high quality research in organic chemistry. Please see our website (http://www.rsc.org/chemcomm/organicwebtheme2009) to access the other papers in this issue.

‡ Electronic supplementary information (ESI) available: Characterization data. See DOI: 10.1039/b912895f

Table 1 Effect of ligands on palladium-catalysed phenylative cyclisation reaction of **1a** and competitive Mizoroki–Heck reaction



Entry	Ligand[a]	**2a** (%)	**3a** (%)
1	SPhos	75	16
2	RuPhos	78	19
3	XPhos	0	45
4	DavePhos	55	25
5	P1	12	21
6	Xantphos	76	24
7	t-Bu_3P	70	30
8[b]	SPhos	76	12

[a] See Fig. 1. [b] 1.5 equiv. of t-BuONa, 1.2 equiv. of PhBr, and 1.5 mL of toluene were used.

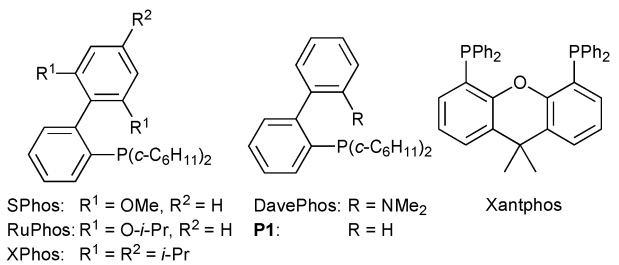
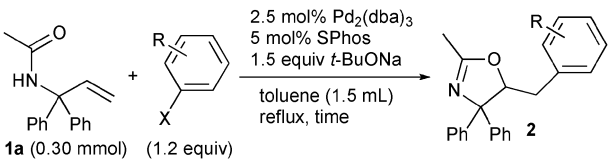


Fig. 1 Structures of ligands.

Table 2 Scope of aryl halides

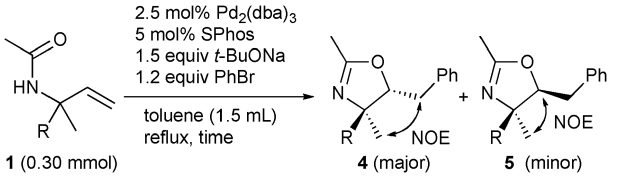


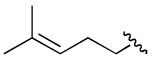
Entry	R	X	Time/h	**2**	Yield (%)[a]
1	H	Cl	4	**2a**	77 (7)
2[b]	2-Me	Br	4	**2b**	84 (5)
3[b]	(1-naphthyl)	Br	6	**2c**	79 (6)
4	4-F	Br	8	**2d**	76 (6)
5	4-CF_3	Br	8	**2e**	80 (4)
6	4-CO_2-t-Bu	Br	12	**2f**	61 (6)
7	4-$CONEt_2$	Cl	10	**2g**	67 (15)
8	4-CN	Cl	10	**2h**	59 (3)
9	4-MeO	Br	10	**2i**	50 (24)
10	2-MeO	Br	8	**2j**	69 (9)

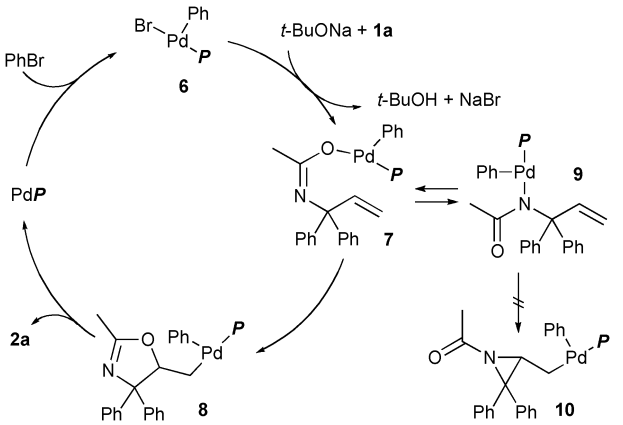
[a] Isolated yields of **2**. The NMR yields of the corresponding Mizoroki–Heck byproducts are in parentheses. The byproducts were easily separable from **2** by chromatographic purification. [b] RuPhos was used instead of SPhos.

oxypalladation to give **8**. Smooth reductive elimination with the aid of the bulky phosphine ligand affords product **2a** and regenerates the initial palladium species. There can be an

Table 3 Diastereoselective cyclisation



Entry	**1**	R	Time/h	Yield (%)	**4**/**5**
1	**1b**	Ph	10	61	**4b**/**5b** = 73 : 27
2	**1c**	1-naphthyl	12	68	**4c**/**5c** = 84 : 16
3	**1d**		10	66	**4d**/**5d** = 73 : 27

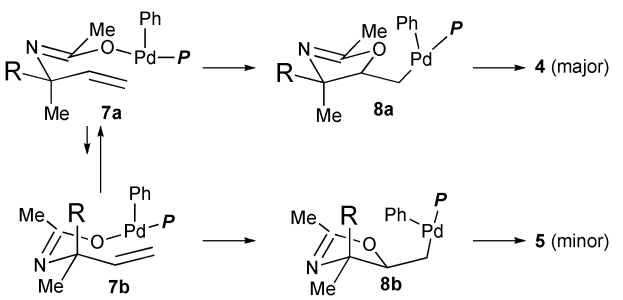


Scheme 2 Plausible reaction mechanism.

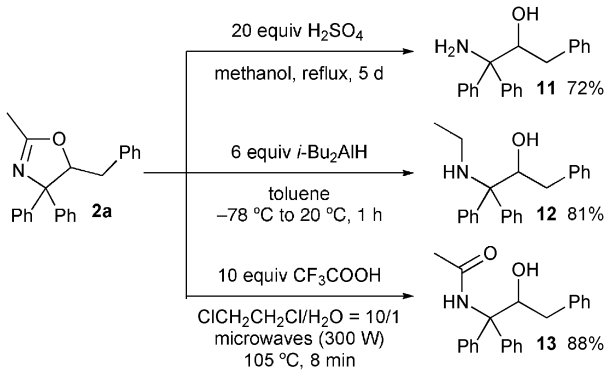
equilibrium between **7** and palladium amide **9**. However, cyclisation of **9** that forms an aziridine skeleton could not occur.

The stereoselectivity is rationalised by considering that the larger R group would prefer locating at the pseudo-equatorial position prior to cyclisation (Scheme 3). Intermediate **7a** would be thus more stable than **7b**, and the formation of oxazoline **8a** predominated to lead to **4** with high diastereoselectivity.

Finally, transformation of oxazoline **2a** was examined (Scheme 4). Methanolysis of **2a** occurred under acidic conditions[12] to yield amino alcohol **11**. Reduction of **2a** with diisobutylaluminium hydride provided *N*-ethyl amino



Scheme 3 Origin of stereoselectivity.



Scheme 4 Transformation of oxazoline **2a**.

alcohol **12**. Oxazoline **2a** was converted to acetamide **13** by acidic hydrolysis with trifluoroacetic acid.[13] The overall transformation of **1a** to **13** represents regioselective carbohydroxylation of *N*-allylacetamide.

In summary, we have developed palladium-catalysed carboetherification reactions of *N*-allylacetamides with aryl halides. The reactions provided benzyl-substituted oxazolines without the conceivable formation of aziridines.[5] In light of the importance of oxazolines, the method offers a useful tool in organic synthesis. We are pursuing higher diastereoselectivity and asymmetric cyclization and mechanistic studies are underway.

This work was supported by Grants-in-Aid for Scientific Research and for GCOE Research from MEXT and JSPS. S.H. acknowledges JSPS for financial support. H.Y. acknowledges financial support from Eisai and Kyoto University.

Notes and references

1 (*a*) R. J. Bergeron, *Chem. Rev.*, 1984, **84**, 587; (*b*) R. S. Roy, A. M. Gehring, J. C. Milne, P. J. Belshaw and C. T. Walsh, *Nat. Prod. Rep.*, 1999, **16**, 249; (*c*) J. R. Lewis, *Nat. Prod. Rep.*, 2002, **19**, 223; (*d*) Z. Jin, *Nat. Prod. Rep.*, 2003, **20**, 584.

2 (*a*) R. H. Wiley and L. L. Bennett, *Chem. Rev.*, 1949, **44**, 447; (*b*) J. A. Frump, *Chem. Rev.*, 1971, **71**, 483; (*c*) T. G. Gant and A. I. Meyers, *Tetrahedron*, 1994, **50**, 2297; (*d*) A. I. Meyers, *Acc. Chem. Res.*, 1978, **11**, 375; (*e*) Y. Langlois, *Curr. Org. Chem.*, 1998, **2**, 1.

3 (*a*) A. K. Ghosh, P. Mathivanan and J. Capplello, *Tetrahedron: Asymmetry*, 1998, **9**, 1; (*b*) J. S. Johnson and D. A. Evans, *Acc. Chem. Res.*, 2000, **33**, 325; (*c*) H. Nishiyama, J. Ito, T. Shiomi, T. Hashimoto, T. Miyakawa and M. Kitase, *Pure Appl. Chem.*, 2008, **80**, 743.

4 (*a*) Z. K. M. Abd El Samii, M. I. A. Ashmawy and J. M. Mellor, *Tetrahedron Lett.*, 1987, **28**, 1949; (*b*) M. Tiecco, L. Testaferri and M. Tingoli, *Tetrahedron*, 1993, **49**, 5351; (*c*) G. Cardillo, M. Orena and S. Sandri, *J. Chem. Soc., Chem. Commun.*, 1983, 1489; (*d*) S. Minakata, Y. Morino, Y. Oderaotoshi and M. Komatsu, *Org. Lett.*, 2006, **8**, 3335; (*e*) Y. Morino, I. Hidaka, Y. Oderaotoshi, M. Komatsu and S. Minakata, *Tetrahedron*, 2006, **62**, 12247; (*f*) T. Kato, K. Marubayashi, S. Takizawa and H. Sasai, *Tetrahedron: Asymmetry*, 2004, **15**, 3693.

5 S. Hayashi, H. Yorimitsu and K. Oshima, *Angew. Chem., Int. Ed.*, 2009, **48**, DOI: 10.1002/anie.200903178, in press.

6 Cyclisation of *N*-(4-acetoxy-2-butenyl)benzamides and decarboxylative cyclisation of 3-acyl-5-vinyloxazolidinones were reported to yield 5-vinyloxazolines *via* π-allylpalladium intermediates: (*a*) K.-Y. Lee, Y.-H. Kim, M.-S. Park, C.-Y. Oh and W.-H. Ham, *J. Org. Chem.*, 1999, **64**, 9450; (*b*) G. R. Cook and P. S. Shanker, *Tetrahedron Lett.*, 1998, **39**, 3405.

7 Palladium-catalysed addition of aryl iodides to *N*-(2,3-butadienyl)-benzamide followed by cyclisation was reported to afford 5-vinyloxazolines *via* π-allylpalladium intermediates: G. R. Cook and W. Xu, *Heterocycles*, 2006, **67**, 215.

8 (*a*) J. S. Nakhla, J. W. Kampf and J. P. Wolfe, *J. Am. Chem. Soc.*, 2006, **128**, 2893; (*b*) M. B. Hay and J. P. Wolfe, *J. Am. Chem. Soc.*, 2005, **127**, 16468; (*c*) M. B. Hay, A. R. Hardin and J. P. Wolfe, *J. Org. Chem.*, 2005, **70**, 3099; (*d*) J. P. Wolfe and M. A. Rossi, *J. Am. Chem. Soc.*, 2004, **126**, 1620; (*e*) D. Jiang, J. Peng and Y. Chen, *Org. Lett.*, 2008, **10**, 1695; (*f*) K. G. Dongol and B. Y. Tay, *Tetrahedron Lett.*, 2006, **47**, 927; (*g*) M. B. Hay and J. P. Wolfe, *Angew. Chem., Int. Ed.*, 2007, **46**, 6492; (*h*) D. Jiang, J. Peng and Y. Chen, *Tetrahedron*, 2008, **64**, 1641. Reviews: (*i*) J. P. Wolfe, *Eur. J. Org. Chem.*, 2007, 571; (*j*) J. P. Wolfe, *Synlett*, 2008, 2913.

9 Experimental Procedure: Sodium *t*-butoxide (43 mg, 0.45 mmol) was added to a 30-mL two-necked reaction flask equipped with a Dimroth condenser and was dried *in vacuo* with heating by a hair dryer for 1 min. Tris(dibenzylideneacetone)dipalladium (6.9 mg, 0.0075 mmol) and 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos, 6.2 mg, 0.015 mmol) were added to the flask, and the flask was filled with argon by using the standard Schlenck technique. Toluene (0.5 mL) was then added at room temperature. After the suspension was stirred for 10 min, a mixture of **1a** (75.4 mg, 0.30 mmol) and bromobenzene (56.5 mg, 0.36 mmol) dissolved in toluene (1.0 mL) was added to the flask at ambient temperature. The mixture was heated at reflux for 4 h with an oil bath. After the flask was cooled to room temperature, water (20 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate three times. The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/AcOEt = 3/1) to provide 5-benzyl-2-methyl-4,4-diphenyl-4,5-dihydrooxazole **2a** (74.7 mg, 0.228 mmol, 76%, R_f = 0.37). *N*-Cinnamylacetamide **3a** appeared at R_f = 0.20 (hexane/AcOEt = 3/1). IR (nujol) 3024, 1665, 1448, 1258, 973, 758, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H), 2.32 (dd, J = 15.0, 11.0 Hz, 1H), 2.57 (dd, J = 15.0, 2.5 Hz, 1H), 5.34 (dd, J = 11.0, 2.5 Hz, 1H), 7.15–7.20 (m, 4H), 7.21–7.34 (m, 7H), 7.35–7.40 (m, 2H), 7.44–7.48 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.64, 39.81, 81.07, 88.45, 126.76, 127.11, 127.39, 127.45, 128.16, 128.18, 128.64, 128.73, 129.21, 138.60, 142.14, 145.78, 164.15; Found: C, 84.12; H, 6.58%. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.46%. m.p. 116.0–117.5 °C.

10 Exposure of **3a** to the reaction conditions resulted in no reaction. This result strongly suggests that **3a** is not an intermediate *en route* to **2a**.

11 When the reaction was performed in the presence of silver salts, yield of **2a** was not improved.

12 M. Braun, R. Fleischer, B. Mai, M.-A. Schneider and S. Lachenicht, *Adv. Synth. Catal.*, 2004, **346**, 474.

13 F. Benfatti, G. Cardillo, L. Gentilucci, A. Tolomelli, M. Monari and F. Piccinelli, *Adv. Synth. Catal.*, 2007, **349**, 1256.

