Palladium-Catalyzed Sequential Alkylation−Alkenylation Reactions. Application to the Synthesis of 2-Substituted-4-Benzoxepines and 2,5-Disubstituted-4-Benzoxepines

Mark Lautens,* Jean-François Paquin, and Sandrine Piguel†

Davenport Laboratories, Chemistry Department, University of Toronto, Toronto, Ontario, Canada M5S 3H6

mlautens@chem.utoronto.ca

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Abstract: The synthesis of 2-substituted-4-benzoxepines and 2,5-disubstituted-4-benzoxepines from aryl iodides and bromoenoates is described. This methodology is based on a palladium-catalyzed aromatic substitution followed by an intramolecular Heck sequence. Under the reaction conditions ($Pd(OAc)_2$ (10 mol %), tri-2-furylphosphine (20 mol %), norbornene (2 equiv), Cs_2CO_3 (2 equiv), CH_3CN, 85 °C), moderate to excellent yields of benzoxepines bearing numerous substituents (Me, F, Cl, etc.) are obtained.

In recent times, seven-membered-ring oxacycles[1] and particularly benzoxepine derivatives have received increasing interest because of their occurrence in natural products[2], their biological activities,[2b,3,4] and their use as natural herbicides.[5]

We recently reported a new methodology for the formation of fused aromatic rings from the reaction of aryl iodides and bromoenoates under palladium catalysis in which two carbon−carbon bonds are formed in a one-pot process.[6,7] We now report an extension of this methodology for the synthesis of 2-substituted-4-benzoxepines **1a** and 2,5-disubstituted-4-benzoxepines **1b** from aryl iodides **2** and bromoenoates **3** (Figure 1).

To test the feasibility of the reaction, iodobenzene **4** was reacted with the oxygenated difunctional acceptor **5**[8] under our modified Catellani conditions: $Pd(OAc)_2$ (10 mol %), trifurylphosphine[9] (20 mol %), norbornene (2 equiv), Cs_2CO_3 (2 equiv), CH_3CN, 85 °C (Scheme 1). The desired bicyclic compound **6** was obtained in modest yield indicating that the reaction was indeed possible. The reaction probably occurs through the same mechanism described previously for the formation of six- and seven-membered carbocycles.[6,7,10]

We then examined aryl iodides bearing an ortho substituent (Table 1), blocking the second alkylation. The use of different ortho substituents gave the benzoxepine derivatives in moderate to good yield. With R = Me (entry

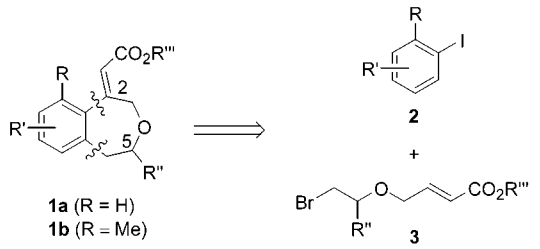


Figure 1.

Scheme 1

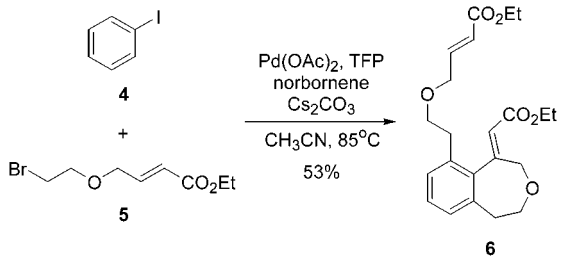
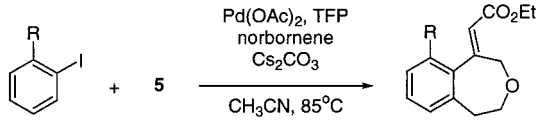


Table 1. Formation of 2-Disubstituted-4-benzoxepines from Ortho-Substituted Aryl Iodides[a]



entry	R	aryl iodide	product	yield (%)[b]
1	Me	**7**	**12**	85
2	CH_2OMe	**8**	**13**	23
3	CH_2OTBS	**9**	**14**	53
4	OMe	**10**	**15**	75
5	CO_2Me	**11**	**16**	0

[a] 4 equiv of the bromoenoate were used, but it was later found that 2 equiv could be used without affecting the yield. [b] Isolated yield.

† Present address: Laboratoire de Synthèse et Electrosynthèse Organique (SESO), Université de Rennes 1, 35042 Rennes, France.

(1) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631−12670.

(2) For recent examples, see: (a) Macías, F. A.; Varela, R. M.; Torres, A.; Molinillon, J. M. G. *Tetrahedron Lett.* **1999**, *40*, 4725−4728 and references therein. (b) Wijnberg, J. B. P. A.; van Veldhuizen, A.; Swarts, H. J.; Frankland, J. C.; Field, J. A. *Tetrahedron Lett.* **1999**, *40*, 5767−5770 and references therein. (c) Asakawa, Y.; Hashimoto, T.; Takikawa, K.; Tori, M.; Ogawa, S. *Phytochemistry* **1991**, *30*, 235−251. (d) Meriçli, F.; Meriçli, A. H.; Becker, H.; Ulubelen, A. *Phytochemistry* **1996**, *42*, 1257−1258.

(3) Zimmermann, K.; Waldmeier, P. C.; Tatton, W. G. *Pure Appl. Chem.* **1999**, *71*, 2039−2046.

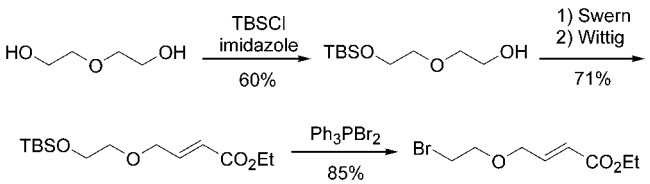
(4) Kaupmann, W.; Ohlendorf, H. W.; Wolf, K. U. *Eur. J. Med. Chem.* **1985**, *20*, 207−212.

(5) Vyvyan, J. R.; Looper, R. E. *Tetrahedron Lett.* **2000**, *41*, 1151−1154.

(6) Lautens, M.; Piguel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1045−1046. For the first report of Pd-catalyzed ortho-alkylation, see ref 10.

(7) Lautens, M.; Paquin, J.-F.; Piguel, S.; Dahlmann, M. *J. Org. Chem.* **2001**, *66*, 8127−8134.

(8) Compound **5** was obtained in three steps from di(ethyleneglycol). For synthesis details, see Supporting Information.



(9) For a review on the use of trifurylphosphine (TFP) in catalysis, see: Anderson, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997−1030.

(10) (a) Catellani, M.; Frignagni, F.; Rangoni, A. *Angew. Chem.* **1997**, *109*, 142−145 and references therein.; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119−122 and references therein. (b) Catellani, M.; Fagnola, M. C. *Angew. Chem.* **1994**, *106*, 2559−2560; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2421−2422. (c) Catellani, M.; Cugini, F. *Tetrahedron* **1999**, *55*, 6595−6602.

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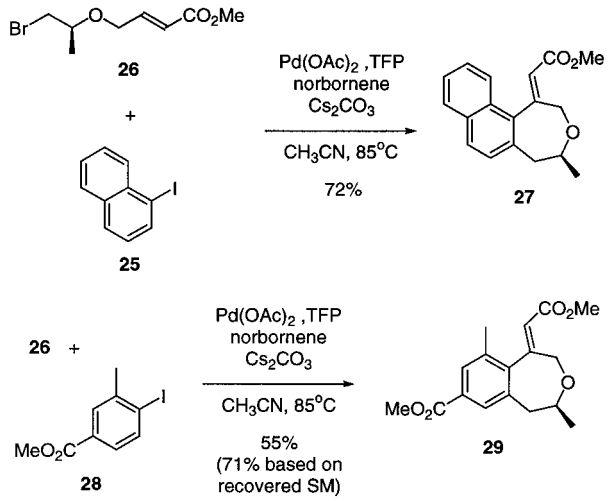
Scheme 2. Synthesis of 2,5-Disubstituted-4-benzoxepines



1), the desired product **12** was isolated in 85% yield. Changing from a methyl ether (entry 2) to a TBS benzyl ether (entry 3) improved the yield from 20 to 41%. This lack of reactivity might be explained by a complexation between the oxygen atom and the palladium center, which inhibits the subsequent steps in the catalytic cycle. We suppose that this phenomenon is minimized in the case of R = CH_2OTBS (entry 3) because of the steric bulk of the silyl group. Interestingly, when R = OMe (entry 4), the desired benzoxepine **15** was obtained in 75%, whereas the use of **11** (R = CO_2Me) gave no desired product.[11] These results correlated with our previous findings on the reactivity of fused aromatic seven-membered rings.[7]

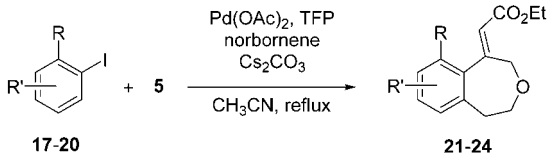
We then studied the functional group tolerance on the aryl iodides (Table 2). Chlorine or fluorine substituents are well tolerated since the desired benzoxepines **21** and **23** were isolated in 84 and 78% yields, respectively. The presence of an amide (entry 2) did not adversely affect the reaction since **22** was obtained in 80% yield. The reaction also proceeds in the presence of a basic nitrogen since 5-iodoquinoline (**20**) reacted to give **24** in 72% yield. It is important to note that the majority of the products allow for further functionalization.

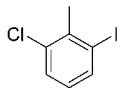
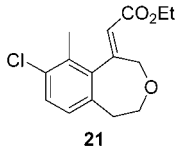
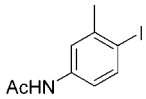
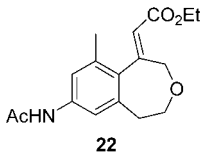
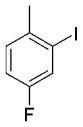
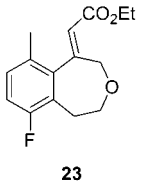
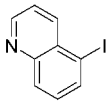
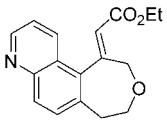
Benzoxepine **21** was a crystalline solid allowing X-ray crystallography[12] to confirm the (*E*)-geometry of the exocyclic double bond as previously indicated by NOE experiments.

We then explored the effect of a substituent adjacent to one of the reactive groups on the difunctional acceptor (Scheme 2). The bromoenoate **26** bearing a methyl substituent was synthesized[13] and submitted to the reaction conditions. 1-Iodonaphthalene (**25**) gave the desired 2,4-disubstituted-4-benzoxepine **27** in 72%. When **26** was reacted with the aryl iodide **28**, the benzoxepine **29** was obtained in 55% yield indicating the lower reactivity of **28**. These results illustrate that α-branching on the alkyl bromide is well tolerated.

In conclusion, we described the synthesis of 2-substituted-4-benzoxepines and 2,5-disubstituted-4-benzoxepines from aryl iodides and bromoenoates under palladium catalysis in which two carbon−carbon bonds are formed in one pot. The bicyclic compounds are obtained in moderate to excellent yields under relatively mild conditions, and substitution is tolerated on both the aryl iodides and the bromoenoate. Application of this methodology to the synthesis of more complex bicyclic compounds as well as bioactive molecules is in progress in our laboratory and will be reported in due course.

Table 2. Formation of 2-Substituted-4-benzoxepines from Polysubstituted Aryl Iodides[a]



entry	aryl iodide	product	yield (%)[b]
1			84
2			80
3			78
4			72

[a] 2 equiv of bromoenoates were used. [b] Isolated yield.

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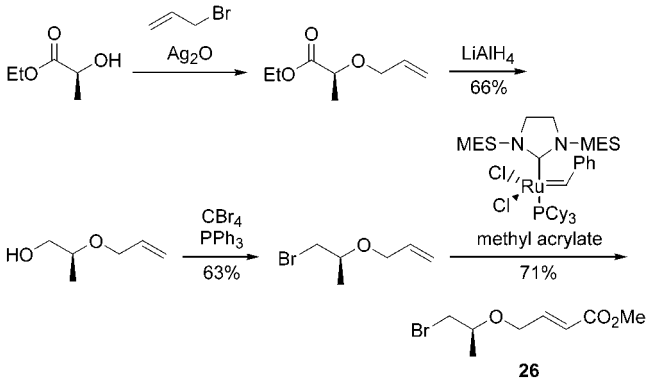
(11) No side products were isolated since only unreacted **5** along with baseline material were detectable by TLC after workup.

(12) See Supporting Information for details.

(13) Compound **26** was synthesized in four steps from ethyl (*S*)-(−)-lactate. For synthesis details, see Supporting Information.



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Supporting Information Available: General experimental procedure for the formation of benzoxepines, details for the synthesis of aryl iodides and difunctional acceptors, as well as spectroscopic data for the new benzoxepines. This material is available free of charge via the Internet at http://pubs.acs.org.

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