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Benzylic Arylation of 2-Methyl-5-membered Heterocycles Using TMP-Bases

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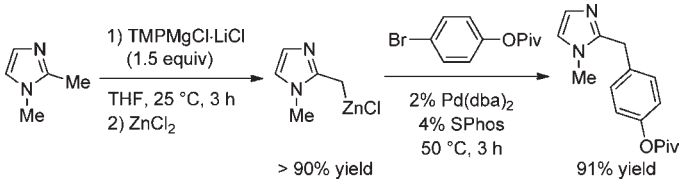
ABSTRACT



A new general Pd-catalyzed arylation of various 2-methyl-5-membered heterocycles is reported. This novel method requires Li−, Mg−, or Zn−TMP bases and allows selective metalation of the benzylic position. Subsequent Negishi cross-coupling provides the corresponding arylated heterocycles.

The benzylic arylation of pyridines and related *N*-heterocycles is of great synthetic interest due to the importance of these heterocycles for pharmaceutical applications.[1] Such arylation reactions on the methylpyridine scaffold often require the preparation of suitable precursors, such as 2-(2-pyridyl)ethanol,[2] *N*-oxides,[3] or *N*-iminopyridinium ylides.[4] Recently, we have shown that a direct benzylic arylation on picolines, lutidines, and methy-substituted quinolines proceeds readily in the presence of TMPZnCl·LiCl (**1**) (TMP = 2,2,6,6-tetramethylpiperidyl) and an appropriate Lewis acid such as $Sc(OTf)_3$.[5] However, the arylation of methyl-substituted 5-membered heterocycles remains by far an unsolved problem.[6] The arylation of 1,2-dimethylimidazole (**2**) occurs usually at position 5, and no "benzylic" C−H activation followed by cross-couplings has been reported.[7,8] Only alkylation reactions on the methyl group have been

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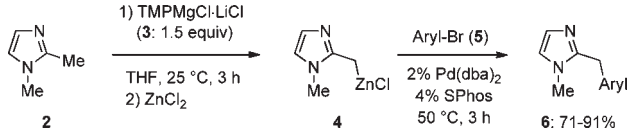
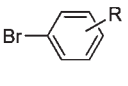
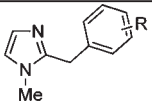
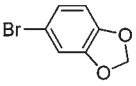
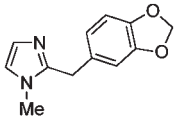
Table 1. Pd-Catalyzed Benzylic Arylation of 1,2-Dimethylimidazole (**2**) Leading to Products of Type **6**



entry	Aryl-Br	product	yield (%)[a]
			
1	**5a** R = 4-CO_2Et	**6a** R = 4-CO_2Et	85
2	**5b** R = 4-CN	**6b** R = 4-CN	71
3	**5c** R = 3-CF_3	**6c** R = 3-CF_3	77
4	**5d** R = 4-OMe	**6d** R = 4-OMe	74
5	**5e** R = 4-OPiv	**6e** R = 4-OPiv	91
6	**5f** R = 3-Me	**6f** R = 3-Me	83
7	**5g** R = 4-NMe_2	**6g** R = 4-NMe_2	79
8	 **5h**	 **6h**	71

[a] Isolated yield of analytically pure product.

performed successfully after deprotonation with *n*-BuLi.[9] In addition, the benzylic metalation and subsequent arylation of 2-methylbenzothiophenes[10] and 2-methylbenzofurans[10b] has not yet been described. Recently, we have developed a range of TMP bases which allow the metalation of various unsaturated molecules under mild conditions.[11] Herein, we wish to report that such a direct benzylic arylation can be performed on a variety of different methyl-substituted 5-membered heterocycles, including 2-methylimidazoles, -benzothiophenes, and -benzofurans and related 5-membered heterocycles.

Thus, by using the magnesium base TMPMgCl·LiCl[12] (**3**) and subsequent transmetalation with $ZnCl_2$, we were able to zincate 1,2-dimethylimidazole (**2**) *selectively* at the 2-methyl position. The resulting zincated reagent **4** was used successfully to perform cross-coupling reactions with various aryl bromides of type **5** affording 2-benzylated imidazoles (**6**) in 71−91% yield (Table 1). For example, the magnesiation of 1,2-dimethylimidazole (**2**) with TMPMgCl·LiCl (**3**: 1.5 equiv) in THF is complete within 3 h at 25 °C.[13] After transmetalation with $ZnCl_2$ (1.5 equiv, 25 °C, 15 min), the zincated imidazole derivative (**4**) is treated with ethyl 4-bromobenzoate (**5a**: 0.8 equiv) in the presence of 2% $Pd(dba)_2$ (dba = dibenzylideneacetone) and 4% SPhos[14] to provide the desired arylated 1,2-dimethylimidazole (**6a**) at 50 °C within 2 h in 85% yield without the formation of a 5-arylated imidazole derivative[7] (Table 1, entry 1). Similarly, cyano- and trifluoromethyl-substituted aryl bromides (**5b**,**c**) can be successfully converted leading to the imidazole derivatives (**6b**,**c**, 71−77%, entries 2 and 3). Also, electron-rich aryl bromides bearing alkoxy, pivaloxy, methyl, or amino substituents undergo the cross-coupling in excellent yields (71−91% yields, entries 4−8) showing the broad scope of this arylation.

Efforts were made to extend this method to even less acidic methyl-substituted 5-membered heterocycles. We found that 2-methylbenzothiophene (**7**) was readily metalated with TMPLi[15] (**8**: 1.15 equiv, −78 °C, 15 min) in THF.[16] After transmetalation with $ZnCl_2$, the resulting heterocyclic benzylic reagent (**9**) was smoothly arylated with various aryl bromides using 2% $Pd(OAc)_2$ and 4% SPhos[14] (50 °C, 2 h) leading to the benzothiophenes (**10a**−**h**) in 68−98% yield (Table 2, entries 1−8). Interestingly, the 2,3-dimethylbenzothiophene (**7b**) undergoes an exclusive lithiation at position 2 providing after cross-coupling the 2-benzylated product (**10i**) in 87% yield (entry 9). A further extension to the 2-methylbenzofuran scaffold was successful using similar conditions. The lithiation of 2-methylbenzofuran (**11**) was complete within 1 h at −78 °C. After transmetalation with $ZnCl_2$ and cross-coupling with various aryl bromides, methyl-substituted benzofurans (**13a**−**d**) were obtained in 52−75% yield (Table 3). In the case of cyano-substituted aryl bromides (**5b** and **5j**), we have found that the addition of 10% $Sc(OTf)_3$[17] improves the cross-coupling yield.[5,18]

The generality of our approach is demonstrated by performing the arylation of other related 5-membered heterocycles such as the 2-methylindole derivative **14**[19] and the 2-methylbenzimidazole **15**.[20] In these cases, TMPZnCl·LiCl (**1**) proved to be a suitable base, and a complete zincation could be obtained within 1 h at 25 °C. Thus, cross-coupling of 2-methylindole (**14**) with 4-bromoanisole **5d** gave the indole

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(9) (a) Field, L. D.; Messerle, B. A.; Vuong, K. Q.; Turner, P. *Dalton Trans.* **2009**, *18*, 3599. (b) Oxenford, S. J.; Wright, J. M.; O'Brien, P.; Panday, N.; Shipton, M. R. *Tetrahedron Lett.* **2005**, *46*, 8315. (c) Sagae, T.; Ogawa, S.; Furukawa, N. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3179.

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(13) The direct zincation with TMPZnCl·LiCl (**1**) is too sluggish at 25 °C.

(14) (a) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem.* **2004**, *116*, 1907. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871. (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (c) Altman, R. A.; Buchwald, S. L. *Nat. Protocols* **2007**, *2*, 3115. (d) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.

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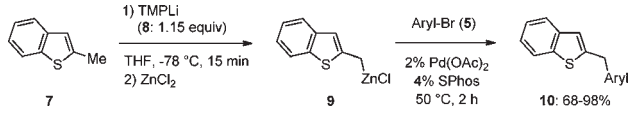
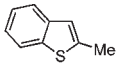
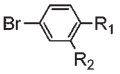
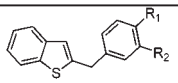
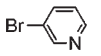
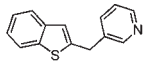
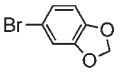
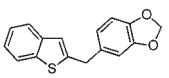
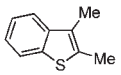
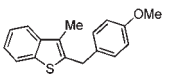
(16) Metalation with TMPMgCl·LiCl (**3**) can only proceed at elevated temperatures and the yield of the subsequent cross-coupling proved to be less high, compared to initial metalation with TMPLi (**8**).

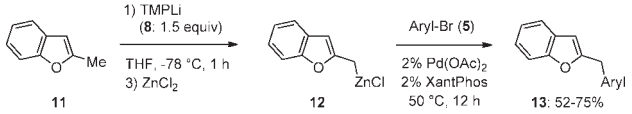
Table 2. Benzylic Cross-Coupling of 2-Methylbenzo-[*b*]thiophene (**7**)

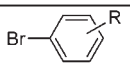
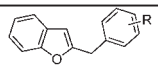


entry	substrate	Aryl-Br	product	yield (%)[a]
				
1	**7a**	**5a** $R_1 = CO_2Et$, $R_2 = H$	**10a** $R_1 = CO_2Et$, $R_2 = H$	86
2	**7a**	**5i** $R_1 = CF_3$, $R_2 = H$	**10b** $R_1 = CF_3$, $R_2 = H$	90
3	**7a**	**5d** $R_1 = OMe$, $R_2 = H$	**10c** $R_1 = OMe$, $R_2 = H$	98
4	**7a**	**5j** $R_1 = OMe$, $R_2 = CN$	**10d** $R_1 = OMe$, $R_2 = CN$	78
5	**7a**	**5e** $R_1 = OPiv$, $R_2 = H$	**10e** $R_1 = OPiv$, $R_2 = H$	97
6	**7a**	**5g** $R_1 = NMe_2$, $R_2 = H$	**10f** $R_1 = NMe_2$, $R_2 = H$	93
7	**7a**	 **5k**	 **10g**	68
8	**7a**	 **5h**	 **10h**	87
9	 **7b**	**5d** $R_1 = OMe$, $R_2 = H$	 **10i**	86

[a] Isolated yield of analytically pure product.

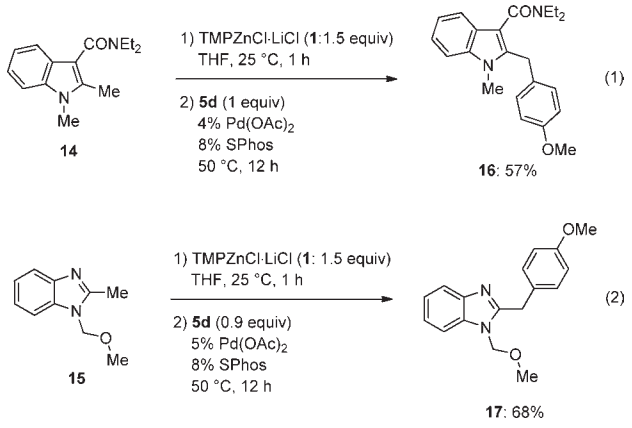
Table 3. Benzylic Arylation of 2-Methylbenzofuran (**11**)



entry	Aryl-Br	product	yield (%)[a]
			
1	**5a** R = 4-CO_2Et	**13a** R = 4-CO_2Et	64
2	**5b** R = 4-CN	**13b** R = 4-CN	52[b]
3	**5j** R = 3-CN, 4-OMe	**13c** R = 3-CN, 4-OMe	75[b,c]
4	**5d** R = 4-OMe	**13d** R = 4-OMe	75[d]

[a] Isolated yield of analytically pure product. [b] 10% $Sc(OTf)_3$ was added. [c] 2% $Pd(dba)_2$ and 4% SPhos was used. [d] 2% $Pd(dba)_2$ and 2% Xantphos was used.

Scheme 1. Benzylic Cross-Coupling of Indole (**14**) and Benzo-[*d*]imidazole (**15**)



16 in 57% yield (Scheme 1). To the best of our knowledge, this example represents the first benzylic cross-coupling on a 2-methylindole.

In addition, 2-methylbenzimidazole (**15**) can be arylated successfully after zincation with TMPZnCl·LiCl (**1**) with 4-bromoanisole (**5d**) to yield the benzoimidazole derivative **17** in 68% yield (Scheme 1).

In conclusion, we have found a new convenient method for the direct arylation of various 2-methyl 5-membered heterocycles with aryl bromides using standard Pd catalysts. Extension of this method to other 5-membered heterocycles is currently underway.

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

The authors declare no competing financial interest.

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(19) For preparation of **14**, see:Macor, J. E.; Ryan, K.; Newman, M. E. *J. Org. Chem.* **1989**, *54*, 4785.

(20) For the preparation of the benzimidazole **15**, see the Supporting Information.