THE USE OF THE *N*-SUBSTITUTED TRIETHYL-(INDOL-2-YL)BORATE FOR THE PALLADIUM CATALYZED CROSS-COUPLING REACTION

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Abstract - The influence of *N*-substituent of triethyl(indol-2-yl)borate (**2**) on the palladium catalyzed cross-coupling reaction was examined, and an efficiency of triethyl(1-*tert*-butoxycarbonylindol-2-yl)borate (**2e**) could be shown.

In the course of our investigations toward the development of an efficient synthetic methodology based on the synthetic capabilities of indolylborate,[1] we have became interested in the replacement of 1-methyl group of indolylborate (**2a**) for a successful and removable group, and demonstrated some interesting reaction features of 1-methoxymethylindolylborate (**2b**) and 1-methoxyindolylborate (**2f**) in the intramolecular alkyl migration reaction in our previous report.[2] The palladium catalyzed cross-coupling reaction is one of the synthetic advantages of indolylborate (**2a**), and studies devoted to develope the synthetic potential of the procedure have been our recent interest.[3] Therefore, we perceived the need to perform a preliminary assessment of the scope of the applicability of *N*-protecting group of indolylborate (**2**) for the cross-coupling reaction.

We first examined the palladium catalyzed cross-coupling reaction of indolylborates (**2a** - **f**), and the experimental results are summarized in Table. The lithiation of *N*-substituted indole (**1**) was simply effected by treating a THF solution of indole (**1**) with *tert*-BuLi or *n*-BuLi under an argon atmosphere, and subsequent addition of triethylborane generated indolylborate (**2**) *in situ*.[4] Only trimethylsilyl migration leading to 2-trimethylsilylindole was observed on the lithiation of 1-trimethylsilylindole (**1g**) with *tert*-

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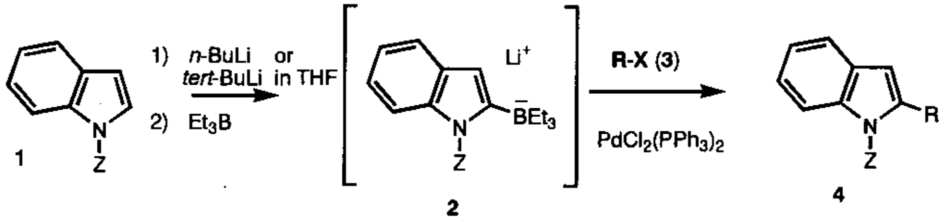
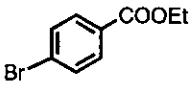
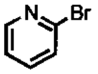
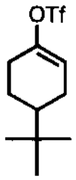
This paper is dedicated to 25th Anniversary of HETEROCYCLES.



a: Z = Me
b: Z = CH_2OMe
c: Z = $CH_2OCH_2CH_2SiMe_3$ (SEM)
d: Z = SO_2Ph
e: Z = COO-*tert*-Bu (Boc)
f : Z = OMe
g: Z = $SiMe_3$
h: Z = $SiMe_2$ *tert*-Bu

Scheme 1

Table The palladium catalyzed cross-coupling reaction of indolylborate (**2**) with R-X (**3**)

R-X (3)	Z in **2**	Yield (%) of **4**[a)]
Ph-I	Me	80
	Boc	80
	SO_2Ph	35
	MOM	—[b)]
	SEM	35
	OMe	70
Ph-Br	Me	80
	Boc	79
	Me	73
	Boc	72
	Me	60
	Boc	41
Ph-CH=CH-Br	Me	80
	Boc	78
	SO_2Ph	15
	MOM	—[b)]
	SEM	30
	OMe	60
	Me	80
	Boc	77
	SEM	21
	OMe	73

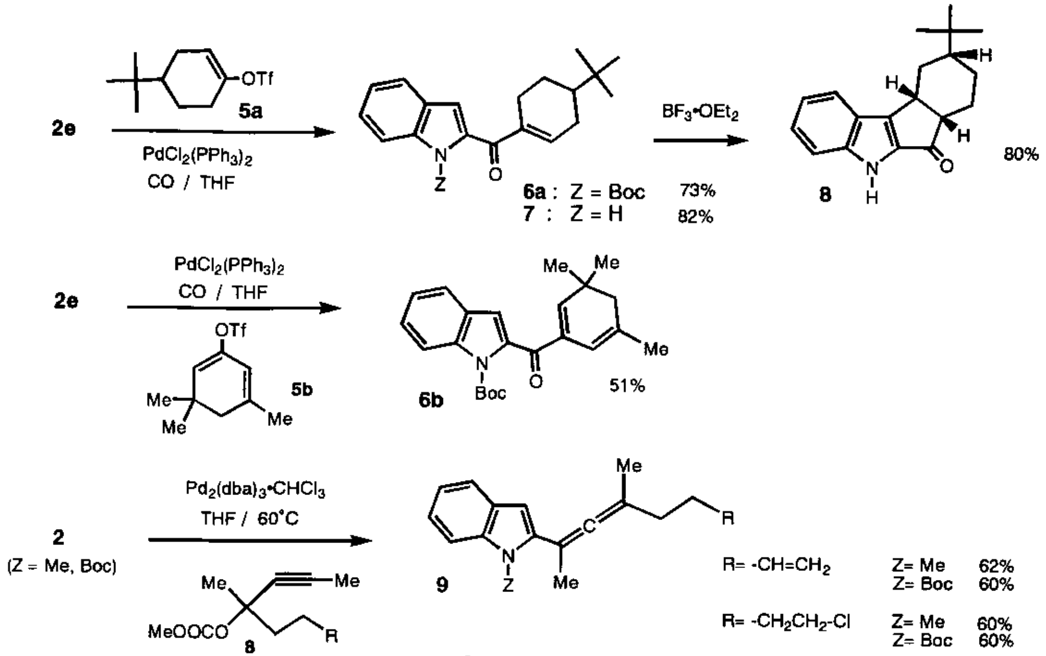
[a)] All yields are based on indole (**1**) [b)] No isolable products

BuLi, and bulky *tert*-butyldimethylsilyl substituted indole (**1h**) did not undergo any lithiation with *tert*-BuLi.[5] The cross-coupling reaction was undertaken by heating a mixture of indolylborate (**2**) with R-X (**3**) (1.5 equiv.) in the presence of $PdCl_2(PPh_3)_2$ (5 mol%) in THF at 60°C under an argon atmosphere for 0.5 h, except for the case of indolylborate (**2d**) for 2 h.

As reported previously,[2] the problem with indolylborate (**2b**) in the intramolecular alkyl migration process was an unexpected reduction of methoxymethyl (MOM) group to methyl group. The use of **2b** for the present cross-coupling reaction was initially attempted, but with very little success. Subsequently, we turned to the reaction of indolylborate (**2c**) with *N*-trimethylsilylethoxymethyl (SEM) group exerting higher stability,[6] which permitted the formation of the cross-coupling products (**4**) in still low yields. Less efficiency of indolylborate (**2d**) with strongly electron withdrawing benzenesulfonyl group in this reaction suggested the requirement of the increased electron density at the indole enamine system, as anticipated. However, using weaker electron withdrawing Boc group,[7] the reaction allowed the formation of the expected cross-coupling products (**4**) from indolylborate (**2e**) in comparable yields to those of **2a**. The thermolability of 1-methoxyindole increases with an increase in temperature,[8] but 1-methoxyindolylborate (**2f**) nevertheless appeared to be applicable to the present reaction.

Furthermore, indolylborate (**2e**) could be employed for the carbonylative cross-coupling process.[9] Treatment of **2e** with vinyltriflates (**5**) in the presence of $PdCl_2(PPh_3)_2$ (5 mol%) in THF at 60°C under carbon monoxide atmosphere (10 atm) for 60 h afforded indolylketones (**6**) in moderate to good yields (the reaction of **2a** with **5a** and **5b** produced the corresponding ketones in 77% and 69%, respectively). The deprotection of indole nitrogen of **6a** under an acidic condition gave ketone (**7**) in 82% yield, and subsequent exposure of **7** to the cyclization reaction with $BF_3{\bullet}OEt_2$ in benzene provided cyclopenta-[*b*]indole (**8**) in 80% yield. Also, the use of **2e** could be extended to the reaction with propargyl carbonate (**9**) in the presence of $Pd_2(dba)_3{\bullet}CHCl_3$ (5 mol%) in THF at 60°C,[10] producing 2-allenylindoles (**10**) as well as **2a**.

We have demonstrated that triethyl(1-*tert*-butoxycarbonylindol-2-yl)borate (**2e**) can be used for the palladium catalyzed cross-coupling reaction, and we are currently exploiting the use of **2e** as a potential intermediate for the construction of more complex indole derivatives.



Scheme 2

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3. a) M. Ishikura and M. Terashima, *J. Chem. Soc., Chem. Commun.*, 1989, 135; b) M. Ishikura, Y. Matsuzaki, and I. Agata, *Chem. Commun.*, 1996, 2409; c) M. Ishikura, T. Yaginuma, I. Agata, Y. Miwa, R. Yanada, and T. Taga, *Synlett*, 1997, 214.
4. Lithiation conditions: **1a**[8] and **1b**[5] with *tert*-BuLi in THF at rt for 1h; **1c**[7] with *tert*-BuLi at -78°C in THF for 2 h; **1d**,[2] **1e**[8] and **1f**[2] with *n*-BuLi in THF at -20°C for 20 min.
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