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Palladium-Catalyzed γ-Selective Arylation of Zincated Boc-Allylamines

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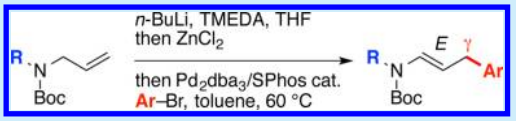
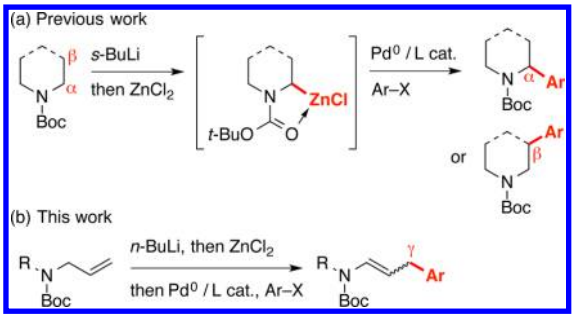
Supporting Information

ABSTRACT: The regio- and diastereoselective arylation of Boc-protected allylamines was performed via a one-pot lithiation/transmetalation to zinc/cross-coupling sequence, through an appropriate choice of a phosphine ligand. A variety of γ-arylated products were obtained in moderate to good yield, and the products could be directly transformed into valuable γ-arylamines and β-aryl aldehydes.



The Negishi coupling of α-zincated saturated Boc-amines, obtained by directed α-lithiation and transmetalation to zinc, has been established as a powerful method to access α-arylated amines (Scheme 1a).[1] By employing a less bulky and more flexible biarylphosphine ligand in the Pd-catalyzed step, we have shown that the migrative Negishi coupling of the intermediate α-zincated Boc-amine can be favored, giving rise to β-arylated Boc-amines in a selective manner (Scheme 1a).[1e,2] However, we were unable to selectively arylate homologous Boc-protected *n*-propylamines at the γ-position. To access these valuable γ-arylated amines[3] in a site-selective manner, we thus turned to a different strategy. Beak and co-workers have described the lithiation of Boc-allylamines with the *n*-BuLi/sparteine combination and have reacted the resulting configurationally stable allyllithium species with a variety of electrophiles to give enantiopure γ-functionalized allylamines.[4] We thought that these lithiated Boc-allylamines should be able to undergo transmetalation with a zinc(II) halide to generate an allylzinc species, which would then undergo one-pot Negishi coupling to furnish the corresponding γ-arylated allylamines (Scheme 1b). In turn, the latter should lead to γ-arylamines upon reduction of the double bond. At this point, two potential issues were to be addressed: the control of the γ- vs α-arylation selectivity and the control of the *E*/*Z* configuration of the formed substituted double bond. The γ- vs α-functionalization selectivity of lithiated Boc-allylamines was shown to depend on the nature of the electrophile, with carbon-based electrophiles generally giving rise to γ-functionalization, and the corresponding γ-functionalized products were obtained as major *Z* geometrical isomers.[4] However, to the best of our knowledge, the reactivity of the corresponding allylzinc reagents has not been reported.[5]

Scheme 1. Site-Selective Arylation of Zincated Boc-Amines



We first studied the lithiation/transmetalation/Negishi coupling of Boc-allylmethylamine **1a** (Table 1). As shown by quenching experiments with dimethyl sulfate,[6] the initial lithiation step was best performed with *n*-BuLi in THF at −78 °C as previously described (84% yield),[4] but lithium amides such as LDA could be also employed with similar results, which might be useful for more sensitive substrates. After in situ transmetalation of the so formed allyllithium species with zinc(II) chloride (1 equiv), the cross-coupling step was performed with *p*-trifluoromethylbromobenzene as the electrophile under various conditions (Table 1). Importantly, in all cases, the coupling occurred exclusively at the γ-position. First, the influence of various phosphine ligands was analyzed (entries 1−10). Interestingly, monophosphines of different types (entries 1−4) furnished coupling product **2a** in a completely *E*-selective manner albeit in low yield, with PCy_3 being the most efficient ligand (entry 3). In contrast, diphosphines such as dppf, dppe, and BINAP provided a separable mixture of *E* and *Z* isomers, with the *Z* isomer **2b** being the major product (entries 5−7). With Buchwald's biarylphosphine ligands $\mathbf{L^1}$−$\mathbf{L^3}$ (entries 8−10), **2a** was again obtained as the major diastereoisomer, with SPhos $\mathbf{L^2}$ being optimal (entry 9). With this ligand, further improvements in the yield were found with a lower excess of zincated **1a** (1.25 equiv) with regard to the aryl bromide (entry 11) and a lower temperature of 60 °C (entries 12−13). The recently introduced precatalyst **3** could be also employed instead of the $Pd_2dba_3/\mathbf{L^2}$ in situ combination,[7] albeit with slightly reduced efficiency (entry 14). Finally, the catalyst loading could be decreased to 2 mol % without detrimental effect on the yield

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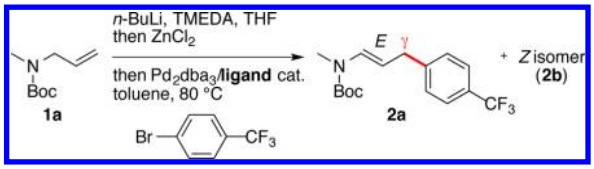
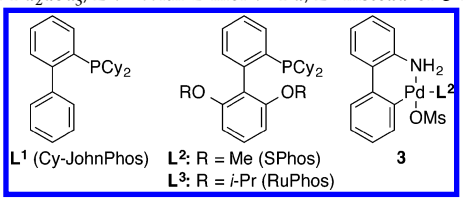
Table 1. Optimization of the Negishi Coupling of Boc-Allylmethylamine 1a[a]



entry	ligand	temp (°C)	E/Z[b]	yield of **2a** (%)[c]
1	PPh_3	80	>95:5	42
2	$P(t\text{-}Bu)_3$[d]	80	>95:5	34
3	PCy_3[d]	80	>95:5	51
4	PEt_3[d]	80	>95:5	14
5	dppf	80	40:60	31(23)[e]
6	dppe	80	44:56	27(28)[e]
7	BINAP	80	27:73	16(35)[e]
8	**L**[1]	80	90:10	57
9	**L**[2]	80	92:8	57
10	**L**[3]	80	80:20	49
11	**L**[2]	80	93:7	64[f]
12	**L**[2]	**60**	**95:5**	**75**[f]
13	**L**[2]	40	86:14	58[f]
14	**L**[2]	60	95:5	58[f,g]
15	**L**[2]	60	96:4	73[f,h]

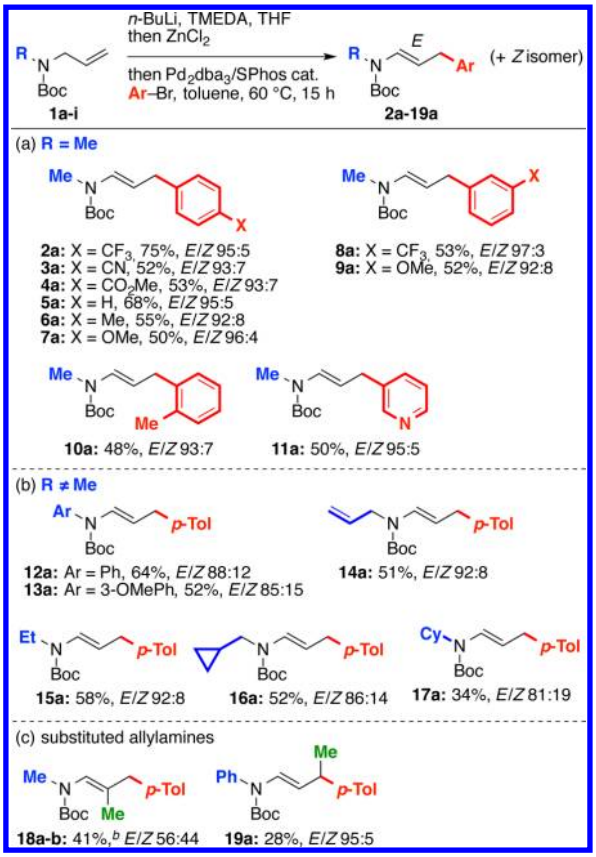
[a]Reaction conditions: **1a** (1.4 equiv), *n*-BuLi (1.4 equiv), TMEDA (1.4 equiv), THF, −78 °C, 1 h, then $ZnCl_2$ (1.4 equiv), −78 → 20 °C, then removal of volatiles under vacuum, then toluene, Pd_2dba_3 (2.5 mol %), ligand (5 mol %), 4-trifluoromethylbromobenzene (1.0 equiv), 80 °C, 15 h. [b]Determined by GCMS analysis of the crude mixture. [c]Yield of the isolated *E* isomer. [d]Introduced as HBF_4 salt. [e]Yield of the isolated *Z* isomer. [f]With 1.25 equiv of **1a**/*n*-BuLi/TMEDA/$ZnCl_2$ instead of 1.4 equiv. [g]With precatalyst **3** (5 mol %) instead of Pd_2dba_3/**L**[2]. [h]With 2 mol % Pd/**L**[2] instead of 5 mol %.



(entry 15). Under optimal conditions, *E*-configured coupling product **2a** was isolated in 75% yield (entry 12).[8]

The scope and limitations of this γ-arylation process were next evaluated under the optimal conditions (Scheme 2). First, a number of substituents were tolerated on the (hetero)aryl electrophile, with homogeneously good E/Z ratios (92%−97% of *E* isomer) and yields of the isolated *E* isomer in the range 48%−75% (Scheme 1a). Then the *N*-methyl group of **1a** was replaced with other substituents and the lithiation/transmetalation/arylation sequence was performed with *p*-bromotoluene as an unbiased electrophile (Scheme 1b). *N*-Aryl substituents displayed good performances in this three-step one-pot sequence (**12a**−**13a**). Allyl (**14a**), ethyl (**15a**), and methylcyclopropyl (**16a**) groups furnished moderate yields of the *E* isomer (51−58%), whereas the yield dropped with a cyclohexyl substituent (**17a**). This lower yield of **17a** can be ascribed to a more difficult lithiation due to increased steric hindrance,[1e,4] as indicated by the observation of larger quantities of the coupling product of *n*-BuZnCl (1-(*n*-butyl)-4-methylbenzene) by GCMS analysis. Further limitations were found in the reaction of Boc-allylmethylamines bearing an additional Me group at the β- or γ-position, which furnished the corresponding γ-arylated products in low yield (Scheme 2c). In the first case

Scheme 2. Scope and Limitations of the γ-Arylation of Boc-Allylamines[a]

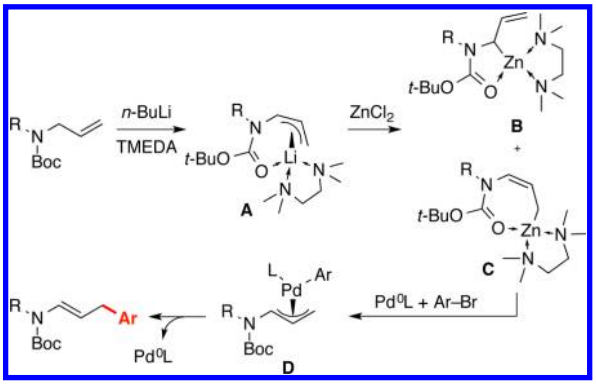


[a]Reaction conditions: Boc-allylamine (1.25 equiv), *n*-BuLi (1.25 equiv), TMEDA (1.25 equiv), THF, −78 °C, 1 h, then $ZnCl_2$ (1.25 equiv), −78 → 20 °C, then removal of volatiles, then toluene, Pd_2dba_3 (2.5 mol %), Sphos **L**[2] (5 mol %), Ar−Br (1.0 equiv), 60 °C, 15 h. Yields refer to the isolated *E* isomer unless otherwise stated. [b] Yield of the E/Z mixture.

(**18a**−**b**), this can be ascribed to a more difficult lithiation step, as indicated by the observation of large amounts of 1-(*n*-butyl)-4-methylbenzene, whereas in the second case (**19a**) the cross-coupling step is implicated, as indicated by the observation of unreacted aryl bromide.

A plausible mechanism of the lithiation/transmetalation/cross-coupling sequence based on previous literature elements is shown in Scheme 3. The lithiation of a Boc-allylamine with *n*-

Scheme 3. Proposed Organometallic Intermediates in the Lithiation/Transmetalation/Cross-Coupling Sequence



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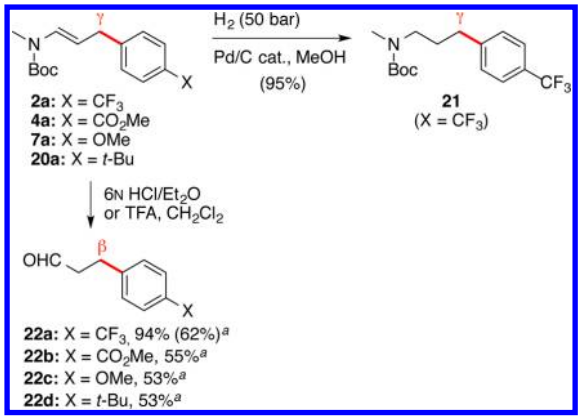
BuLi/TMEDA should lead to Boc-coordinated η^3-allyllithium compound **A**, on the basis of the X-ray diffraction and NMR studies of the analogous sparteine complex isolated by Beak and co-workers.[9] In contrast, allylzinc compounds have been recently shown to exhibit η^1-allyl and not η^3-allyl coordination.[10] On this basis, transmetalation of **A** with zinc chloride is proposed to give rise to Boc-coordinated η^1-allylzinc compound **B** and/or **C**, by analogy with related organotin and organosilicon compounds.[4c] Subsequent transmetalation with the organopalladium species $ArPd^{II}BrL$, arising from oxidative addition of ArBr to monoligated Pd^0L,[11] should furnish η^3-allylpalladium complex **D**.[12] Reductive elimination from **D** at the least hindered γ-position would furnish the observed γ-arylated product. The γ-arylation selectivity and the *E*-diastereoselectivity observed in the current reaction are both consistent with an η^3-allylpalladium intermediate **D** rather than an η^1-allyl coordination mode (analogous to **B** and **C** with Pd instead of Zn).

The α,β-unsaturated γ-arylated enecarbamates obtained through the current method are isomeric to compounds obtained by Heck-type reactions, in which the double bond is located at the β,γ-position and the aryl group at the β- or γ-position,[13] and therefore both cross-coupling methods are complementary. In the present case, the coupling products can be further derivatized to access valuable organic intermediates (Scheme 4). First,

Scheme 4. Postfunctionalizations of γ-Arylated Enecarbamates



[a]Yield for two steps (arylation and hydrolysis).

hydrogenation of the C═C bond of **2a** provided γ-aryl-Boc-amine **21**, thereby nicely complementing our previously described α- and β-arylation of saturated acyclic Boc-amines.[1e] In addition, acidic hydrolysis of the enecarbamate group of **2a** furnished β-arylated aldehyde **22a** in 94% yield. The γ-arylation/hydrolysis sequence could be also conducted without isolation of the enecarbamate intermediate, as illustrated with the synthesis of aldehydes **22a**−**d** in 53%−62% overall yield from the corresponding aryl bromides. Thus, the current method provides a novel and rapid entry into this useful class of aldehydes.

In conclusion, we have developed a new method allowing the selective γ-arylation of Boc-protected allylamines via a one-pot lithiation/transmetalation/cross-coupling sequence. This method is complementary to previously reported α- and β-arylations of Boc-amines. High *E*-stereoselectivity was achieved through the proper choice of a phosphine ligand in the coupling step. A variety of arylated products were obtained in moderate to good yield, and the products could be easily transformed into valuable γ-arylamines and β-aryl aldehydes.

■ ASSOCIATED CONTENT

Supporting Information

Full characterization of all new compounds, detailed experimental procedures, and copies of NMR spectra for target molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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