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Preparation and palladium-mediated cross-coupling of α-benzoyloxyalkylzinc bromides

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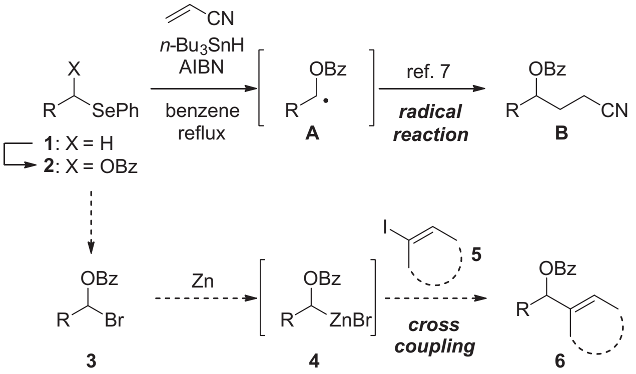
ABSTRACT

Here we report a two-step preparation protocol of α-benzoyloxyalkylzinc bromides from α-benzoyloxyalkyl selenides, and their application to palladium-catalyzed cross-coupling reactions with aryl and vinyl iodides. The developed method effectively provides a variety of benzoyl-protected benzylic and allylic alcohol derivatives through the formation of C(sp^3)–C(sp^2) bonds without affecting various polar functional groups.

The transition metal-mediated cross-coupling reaction between organozinc compounds and organohalides, known as the Negishi coupling reaction, has been utilized as a mild and powerful C–C bond formation.[1] Effective formation of not only C(sp^2)–C(sp^2) bonds but also C(sp^3)–C(sp^2) and C(sp^3)–C(sp^3) bonds has been achieved over the years.[2] Accordingly, Negishi coupling reactions have been implemented in synthetic routes to many architecturally complex natural products.[3]

α-Oxyalkyl metals are versatile reaction intermediates for the introduction of oxygen-substituted sp^3-carbon centers, and their cross-coupling reactions are especially useful for the construction of multiple oxygenated carboskeletons of natural products. Consequently, transition metal-catalyzed reactions of α-oxystannanes[4] and α-oxyborates[5] have been developed to connect the α-oxy carbon centers with C(sp^2) or C(sp^3) centers of the coupling partners. On the other hand, α-oxyalkylzinc reagents are rarely employed for cross-coupling reactions, and only their Cu-mediated reactions have been disclosed.[6] Here we report a two-step preparation protocol of α-benzoyloxyalkylzinc bromides from α-benzoyloxyalkyl selenides, and their application to the Negishi coupling reaction with aryl and vinyl iodides.

Previously, we developed the intermolecular radical reaction of α-acyloxyalkyl selenide **2**, which was prepared by the seleno-Pummerer reaction of alkyl selenide **1** (Scheme 1). The radical species **A**, generated from **2**, efficiently added to C=C double bonds to deliver the adduct **B** via formation of a C(sp^3)–C(sp^3) bond.[7] Due to the reliability in its preparation and chemical stability in its handling, we planned to use selenide **2** as a precursor to highly reactive α-benzoyloxyalkyl bromide **3**. Specifically, displacement of the phenylselenyl group of **2** with a Br atom would generate bromide **3**.[8] Next, zincation of **3** would lead to α-benzoyloxyalkylzinc bromide **4**,[9] which would couple with aryl or vinyl iodide **5** by the action of a palladium catalyst to afford **6** through C(sp^3)–C(sp^2) bond formation. Importantly, product **6** has a characteristic structure that is not accessible by the radical-based methodology. In addition, this reaction sequence would expand the potential utility



Scheme 1. Plan for preparation and cross-coupling of α-benzoyloxyalkylzinc bromides.

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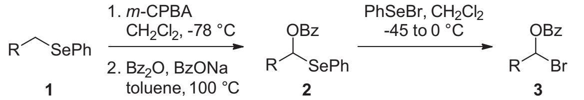
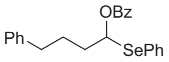
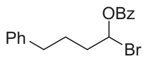
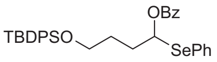
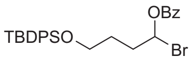
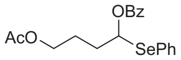
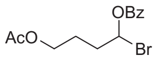
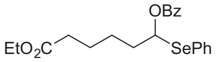
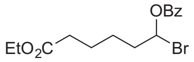
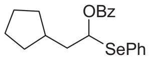
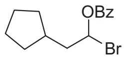
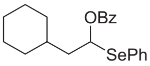
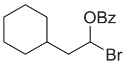
Table 1
Syntheses of α-benzoyloxyalkyl bromides **3**[a]



entry	α-benzoyloxyalkyl selenide **2** and yield	α-benzoyloxyalkyl bromide **3** and yield
1	 **2a**: 88%	 **3a**: 86%
2[b]	 **2b**: 81%	 **3b**: 64%
3	 **2c**: 55%	 **3c**: 90%
4	 **2d**: 46%	 **3d**: 86%
5	 **2e**: 86%	 **3e**: 75%
6	 **2f**: 88%	 **3f**: 74%

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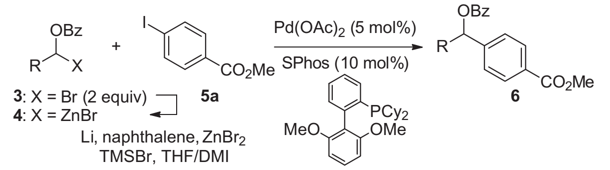
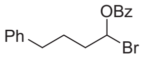
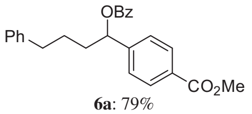
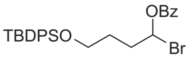
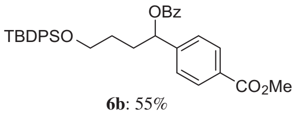
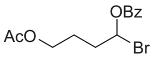
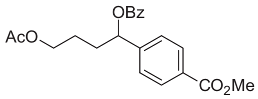
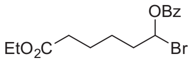
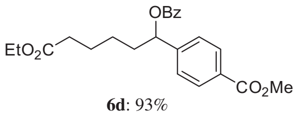
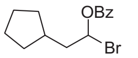
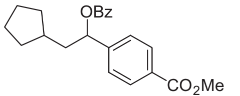
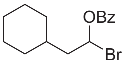
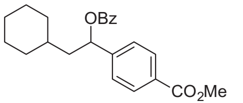
[a] Conditions for bromination: **2**, PhSeBr (1.5 equiv), CH_2Cl_2 (0.1 M).

[b] Conditions for bromination: **2b**, PhSeBr (1.0 equiv), $NaHCO_3$ (1.0 equiv), CH_2Cl_2 (0.1 M), 0 °C.

Table 2
Coupling reactions of various α-benzoyloxyalkyl bromides **3** with aryl iodide **5a**[a]



entry	α-benzoyloxyalkyl bromide **3**	product **6** and yield
1	 **3a**	 **6a**: 79%
2	 **3b**	 **6b**: 55%
3	 **3c**	 **6c**: 78%
4	 **3d**	 **6d**: 93%
5	 **3e**	 **6e**: 92%
6	 **3f**	 **6f**: 98%

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[a] Reagents and conditions: **3** (2.0 equiv), Li (8.0 equiv), naphthalene (8.0 equiv), $ZnBr_2$ (4.0 equiv), TMSBr (0.1 equiv), THF/DMI = 1/1 (0.1–0.2 M), rt; **5a** (1.0 equiv), $Pd(OAc)_2$ (5 mol %), SPhos (10 mol %), rt.

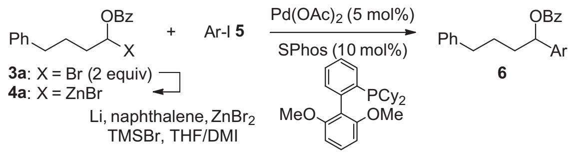
of α-acyloxyalkyl selenide **2** as a stable synthetic intermediate for transition metal catalyzed reactions.

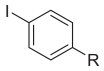
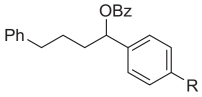
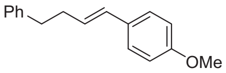
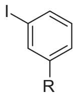
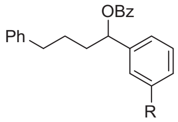
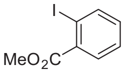
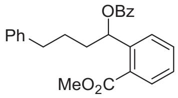
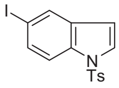
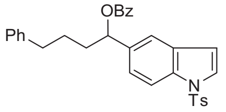
First, the structurally distinct α-benzoyloxyalkyl selenides **2a**–**f** were synthesized from the corresponding selenides **1a**–**f** (Table 1), demonstrating the high applicability of the seleno-Pummerer reaction.[7,10] The selenoxides, which were produced by *m*-CPBA oxidation of selenides **1a**–**f** at −78 °C, were heated to 100 °C in toluene with Bz_2O and BzONa, leading to the rearranged products **2a**–**f**. Exchange of the phenyl selenide with the bromide was realized by the action of PhSeBr.[11] When **2a** was treated with PhSeBr at −45 °C in CH_2Cl_2, α-benzoyloxyalkyl bromide **3a** was smoothly formed (entry 1). The acid-labile TBDPS protective group was retained during the conversion of **2b** into **3b** (entry 2), although the addition of $NaHCO_3$ as an acid scavenger was necessary. The acetyl and ethoxycarbonyl groups of **2c** and **2d** were compatible with the bromination conditions, affording **3c** and **3d**, respectively (entries 3 and 4). Furthermore, more sterically congested **2e** and **2f** bearing cycloalkane moieties were transformed to **3e** and **3f**, respectively, under the same conditions (entries 5 and 6).

Having established the procedure for syntheses of α-benzoyloxyalkyl bromides **3a**–**f**, we explored their zincation and subsequent Negishi coupling reactions with aryl iodide **5a** (Table 2). After screening the reagents and conditions, Rieke's protocol[12] was adopted for zincation in a 1:1 mixed solvent of THF and 1,3-dimethyl-2-imidazolidinone (DMI),[13,14] and Pd(OAc)/SPhos[15] was applied as the catalyst for the cross-coupling. Namely, organozinc species **4a** was first generated from 2 equiv of **3a** in THF/DMI at room temperature, and then coupled with 1 equiv of aryl iodide **5a** in the presence of $Pd(OAc)_2$ (5 mol %) and SPhos (10 mol %) to afford the adduct **6a** (entry 1). This coupling procedure enabled to the production of **6b**–**d** without affecting the TBDPS (entry 2), Ac (entry 3), and ethoxycarbonyl (entry 4) groups. The alkylzinc compounds **4e** and **4f** with branched carboskeletons were also coupled with **5a** to provide **6e** and **6f**, respectively (entries 5 and 6).

The broad scope of the cross-coupling was demonstrated using aromatic iodides **5b**–**k** having various functional groups on the benzene rings (Table 3). Aryl iodides bearing electron-withdrawing groups at the *para*-position efficiently functioned as the coupling partners of α-benzoyloxyalkylzinc bromide **4a** to provide products **6g**–**k** (entries 1–5). The yields of nitrile **6j** (entry 4) and aldehyde **6k** (entry 5) were modest, but were increased when $Pd(dba)_2$ (10 mol %) and TFP (20 mol %)[16,17] were used as the catalyst instead of $Pd(OAc)_2$/SPhos. The intact aldehyde moiety of the coupled product **6k** highlighted the high chemoselectivity of the present C–C bond formation. While the electron-donating *para*-methoxy group caused β-elimination of the benzoate group of **6l** after the coupling to afford **7** (entry 6), the *meta*-methoxy group induced no elimination, and the adduct **6m** was obtained (entry 7). In contrast to the high-yielding transformations of methyl *para*-iodobenzoate **5a** (79%, entry 1, Table 2) and methyl *meta*-iodobenzoate **5i** (85%, entry 8), the yield of methyl *ortho*-iodobenzoate **5j** was lower (27%, entry 9), suggesting that the methoxycarbonyl group adjacent to the reacting carbon negatively affected the coupling

Table 3
Coupling reactions of α-benzoyloxyalkyl bromide **3a** with various aryl iodides **5**[a]



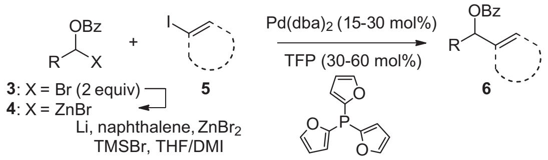
entry	Ar-I **5**	products **6** and yield
		
1	**5b**: R = COMe	**6g**: 95%
2	**5c**: R = CONH$_2$	**6h**: 81%
3	**5d**: R = NO$_2$	**6i**: 77%
4	**5e**: R = CN	**6j**: 72% (90%)[b]
5	**5f**: R = CHO	**6k**: 31% (70%)[b]
6	**5g**: R = OMe	**6l**: 0%
		 **7**: 37%
		
7[c]	**5h**: R = OMe	**6m**: 42%
8	**5i**: R = CO$_2$Me	**6n**: 85%
9	 **5j**	 **6o**: 27%
10	 **5k**	 **6p**: 58%

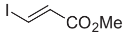
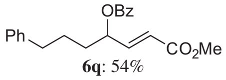
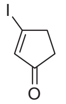
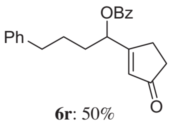
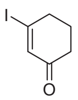
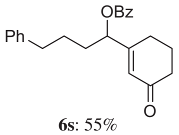
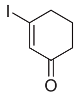
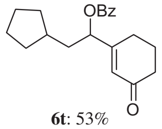
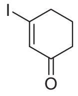
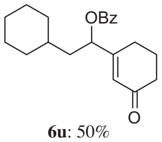
[a] Reagents and conditions: **3a** (2.0 equiv), Li (8.0 equiv), naphthalene (8.0 equiv), ZnBr$_2$ (4.0 equiv), TMSBr (0.1 equiv), THF/DMI = 1/1 (0.1–0.2 M), rt; **5** (1.0 equiv), Pd(OAc)$_2$ (5 mol %), SPhos (10 mol %), rt.

[b] Yield in parentheses was obtained, when Pd(dba)$_2$ (10 mol %) and TFP (20 mol %) were used instead of Pd(OAc)$_2$ and SPhos.

[c] The reaction was performed at 0 °C.

Table 4
Coupling reactions between α-benzoyloxyalkyl bromide **3** and vinyl iodides **5**[a]



entry	**3**	vinyl iodide **5**	product **6** and yield
1[a]	**3a**	 **5l**	 **6q**: 54%
2[a]	**3a**	 **5m**	 **6r**: 50%
3[b]	**3a**	 **5n**	 **6s**: 55%
4[b]	**3e**	 **5n**	 **6t**: 53%
5[b]	**3f**	 **5n**	 **6u**: 50%

[a] Reagents and conditions: **3** (2.0 equiv), Li (8.0 equiv), naphthalene (8.0 equiv), ZnBr$_2$ (4.0 equiv), TMSBr (0.1 equiv), THF/DMI = 1/1 (0.1–0.2 M), rt; **5** (1.0 equiv), Pd(dba)$_2$ (15 mol %), TFP (30 mol %), rt.

[b] Reagents and conditions: **3** (2.0 equiv), Li (8.0 equiv), naphthalene (8.0 equiv), ZnBr$_2$ (4.0 equiv), THF/DMI = 1/1 (0.1–0.2 M), rt; **5n** (1.0 equiv), Pd(dba)$_2$ (30 mol %) and TFP (60 mol %), rt.

efficiency. Finally, indole derivative **5k** was coupled with **4a** to provide **6p** (entry 10).

The versatility of the α-benzoyloxyalkylzinc bromides was further proven by their successful cross-coupling reactions with vinyl iodides (Table 4). For these reactions, the Pd(dba)$_2$/TFP catalyst system was found to be consistently superior to the Pd(OAc)$_2$/SPhos system. Pd(dba)$_2$/TFP indeed promoted the reaction between (*E*)-methyl 3-iodoacrylate **5l** and zinc bromide **4a** to produce the adduct **6q** (entry 1). Cyclic vinyl iodides **5m** and **5n** also participated in the reaction with **4a**, giving rise to **6r** and **6s**, respectively (entries 2 and 3). When organozinc compounds bearing the cycloalkanes (**4e** and **4f**) and the cyclic vinyl iodide **5n** were employed, the cross-coupling reaction delivered **6t** and **6u**, respectively, with the two carbocycles (entries 4 and 5).

In summary, we have developed a two-step protocol for the preparation of α-benzoyloxyalkylzinc bromides from the chemically stable α-benzoyloxyalkyl selenides, and demonstrated the generality of the α-acyloxyzinc reagents as reactive intermediates for palladium-mediated cross-coupling reactions. The present zincation and coupling reactions both proceeded at room temperature under mild conditions, and effectively provided benzylic and allylic alcohol derivatives through formation of C(sp^3)–C(sp^2) bonds without affecting a wide range of potentially reactive electrophilic functional groups.

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Supplementary data

Supplementary data (experimental protocol and characterization data of all newly synthesized compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.114.

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