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Pd-catalyzed γ-arylation of γ,δ-unsaturated *O*-carbamates *via* an unusual haptotropic rearrangement†

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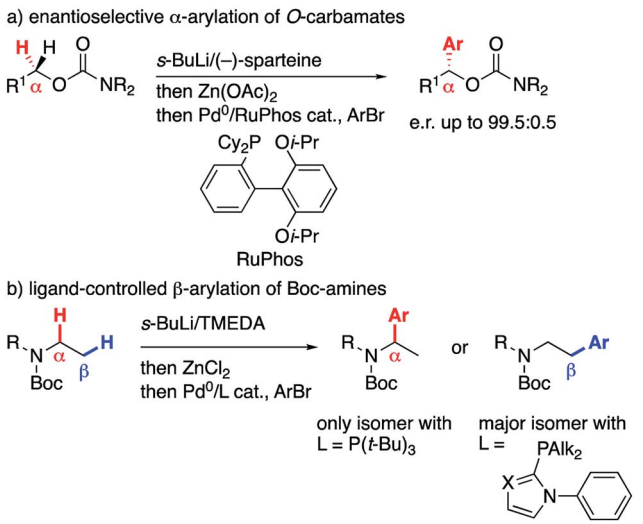
An unusual γ-selectivity was observed in the arylation of γ,δ-unsaturated *O*-carbamates involving directed lithiation, transmetallation to zinc and Negishi coupling, when a specific combination of aryl electrophile and phosphine ligand is employed. Mechanistic studies indicate that an unusual, stereospecific haptotropic rearrangement of the palladium–diene intermediate is involved.

Introduction

The directed α-lithiation of *N*- and *O*-carbamates in the presence of a chiral diamine such as sparteine allows access to synthetically valuable enantioenriched amine and alcohol derivatives.[1] In this context, we recently showed that α-zincated *O*-carbamates, obtained by sparteine-mediated α-lithiation and transmetallation to zinc, could be cross-coupled with aryl bromides to give highly enantioenriched α-arylated *O*-carbamates (Scheme 1a), which were further converted to secondary and tertiary alcohols.[2]

On the other hand, within a research program dedicated to the control of site-selectivity in the Pd-catalyzed cross-coupling of secondary nucleophiles,[3] we reported that α-zincated acyclic Boc-amines undergo α- or β-selective arylation simply by switching the phosphine ligand (Scheme 1b),[4] with the β-arylated product arising from a 'chain walk' mechanism.[5] While we were trying to extend the migratory Negishi coupling from these *N*- to the above-mentioned *O*-carbamates, we uncovered a new reactivity of γ,δ-unsaturated substrates, which we wish to describe therein.



Scheme 1 Previous work relevant to the current study. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

Results and discussion

In our previous work, we showed that the α-lithiation/Li–Zn transmetallation/cross-coupling sequence[6] applied to γ,δ-unsaturated carbamate **1a** gave rise to α-arylated product **2a** exclusively using bromobenzene as the electrophile and RuPhos[7] as the ligand (Table 1, entry 1).[2] When *o*-fluorobromobenzene, which was previously shown to favor Pd migration,[8] was employed instead of PhBr, the same reaction outcome was observed (entry 2). Replacing RuPhos with the less bulky and more conformationally flexible phosphine $\mathbf{L^1}$, which was previously optimized to favor Pd migration,[4,9] did not afford any cross-coupling product (entry 3). After a quick ligand screen,[10] we found that imidazole-based phosphine[11] $\mathbf{L^2}$ furnished a mixture of α, β and γ-arylated products **2–4**, with the latter being obtained as a *Z*/*E* mixture (entry 4). Interestingly, the proportion of these unexpected γ-arylated products increased when the reaction was conducted from the δ-substituted *E*-enecarbamate **1b*E***, which allowed isolation of the mixture of **4b*Z*** and **4b*E*** and confirmation of their structural identity (entry 5). Modifying the ligand structure impacted the yield and *Z*/*E* ratio.[10] For instance, ligand $\mathbf{L^3}$ provided a lower yield of the γ-arylated products but a slightly enhanced *Z*/*E* ratio (entry 6). Despite significant experimentation, the modification

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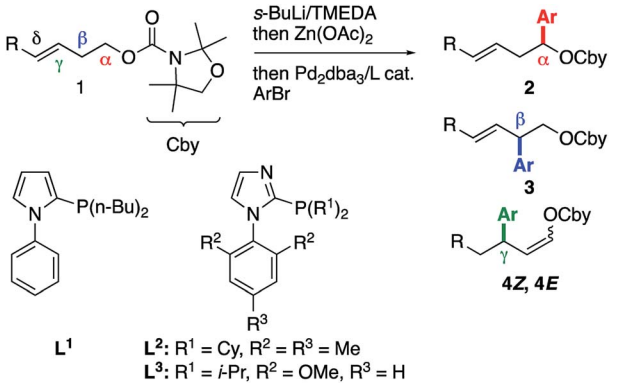
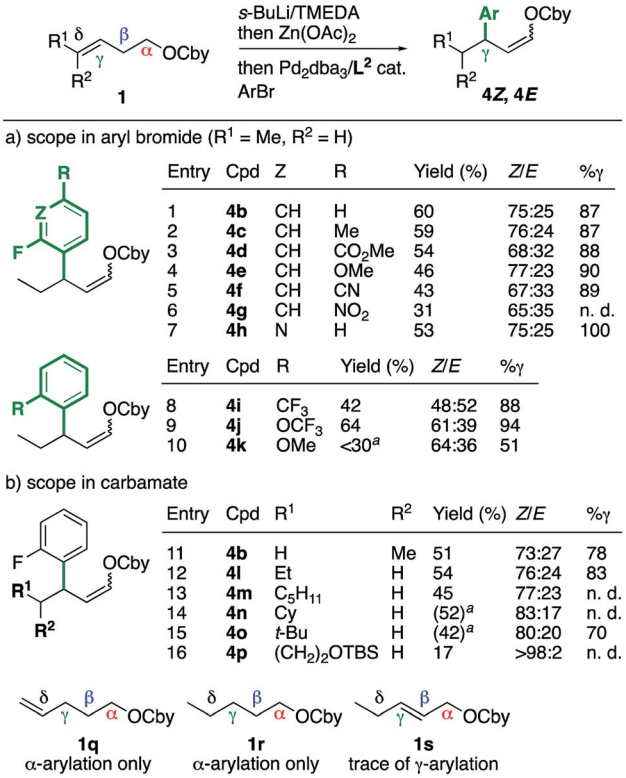
Table 1 Arylation of γ,δ-unsaturated *O*-carbamates[a]



Entry	R	ArBr	Ligand	**2**/**3**/**4Z**/**4E**[b]	Yield[c] (%)
1	H (**1a**)	PhBr	RuPhos	100 : 0 : 0 : 0	60[d]
2	H (**1a**)	2-F-C_6H_4Br	RuPhos	100 : 0 : 0 : 0	54
3	H (**1a**)	2-F-C_6H_4Br	L^1	—	n.r.
4	H (**1a**)	2-F-C_6H_4Br	L^2	18 : 25 : 40 : 17	33
5	Me (**1b*E***)	2-F-C_6H_4Br	L^2	9 : 6 : 64 : 21	61 (60)[e]
6	Me (**1b*E***)	2-F-C_6H_4Br	L^3	16 : 1 : 73 : 10	44
7	Me (**1b*E***)	2-F-C_6H_4Br	RuPhos	70 : 0 : 22 : 7	n.d.
8	Me (**1b*E***)	2-Me-C_6H_4Br	L^2	96 : 0 : 1 : 3	n.d.

[a] Reaction conditions: **1a–b** (1.0 equiv.), s-BuLi (1.4 equiv.), TMEDA (1.4 equiv.), Et_2O, −78 °C, 4 h, then $Zn(OAc)_2$ (1.5 equiv.), −78 → 20 °C, 1 h, then evaporation of volatiles, then Pd_2dba_3 (1.75 mol%), ligand (3.5 mol%), ArBr (0.7 equiv.), toluene, 60 °C, 18 h. [b] Determined by GCMS analysis. [c] Combined NMR yield using trifluorotoluene as the internal standard. [d] Yield of the isolated product. [e] Yield of the isolated mixture of **4b*Z*** and **4b*E***.

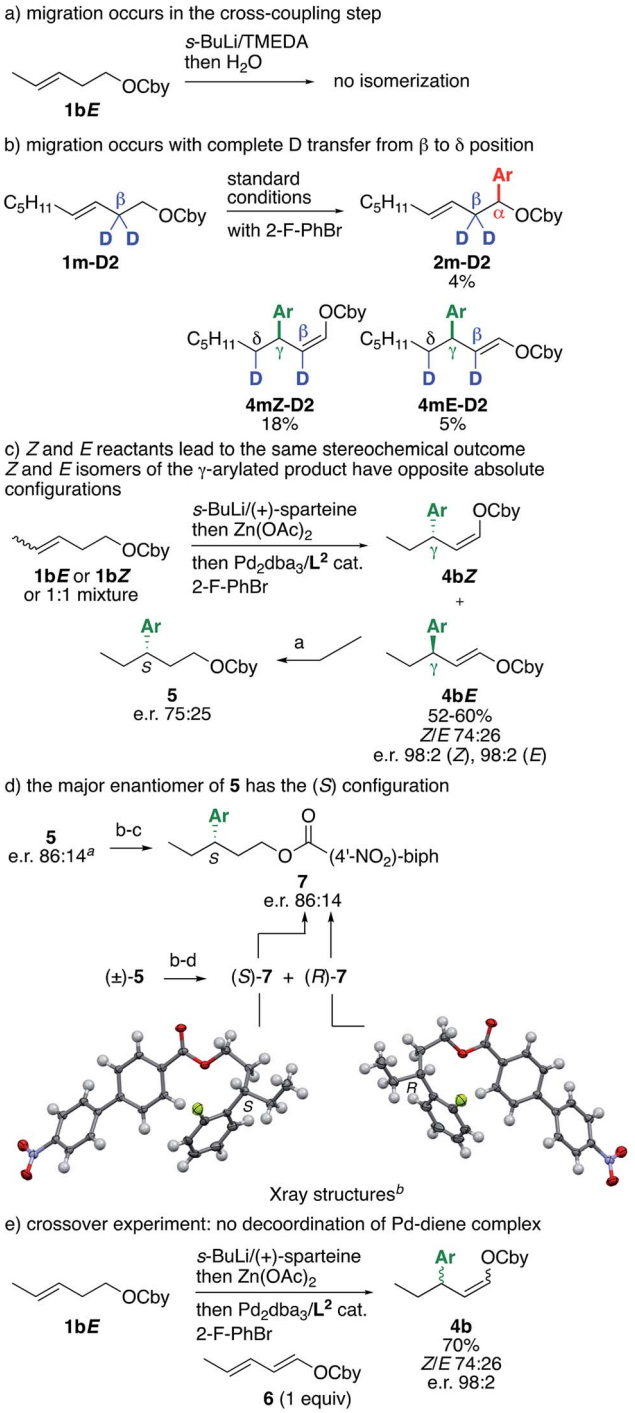


Scheme 2 Scope of the γ-arylation of γ,δ-unsaturated *O*-carbamates. Yields refer to isolated mixtures of *Z*/*E* isomers unless otherwise noted. *Z*/*E* ratios were measured by ^{19}F NMR. % γ refers to the percentage of γ-arylated product *vs.* other arylated products, as measured by GCMS. [a] Yield of the isolated mixture of inseparable arylated products. n. d. = could not be determined.

of other reaction parameters did not lead to substantial improvements of the yield or the *Z*/*E* ratio of product **4b**.[10] Of note, the use of RuPhos (entry 7) or of a less electronically activated electrophile (entry 8) in the reaction of carbamate **1b*E*** mainly furnished the α-arylated product, thereby highlighting the role of both the aryl electrophile and the phosphine ligand on the formation of the γ-arylated products **4**. Moreover, the δ-arylated product was not observed in these experiments. Stimulated by the apparent lack of precedent for the formation of allylic products **4** from a homoallylic precursor such as **1**,[12] we decided to further study this transformation and elucidate its mechanism.

First, we explored the effect of the aryl electrophile on the arylation of γ-enecarbamate **1b*E*** (Scheme 2a). A range of 2-fluoroarenes bearing electron-withdrawing or -donating groups at the 4-position were found compatible (entries 2–6) and had a minor impact on the *Z*/*E* (65 : 35–77 : 23) and γ-selectivity (87–90%), hence further highlighting the main effect of the fluorine atom at the *ortho* position. Interestingly, 3-bromo-2-fluoropyridine had a stronger effect and provided the γ-arylated product **4h** exclusively (entry 7). Other electron-withdrawing *ortho* substituents favored the γ-arylated product, but with lower *Z*/*E* selectivities (entries 8 and 9). A methoxy group afforded a lower γ-selectivity (entry 10), with an effect between a methyl (Table 1, entry 8) and electron-withdrawing groups. Next, other γ-enecarbamates were studied (Scheme 2b). The configuration of the alkene did not have a significant impact on the yield, *Z*/*E* or γ-selectivity (entry 11, compare with entry 1), hence showing that *E* and *Z* alkenes lead to the same reaction intermediate. Other δ-substituted γ-enecarbamates provided a similar outcome (entries 12–16), although the γ-selectivities could not be determined in all cases due to overlaps of the signals of the α, β and γ isomers in the GC analysis. Control experiments with δ-enecarbamate **1q** and saturated enecarbamate **1r** provided the α-arylated product exclusively, whereas the β-enecarbamate **1s** provided traces of γ-arylated products. These results confirm the unique behavior of γ,δ-unsaturated carbamates, leading to reaction intermediates that are not accessible from other types of *O*-carbamates.

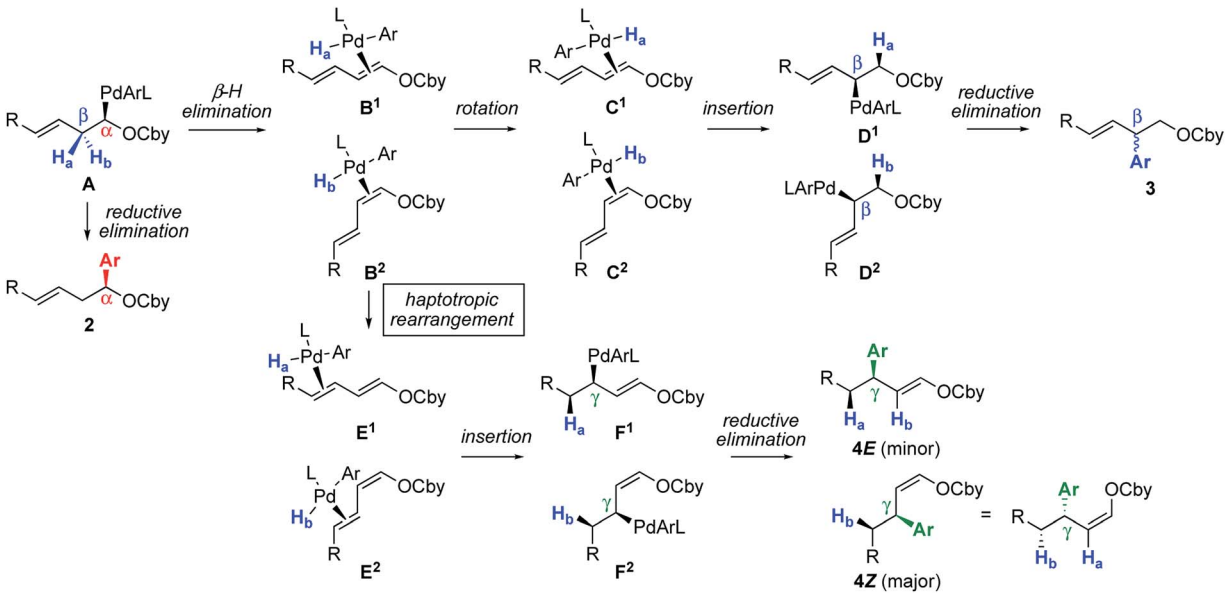
A number of experiments were next performed to probe the reaction mechanism (Scheme 3). First, as an additional control experiment, lithiation of **1b*E*** and quenching with water returned the reactant without isomerization of the alkene (Scheme 3a). This experiment complements the one reported in Table 1, entry 7, using RuPhos as the ligand, and shows that the double bond migration occurs after transmetallation to Pd and is ligand-induced. Performing the reaction under standard conditions from β-deuterated substrate **1m-D2** delivered a mixture of α-, β- and γ-arylated products as expected, which



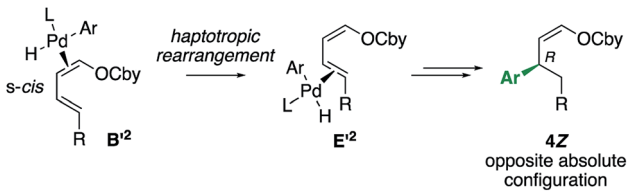
Scheme 3 Mechanistic investigations. Reaction conditions: (a) H_2 (50 bar), Pd/C, EtOH, 50 °C; (b) $MeSO_3H$, MeOH, reflux, then $Ba(OH)_2$, reflux; (c) ClC(O)(4′-NO_2-biphenyl), Et_3N, DMAP, CH_2Cl_2, 23 °C; (d) separation of enantiomers by semipreparative HPLC on a chiral stationary phase. Ar = 2-FC_6H_5. [a] Obtained from **1b*E*** using L^3 instead of L^2 in the cross-coupling step. [b] Thermal ellipsoids at the 50% probability level.

could be purified to isolate a small quantity of α- and γ-arylated products (Scheme 3b). The α-arylated product **2m-D2** retained a fully deuterated β position, whereas the γ-arylated products **4mZ-D2** and **4mE-D2** both showed a complete shift of one deuterium from the β to the δ position, consistent with a β-H elimination/insertion mechanism. Performing the lithiation with (+)-sparteine instead of TMEDA[2] afforded other crucial pieces of information (Scheme 3c). Enecarbamates **1b*E***, **1b*Z*** or a 1 : 1 mixture thereof led to the same 74 : 26 *Z*/*E* mixture of γ-arylated products **4b*Z*/4b*E***, with an e.r. of 98 : 2 for both *Z* and *E* isomers. Hence, the absolute configuration of **4b*Z*** and **4b*E*** does not depend on the geometry of the starting alkene. Hydrogenating this mixture provided saturated compound **5** with an e.r. of 75 : 25, showing that **4b*Z*** and **4b*E*** have opposite absolute configurations – if they had the same absolute configuration, the e.r. of **5** would be also 98 : 2. This experiment was repeated several times and was found to be reproducible. Similarly, an 87 : 13 mixture of **4b*Z*/4b*E*** obtained using ligand L^3 instead of L^1 (see Table 1, entry 6) led to an 86 : 14 e.r. for hydrogenated product **5** (Scheme 3d). Determining the absolute configuration of the major enantiomer of **5** was key to elucidate the reaction mechanism (*vide infra*), however it also turned out to be a bigger challenge than expected. After significant experimentation, we found that the heavy *p*-nitrobiphenyl ester **7**, obtained through cleavage of the Cby carbamate under Hoppe's conditions[13] and esterification, was suitable for obtaining single crystals (Scheme 3d). First, a racemic sample of **7** was prepared using TMEDA instead of (+)-sparteine in the lithiation step, then the enantiomers were separated by semipreparative HPLC on a chiral column.[10] Both enantiomers were crystallized and analyzed by X-ray diffraction, which allowed to ascribe their absolute configurations. The (*S*) and (*R*) enantiomers corresponded to the major and minor enantiomers, respectively, obtained through the (+)-sparteine-mediated sequence, and hence the absolute configuration of the major enantiomers of precursors **5** and **4b*Z*** can be also ascribed as (*S*).

The ensemble of collected experimental information allows to propose the following mechanism (Scheme 4). As shown previously, the initial organopalladium **A** obtained by (+)-sparteine-mediated lithiation and stereoretentive Li–Zn and Zn–Pd transmetallations undergoes direct reductive elimination in the presence of usual ligands and electrophiles to give the α-arylated product **2** with the shown absolute configuration.[2] Alternatively, ligand-enabled *syn*-stereospecific β-elimination of H_a or H_b provides π-complexes $\mathbf{B^1}$ or $\mathbf{B^2}$, respectively. From this point, two pathways are accessible: π-bond rotation and *syn*-insertion[4,8a,14] to give complexes $\mathbf{D^1}$ and $\mathbf{D^2}$ *via* $\mathbf{C^1}$ and $\mathbf{C^2}$, and reductive elimination to give the β-arylated product **3** (the absolute configuration of which could not be determined). Alternatively, sterically favored migration of the Pd complex to the other double bond, known as haptotropic rearrangement,[15] provides isomers $\mathbf{E^1}$–$\mathbf{E^2}$. Such a stereospecific haptotropic rearrangement along a conjugated polyene is extremely rare.[16,17] Of note, π-complexes $\mathbf{B^1}$–$\mathbf{B^2}$ and $\mathbf{E^1}$–$\mathbf{E^2}$ are stable and do not undergo reversible decoordination–coordination, as indicated by the lack of observed racemization when the reaction was performed in the presence of dienecarbamate **6** (Scheme 3e). From $\mathbf{E^1}$ and $\mathbf{E^2}$, *syn*-insertion and reductive elimination lead to products **4*E*** and **4*Z***, respectively, *via* $\mathbf{F^1}$ and $\mathbf{F^2}$. The deuterium-labelling experiment shown in Scheme 3b is consistent with the pathway **A** → $\mathbf{F^1}$–$\mathbf{F^2}$. The opposite absolute configurations of the



Scheme 4 Proposed mechanism.



Scheme 5 Haptotropic rearrangement from the s-*cis* conformation.

major enantiomers of **4b*Z*** and **4b*E*** deduced from Scheme 3c and d are also consistent with this pathway, wherein all elementary steps are stereospecific. This mechanistic proposal also explains the fact that both *E* and *Z* geometrical isomers of **A** furnish the same stereochemical outcome (Scheme 3c).

Moreover, the absolute configuration of **4b*Z*** and **4b*E*** allows to specify that the haptotropic rearrangement occurs from the s-*trans* conformation for dienic intermediates $\mathbf{B^1}$ and $\mathbf{B^2}$. Haptotropic rearrangement from the s-*cis* conformer $\mathbf{B'^2}$ would lead to the main stereoisomer **4*Z*** with the opposite, wrong absolute configuration (Scheme 5).

Conclusions

The arylation of γ,δ-unsaturated *O*-carbamates *via* directed lithiation, transmetallation to zinc and Negishi coupling occurs with an unusual γ-selectivity when a specific combination of *ortho*-substituted aryl electrophile and phosphine ligand is employed. Mechanistic studies indicate that an unusual, stereospecific haptotropic rearrangement of the palladium–diene intermediate is involved.

Conflicts of interest

There are no conflicts to declare.

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