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C–H Functionalization

Stereochemical and Mechanistic Investigations of a Palladium-Catalyzed Annulation of Secondary Alkyl Iodides**

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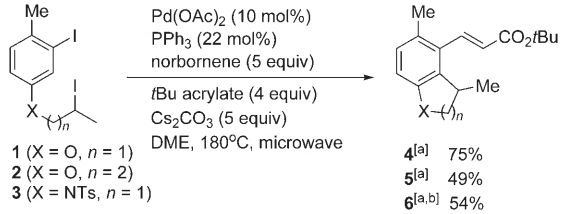
Transition-metal-catalyzed reactions are widely used as valuable tools for carbon–carbon bond formation.[1] Whereas palladium and nickel have classically occupied a central role in the synthesis of C_{sp^2}–C_{sp^2} bonds, the use of these transition metals in coupling reactions of β-hydrogen-containing substrates remains a challenge. β-Hydride elimination and hydrodehalogenation are significant problems particularly with secondary alkyl halides and sulfonates, in spite of recent progress in this area.[2]

We previously reported the synthesis of functionalized fused aromatic carbo- and heterocycles[3] by using primary alkyl halides under modified Catellani conditions.[4] A key extension of our methodology would be the use of secondary alkyl halides in an intramolecular fashion. Catellani and Cugini have previously reported a Pd-catalyzed intermolecular cross-coupling reaction with the use of isopropyl iodide, which proceeded with 31% conversion.[4d] The use of enantioenriched secondary halides should provide further insight into the reaction mechanism, as it is not known whether this reaction proceeds with overall retention or inversion of stereochemistry. Furthermore there are very few reports on the stereochemical outcome of reactions that undergo oxidative addition from a Pd^{II} to a Pd^{IV} intermediate,[5] which was suggested as a mechanistic pathway for this reaction. Herein, we report our findings on the stereochemical outcome of this Pd-catalyzed annulation reaction, which includes a C–H functionalization step and oxidative addition of unactivated enantioenriched secondary alkyl iodides.

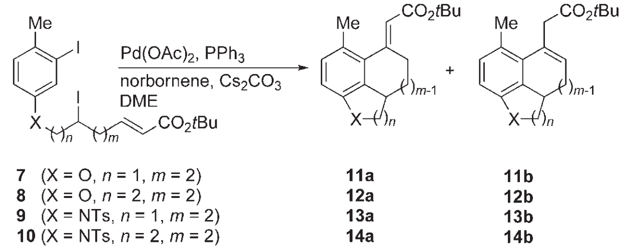
Historically, good yields for intermolecular cross-coupling reactions with secondary alkyl halides were only obtained by using Ni or Fe complexes.[2d–g,i–k,m–q,u,v] Of these, few examples employ enantiopure substrates.[2k,o] We needed to develop suitable conditions for the intramolecular Pd-catalyzed reaction of secondary alkyl halides prior to the mechanistic studies. By using racemic alkyl iodides[6] **1**–**3**, the annulation to form 5- and 6-membered ring systems proceeded in moderate to good yields (Scheme 1).



Scheme 1. Palladium-catalyzed synthesis of fused aromatic bicyclic systems. Ts = toluene-4-sulfonyl, DME = 1,2-dimethoxyethane. [a] Yields of isolated products. [b] Reaction run with the use of $Pd(OAc)_2$ (20 mol%), PPh_3 (44 mol%), norbornene (5 equiv), and Cs_2CO_3 (3 equiv) in DME (0.1 M) for 12 min, at 180°C.

We also examined a route to fused tricyclic ring systems through a tandem intramolecular *ortho* alkylation Heck reaction sequence. Formation of both oxygen- and nitrogen-containing 6,5,6- and 6,6,6-membered systems (Table 1, entries 1–4) proceeded in good yield.[7]

Table 1: Palladium-catalyzed synthesis of fused aromatic tricyclic ring systems.



Entry	Substrate	Product	Ratio	Yield [%][a]
1[b]	**7**	**11a** + **11b**	5:1	78[c]
2[b]	**8**	**12a** + **12b**	–[d]	74[e]
3[f]	**9**	**13a**	–	68
4[f]	**10**	**14a**	–	62

[a] Yields of isolated products. [b] Reaction run by using $Pd(OAc)_2$ (15 mol%), PPh_3 (33 mol%), norbornene (7 equiv), and Cs_2CO_3 (5 equiv) in DME (0.03 M) for 5 min, under thermal conditions at 180°C. [c] Product obtained in 82% yield, 2:1 mixture of **11a**:**11b** when reaction was run at 180°C for 7 min in the microwave. [d] Relative ratio could not be determined as **12b** was only observed in trace amounts. See the Supporting Information. [e] Yield of **12a** only. [f] Reaction run by using $Pd(OAc)_2$ (20 mol%), PPh_3 (44 mol%), norbornene (7 equiv), and Cs_2CO_3 (3 equiv) in DME (0.03 M) for 12 min, under thermal conditions at 150°C.

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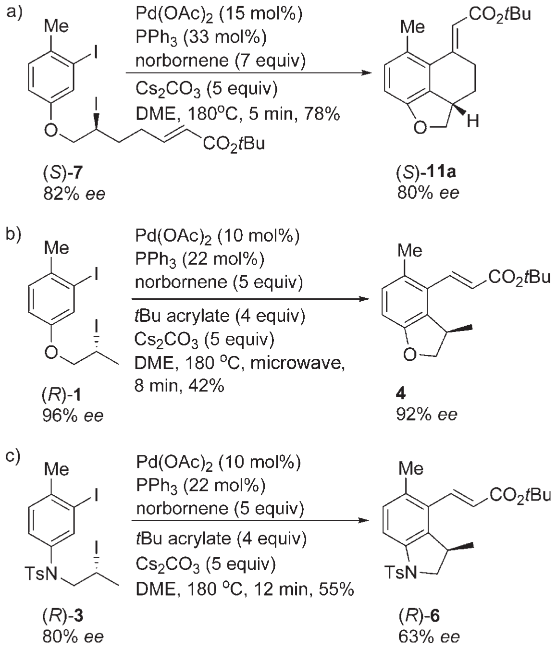
We anticipate that the annulation of secondary alkyl iodides follows the same reaction mechanism (Scheme 2) as that proposed for the corresponding reaction of primary alkyl halides.[3h] The reaction begins with oxidative addition of Pd^0 to the aryl iodide bond to give intermediate **A**. Carbopalladation of norbornene provides **B**, followed by functionalization of the C–H aryl bond to give palladacycle **C**. Oxidative addition of the intramolecular secondary alkyl iodide leads to Pd^{IV} intermediate **D**. Reductive elimination forms the first C–C bond (**E**). Extrusion of norbornene (**F**) followed by a Heck reaction (**G**) forms the desired product (**H**).

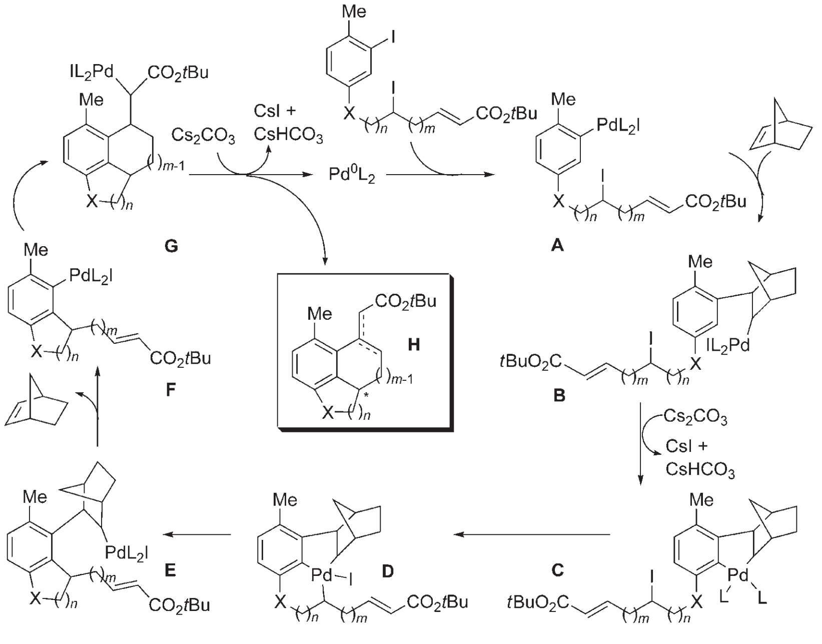
With a viable route to produce various annulated products, we prepared enantioenriched substrates to determine the fate of the stereochemical information during the reaction. For the annulation of substrates (*S*)-**7** and (*R*)-**1**,[8] the corresponding bicyclic and tricyclic products[9] were obtained with almost no loss of stereochemical information (Scheme 3a,b). For the annulation of (*R*)-**3**, a decrease in the *ee* value for product (*R*)-**6** was observed. To the best of our knowledge, these are the first examples that successfully utilize enantioenriched secondary alkyl iodides in a cross-coupling reaction with Pd as a catalyst.

Our next goal was to determine whether the reaction proceeds with overall retention or inversion of configuration. X-ray structures of (*R*)-**3** (Figure 1a) and (*R*)-**15** (Scheme 4 and Figure 1b)[10] were obtained, which revealed that the annulation reaction proceeded with overall inversion of configuration. We believe that this conclusion may be generalized to both nitrogen- and oxygen-containing systems (Scheme 3) on the basis of our results in Scheme 3a.[11]

Previous investigations of transmetalation[12] to Pd^{II} and cross-coupling reactions[13] with Pd^0/Pd^{II} systems have shown that the stereochemistry (overall inversion or retention) may depend on the substrate class[12a] and/or the reaction conditions.[12e] With regard to this reaction, if reductive elimination from the Pd^{IV} species of the Pd-catalyzed annulation proceeds with retention of configuration,[14] then we propose that the inversion of stereochemistry in this reaction likely occurs during the oxidative addition[15] of the secondary alkyl iodide to Pd^{II} to form the Pd^{IV} intermediate.



Scheme 3. Synthesis of enantioenriched bi- and tricyclic products.



Scheme 2. Proposed reaction mechanism.

In summary, we have shown that secondary alkyl iodides can be successfully applied to this tandem palladium-catalyzed coupling reaction, which proceeds by a C–H functionalization pathway. Tricyclic products can be formed with the use of a secondary iodide and a Heck acceptor tethered to an oxygen or nitrogen atom. The reaction can also be applied to enantioenriched substrates, which gives the corresponding products with minimal loss of stereochemical information. The first successful application of enantioenriched secondary iodides to a palladium-catalyzed process allows the straightforward synthesis of complex and enantioenriched fused ring systems. Furthermore, the use of enantioenriched substrates has given us insight into the mechanism, which suggests that the reaction proceeds with overall inversion of configuration via a Pd^{IV} intermediate. Development of this reaction for the preparation of a broader range of products is currently underway.

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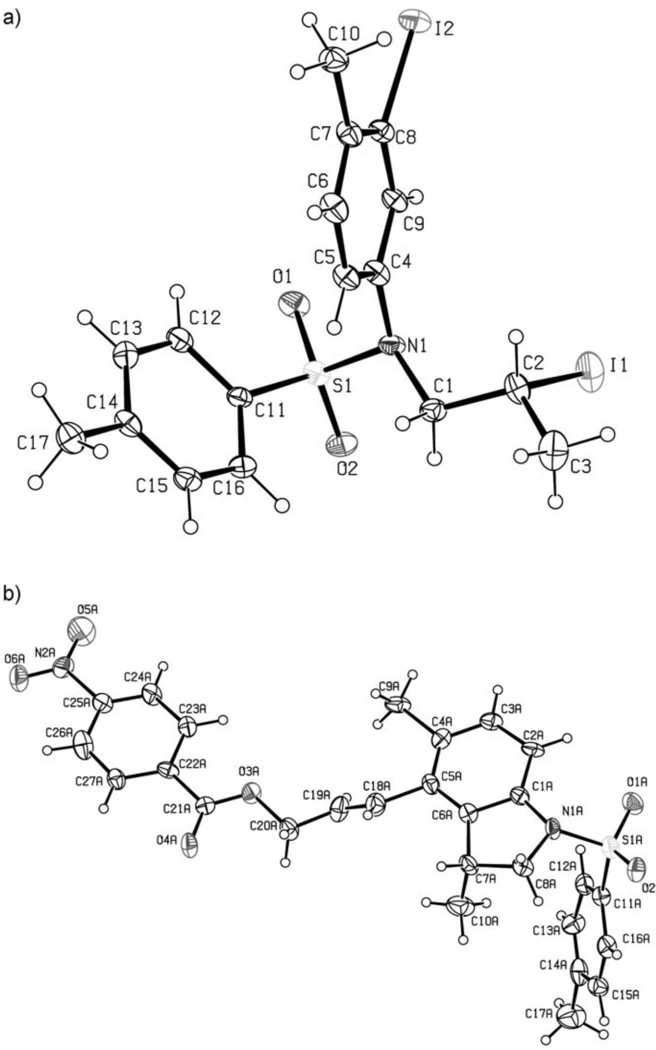
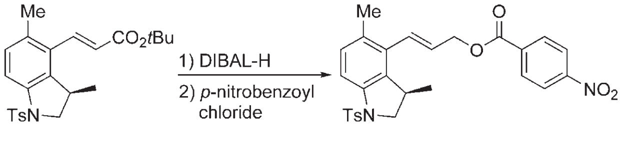


Figure 1. a) ORTEP diagram of (*R*)-**3**; b) ORTEP diagram of (*R*)-**15**. Thermal ellipsoids drawn at 30% probability



(*R*)-**6**

(*R*)-**15**
59% *ee*

Scheme 4. Conversion of (*R*)-**6** into (*R*)-**15**. DIBAL-H = diisobutylaluminum hydride.

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[6] The reaction with secondary alkyl bromides led to lower yields of the annulated products.

[7] The regiochemistry of the double bond isomers was determined by COSY, HSQC, and 1D ROESY NMR spectroscopy.

[8] The configurations of (*S*)-**7** and (*R*)-**1** are solely based on their preparation. See the Supporting Information for details.

[9] The absolute configuration of (*S*)-**11a** is based on X-ray analysis of a *p*-bromobenzoate derivative (*S*)-**16**. CCDC-619350 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for details. The absolute configuration of **4** (Scheme 3b) was not determined,

although we propose the *R* configuration on the basis of the results of this mechanistic study.

[10] CCDC-619351 [(*R*)-**6**] and CCDC-627191 [(*R*)-**15**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] On the basis of the synthesis of **7**, we believe its absolute configuration to be *S*. We have determined by X-ray crystallography that the configuration of **11a** is *S*, which indicates that the annulation of oxygen-containing substrates also proceeds with overall inversion.

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