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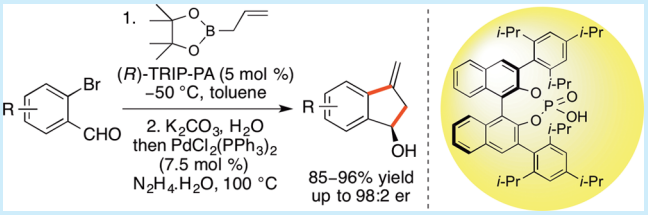
Enantioselective Synthesis of 3-Methyleneindan-1-ols via a One-Pot Allylboration−Heck Reaction of 2-Bromobenzaldehydes

Ewen D. D. Calder and Andrew Sutherland*

WestCHEM, School of Chemistry, The Joseph Black Building, University of Glasgow, Glasgow G12 8QQ, U.K.

Supporting Information

ABSTRACT: A novel, one-pot allylboration−Heck reaction of 2-bromobenzaldehydes has been developed for the general and efficient synthesis of 3-methyleneindan-1-ols. Modification of the one-pot procedure to include chiral Brønsted acid catalyzed allylation has allowed the preparation of these building blocks in high enantioselectivity and excellent yields.



Chiral functionalized indan-1-ols are important compounds that make up the core of many pharmacologically active agents and natural products.[1] In addition, indan-1-ols have been used as key synthetic intermediates in the preparation of monoamine reuptake blockers for the treatment of cocaine abuse,[2a] the muscarinic receptor antagonist (*R*)-tolterodine[2b] as well as in the formal total synthesis of the sesquiterpene toxin, anisatin.[3]

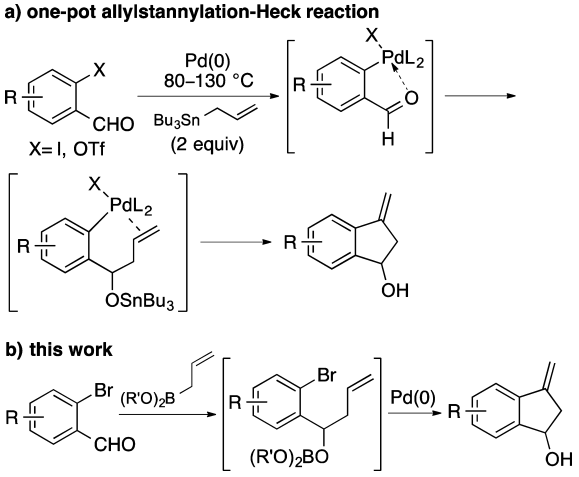
In recent years, methods for the preparation of 3-methyleneindan-1-ols have attracted a great deal of interest.[4−6] The most general strategy involved stepwise allylation of 2-halobenzaldehydes with allylmagnesium[4a,f] or allylindium reagents,[4e] followed by an intramolecular Heck reaction of the resulting homoallylic alcohol. In a similar fashion, 3-methyleneindan-1-ols have also been prepared using a Sakurai−Hosomi−Yamamoto allylation of 2-halobenzaldehydes with various organosilicon reagents as the key step.[4b,d]

A significant advance in the synthesis of these compounds was reported by Schmalz and co-workers, who showed that 2-iodobenzaldehydes or *o*-formylaryl triflates could undergo a one-pot, domino allylstannylation and intramolecular Heck reaction, generating 3-methyleneindan-1-ols in good yields (45−96%) (Scheme 1a).[5a] Mechanistic studies showed that *ortho*-palladation by oxidative addition resulted in intramolecular electrophilic activation of the aldehyde. This was followed by allylstannylation and Heck coupling to complete the process. More recently, this approach has been modified for the asymmetric synthesis of 3-methyleneindan-1-ols.[5b,6] Schmalz and co-workers used Taniaphos as a chiral palladium ligand for the preparation of 3-methylene-1*H*-indanol from 3-iodobenzaldehyde in 52% yield and 98:2 enantiomeric ratio,[5b] while the group of Fukuzawa used Pd/ClickFerrophos complexes for the asymmetric synthesis of a number of compounds from *o*-formylaryl triflates in yields of 16−91% and with generally high er (from 65.5:34.5 up to 99:1).[6]

While the one-pot, domino allylstannylation−Heck reaction represents a rapid method for the preparation of 3-methyleneindan-1-ols, there are some limitations. These include the "pronounced air sensitivity" of the preferred substrates *o*-formylaryl triflates,[5a] the general use of 2 equiv of allyltributylstannane, which can form diallyl and Stille byproducts,[6] and the restricted substrate scope. For example, the use of *o*-formylaryl triflates with electron-withdrawing carbomethoxy and nitro groups gave low yields of the corresponding indanols (33% and 0%, respectively).[6]

For these reasons, we were interested in developing an alternative one-pot method for the synthesis of chiral 3-methyleneindan-1-ols. It was proposed that allylboration of 2-bromobenzaldehydes with air- and water-stable, nontoxic allylboronic acid pinacol ester would generate homoallylic alcohols more cleanly and that this step could be used in combination with a Heck reaction for the one-pot synthesis of 3-methyleneindan-1-ols (Scheme 1b). This seemed an

Scheme 1. One-Pot Methods for the Synthesis of 3-Methyleneindan-1-ols



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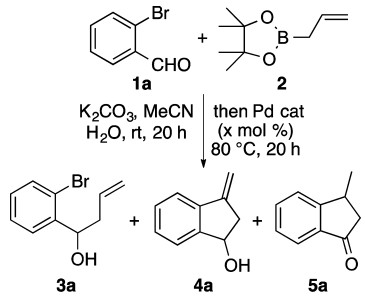
attractive strategy considering the highly effective Brønsted acid-catalyzed procedures for asymmetric allylboration of benzaldehydes.[7] Herein, we now report a novel, one-pot method for the general synthesis of 3-methyleneindan-1-ols bearing either electron-donating or electron-withdrawing groups. Use of chiral binaphthyl-derived phosphoric acid catalysts during the allylboration step for the asymmetric synthesis of these compounds is also described.

The study began with the optimization of a one-pot allylboration−Heck reaction of 2-bromobenzaldehyde (**1a**) with allylboronic acid pinacol ester (**2**).[8] Initial attempts involved adding all reagents, including the Pd catalyst, at the start of the process. While this gave homoallylic alcohol **3a** cleanly, conversion to 3-methyleneindan-1-ols **4a** was not detected. Therefore, a procedure involving stepwise addition of reagents for each stage of the one-pot process was investigated. As expected, allylboration proceeded with complete conversion in all attempts; however, optimization of the Heck reaction was required. The key developments are summarized in Table 1.

Table 1. Optimization of the One-Pot Procedure[a]



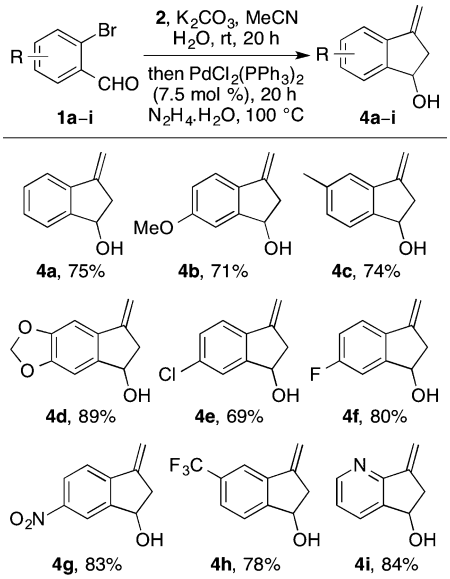
entry	Pd catalyst	x (mol %)	**3a**:**4a**:**5a**[b]	yield (%)[c]
1	$Pd(PPh_3)_4$	5	9:23:1	39
2[d]	$PdCl_2(PPh_3)_2$	5	9:29:1	33
3[d]	$PdCl_2(PPh_3)_2$	7.5	2:16:1	69
4[d,e]	$PdCl_2(PPh_3)_2$	7.5	0:8:1	75

[a]Unless otherwise noted, all reactions were performed with **2** (1.1 equiv), K_2CO_3 (5.0 equiv), and H_2O (4.0 equiv). [b]Ratio determined through analysis of ^1H NMR spectra of crude reaction mixture. [c]Isolated yield of **4a**. [d]$N_2H_4{\cdot}H_2O$ (0.4 equiv) was added with Pd cat. [e]Temperature of the Heck reaction was increased to 100 °C.

The use of $Pd(PPh_3)_4$ (5 mol %) for the Heck reaction gave **4a** as the major product in 39% yield. Similar results were obtained using $PdCl_2(PPh_3)_2$, which was reduced in situ with hydrazine hydrate (entry 2).[9] In an effort to improve conversion from homoallylic alcohol **3a** to indanol **4a**, the catalyst loading was increased to 7.5 mol % (entry 3). This gave **4a** in 69% yield. Finally, an increase in temperature of the Heck reaction to 100 °C was examined (entry 4). While this did convert all of **3a** to **4a**, the more forcing conditions led to an increase of cyclopentanone **5a**, a compound likely formed via a redox-relay process.[10] Nevertheless, these reaction conditions gave the highest yield (75%) for **4a**.

Having identified optimal conditions for the one-pot allylboration−Heck process, the substrate scope was explored using a range of 2-bromobenzaldehydes (Scheme 2). As expected, electron-rich substrates gave the corresponding indanols (**4b−d**) in high yields. In each case, the cyclopentanone byproduct was observed in the crude reaction material (<10%), but this was easily separated using column chromatography. Electron-deficient substrates were also converted efficiently to the corresponding indanols (**4e−h**). In particular, 2-bromo-4-nitrobenzaldehyde (**1g**) gave indanol **4g** as the sole product in 83% yield. This is in contrast to the domino allylstannylation−Heck process, which produced none of the indanol for this substrate.[6] The scope was extended to include a heteroaromatic example with the synthesis of the pyridine-derived indanol **4i** in 84% yield.

Scheme 2. Substrate Scope[a]



[a]Isolated yields of indanols **4a−i**.

In the next stage of this project, the development of a one-pot synthesis of optically active 3-methyleneindan-1-ols was investigated.[11] While there are a number of excellent catalytic asymmetric methods for allylboration of aldehydes,[7,11] we examined the use of the widely available binaphthyl-derived chiral phosphoric acids.[12] In 2010, Jain and Antilla showed that allylboration of aldehydes could be catalyzed using the Brønsted acid (*R*)-TRIP-PA (**7b**).[7e] Although this transformation allowed excellent enantioselectivity for a range of *meta*- or *para*-substituted benzaldehydes with allylboronic acid pinacol ester (**2**), only one *ortho*-analogue was studied and was shown to be less selective. Asymmetric allylation of *ortho*-substituted benzaldehydes with various reagents often show lower levels of induction, and this has prompted recent studies by the groups of Hu and Kotora in overcoming this issue.[7f,13]

As we were aware of the challenges associated with the asymmetric allylation of *ortho*-substituted benzaldehydes, it was decided to screen a number of binaphthyl-derived chiral phosphoric acids with 2-bromobenzaldehyde (**1a**).[14] Allylboration using these catalysts is generally performed in toluene,[7e,13] and so the one-pot procedure was modified for optimal synthesis of indanol **4a** using this solvent (Table 2, entry 1). The main changes involved performing allylation under anhydrous conditions before addition of base to hydrolyze the borate ester intermediate followed by palladium catalyst to complete the one-pot process. Interestingly, under these less polar conditions (cf. Table 1), none of the redox-relay product cyclopentanone **5a** was observed, resulting in cleaner reactions and an increase in the yield of **4a** (80%). The one-pot process was then performed with various Brønsted acid catalysts (5 mol %) at −30 °C (entries 2−5).[15] In accordance with results of various transformations catalyzed by binaphthyl-derived chiral

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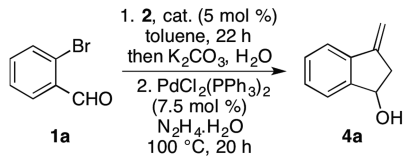
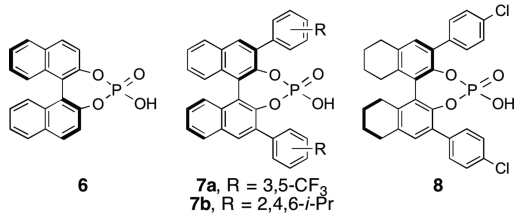
Table 2. Optimization of the Asymmetric One-Pot Procedure[a]





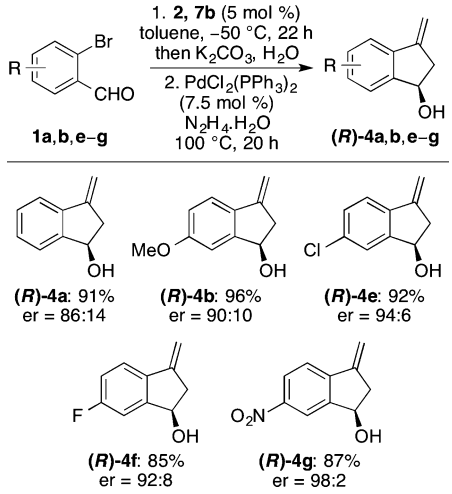
entry	catalyst	temp (°C)	yield (%)[b]	er[c]
1		rt	80	
2	**6**	−30	90	50:50
3	**7a**	−30	88	55:45
4	**7b**	−30	83	77:23
5	**8**	−30	82	52:48
6[d]	**7b**	−30	97[e]	75:25[e]
7[f]		−30	51	
8	**7b**	−50	91	86:14

[a]Unless otherwise noted, all reactions were performed with **2** (1.2 equiv), K_2CO_3 (6.0 equiv), and H_2O (10.0 equiv). [b]Isolated yield of **4a**. [c]er was determined using chiral HPLC analysis (see the Supporting Information). [d]Reaction was stopped after the allylboration step, and the homoallylic alcohol **3a** was isolated. [e]Yield and er for **3a**. [f]No allylboration catalyst present.

phosphoric acids,[7e,14a] only sterically congested (*R*)-TRIP-PA (**7b**) showed any reasonable levels of enantioselectivity (77:23) (entry 4). To probe whether the conditions of the Heck reaction were eroding the levels of asymmetric induction achieved during the first stage of the one-pot process, allylboration with (*R*)-TRIP-PA (**7b**) was done as a single step (entry 6). The enantiomeric ratio of homoallylic alcohol **3a** generated from this reaction showed similar levels to indanol **4a** formed from the one-pot process (entry 4), confirming that the Heck reaction had no effect on the stereochemical outcome. It was proposed that the modest levels of induction at −30 °C may in part be due to uncatalyzed allylboration. To investigate this, the one-pot process was repeated without the presence of (*R*)-TRIP-PA (**7b**), and surprisingly, this gave **4a** in 51% yield (entry 7). To minimize the involvement of background (uncatalyzed) allylboration during a reaction with (*R*)-TRIP-PA (**7b**), the use of lower temperatures was next investigated.[16] Solubility issues of reagents and catalyst at −80 °C were found to suppress both yields and levels of enantioselectivity.[17] A temperature of −50 °C was found to be a good compromise, giving indanol **4a** in excellent yield (91%) and with higher enantiomeric ratio (86:14) (entry 8).

The optimized conditions for the one-pot asymmetric process were then utilized for the preparation of a number of 3-methyleneindan-1-ol analogues (Scheme 3).[18,19] Under these conditions, benzaldehydes bearing electron-rich or electron-deficient substituents were converted to the corresponding indanols as the sole products, in excellent yields (85−96%) and with high enantiomeric ratios (86:14 to 98:2). In agreement with other allylboration studies,[7a] we found that higher

Scheme 3. Substrate Scope[a,b]



[a]Isolated yields of indanols. [b]er was determined using chiral HPLC analysis (see the Supporting Information).

enantiomeric ratios were obtained with benzaldehydes bearing electron-deficient groups.

In summary, an operationally simple, one-pot allylboration-Heck reaction of widely available 2-bromobenzaldehydes with allylboronic acid pinacol ester has been developed for the efficient synthesis of 3-methyleneindan-1-ols. The use of a robust allylation method has resulted in a very general process that allows the preparation of these synthetic building blocks with either electron-rich or electron-deficient substituents. Conditions for the asymmetric synthesis of the indanols using a binaphthyl-derived chiral phosphoric acid were also identified. It should be emphasized that both enantiomers of TRIP-PA are commercially available, and so either indanol enantiomer can be accessed using this method. Studies are currently underway to modify this and other one-pot multibond forming processes for the preparation of highly functional polycyclic synthetic building blocks.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, compound characterization, and NMR spectra for all compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01047.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: andrew.sutherland@glasgow.ac.uk.

Notes

The authors declare no competing financial interest.

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(17) For example, reaction of **1b** with (*R*)-TRIP-PA **7b** at −50 °C gave (***R***)-**4b** in 96% yield and 90:10 er. At −80 °C, (***R***)-**4b** was isolated in 59% yield and 80:20 er.
(18) The one-pot asymmetric process was not attempted using aryl bromides **1d** and **1i** as these compounds were found be insoluble in toluene at −50 °C.
(19) The assignment of the absolute configuration of 3-methyleneindan-1-ols prepared in this study was based on comparison of optical rotations and HPLC data of known compounds (see refs 4d, 5b, and 6).

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