ChemComm

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Nickel-catalyzed, ligand-free, diastereoselective synthesis of 3-methyleneindan-1-ols†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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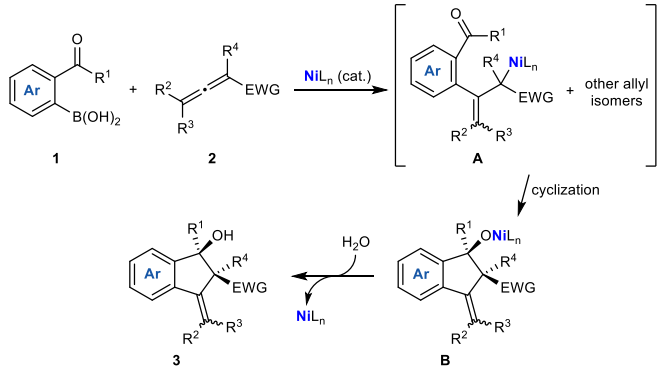
Nickel-catalyzed, highly diastereoselective annulations between activated allenes and 2-acetylarylboronic acid or 2-formylarylboronic acids are reported. No ligand for nickel is required, and the reactions proceed efficiently at room temperature to give a broad range of substituted 3-methyleneindan-1-ols. Preliminary results of an enantioselective variant are also described.

Indanes and their derivatives are important carbocycles that appear in numerous drugs and biologically active natural products, and therefore, the development of efficient methods for synthesizing these structures has been the focus of significant attention.[1] One common approach is the one- or two-step annulation of *ortho*-functionalized aromatic aldehydes, ketones, or imines with various unsaturated partners.[2,3] Two groups have described the use of allenes as the annulation partners, which give 3-methyleneindan-1-ols.[2a,c] In 2000, Grigg and co-workers reported the palladium-catalyzed reaction of allene itself with four *ortho*-halo aromatic aldehydes or ketones,[2a] whereas in 2009, Yu and Lu described the palladium-catalyzed reaction of activated allenes with 2-formylarylboronic acids or 2-acetylarylboronic acid.[2c] This latter work also included examples of enantioselective reactions to give the products in modest enantiomeric excesses.[2c] Although these studies[2a,c] provide important proof of concept, there are several areas where the substrate scope could be improved. For example, 1,1-disubstituted allenes were reported to be unreactive,[2c] and the allene activating groups are currently limited to esters or ketones.[2c]

Our group has shown that nickel complexes catalyze a range of domino addition–cyclization reactions of arylboronic acids with alkyne-[4] or allene-tethered electrophiles.[5] We have also demonstrated that they promote the enantioselective annulation of 2-formylphenylboronic acid with alkynes.[4a] We therefore hoped that a nickel-catalyzed annulation of 2-carbonylarylboronic acids with activated allenes could be developed that might offer increased substrate scope compared with previous work[2c] (Scheme 1). Here, nickel-catalyzed



Scheme 1 Proposed annulation approach to 3-methyleneindan-1-ols.

addition of a 2-carbonylarylboronic acid **1** to an activated allene **2** could provide an allylnickel species **A** (which could interconvert with π-allyl and other σ-allyl isomers). Cyclization of **A** (or an isomer) by nucleophilic addition to the carbonyl group would provide nickel alkoxide **B**, which upon protonolysis would release the Ni(II) catalyst and give a 3-methyleneindan-1-ol **3**.[6]

We began this investigation by heating a mixture of 2-acetylphenylboronic acid **1a** (2.0 equiv), benzyl allenoate **2a**, $Ni(OAc)_2{\cdot}4H_2O$ (10 mol%), and pyphos (**L1**, 10 mol%) in MeCN/1,4-dioxane (3:2) at 80 °C for 24 h (Table 1, entry 1). After workup, ^1H NMR analysis of the crude reaction mixture using an internal standard showed complete consumption of **2a** and formation of 3-methyleneindan-1-ol **3aa** in 62% yield as a single observable diastereomer (>19:1 dr).[7] No reaction occurred in the absence of $Ni(OAc)_2{\cdot}4H_2O$, but in the absence of pyphos, **3aa** was still obtained in 53% yield (entry 2). Without pyphos, significantly improved results (97% yield of **3aa**) were achieved at room temperature (entry 3). Use of MeCN (entry 4) or 1,4-dioxane alone (entry 5) gave inferior results to the mixed solvent system (entry 3). The conditions of entry 3 were therefore used in subsequent experiments.

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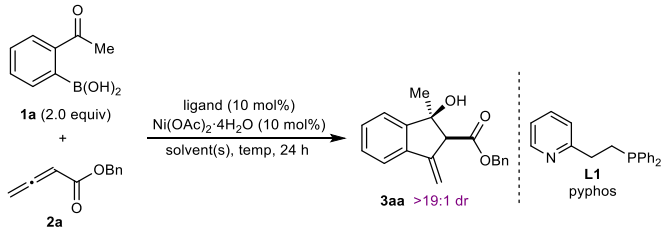
† Electronic Supplementary Information (ESI) available: Experimental procedures, full spectroscopic data for new compounds, and crystallographic data for **3ai**, **3an**, and **3ao.** CCDC 1858962–1858964. See DOI: 10.1039/x0xx00000x

Table 1 Evaluation of reaction conditions[a]

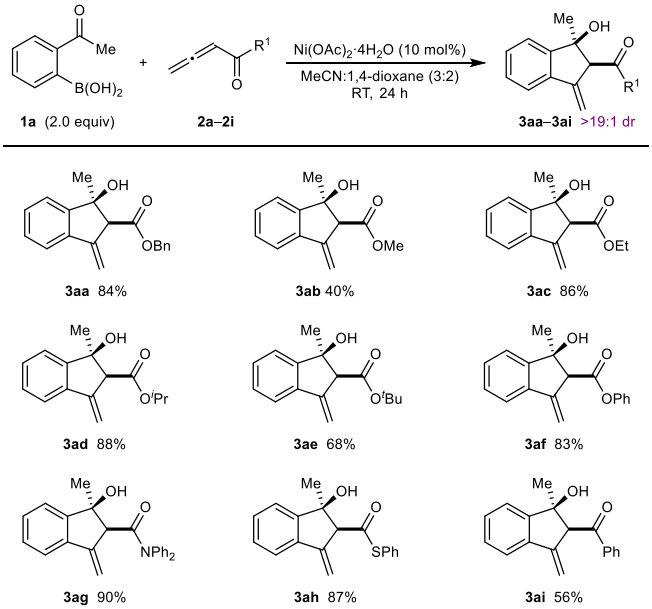


Entry	Ligand	Solvent(s)	Temp (°C)	Yield (%)[b]
1	**L1**	MeCN:1,4-dioxane (3:2)	80	62
2	–	MeCN:1,4-dioxane (3:2)	80	53
3	–	MeCN:1,4-dioxane (3:2)	RT[c]	97
4	–	1,4-dioxane	RT[c]	82
5	–	MeCN	RT[c]	41

[a] Reactions were conducted using 0.10 mmol of **2a**. [b] Determined by ^{1}H NMR analysis of the crude reactions using 1,3,5-dimethoxybenzene as an internal standard. [c] RT was measured as 23 °C.

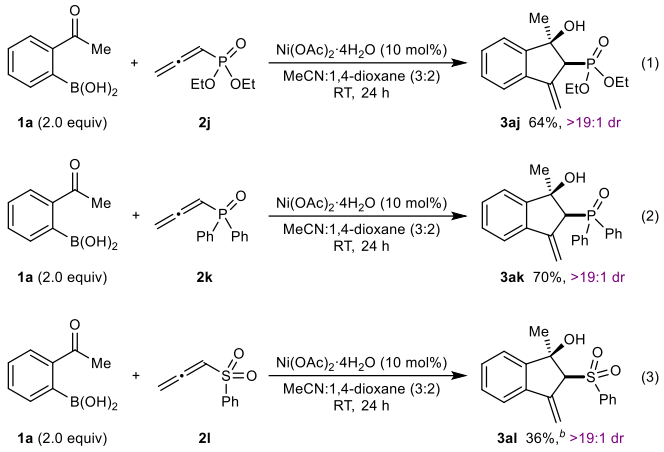
With effective conditions available, the scope of this process was explored by reacting 2-acetylphenylboronic acid **1a** with a range of allenes (Table 2). Allenoates **2a**–**2f** gave the corresponding 3-methyleneindan-1-ols **3aa**–**3af** in moderate to excellent yields as single observable diastereomers (>19:1 dr). Primary alkyl (**3aa**–**3ac**), secondary alkyl (**3ad**), and tertiary alkyl (**3ae**) ester substituents are tolerated, as is a phenyl ester (**3af**). Allenes with amide, thioester, or phenyl ketone groups also reacted smoothly to give **3ag**–**3ai** in up to 90% yield.[7]

Table 2 Evaluation of monosubstituted allenes[a]



[a] Reactions were conducted with 0.30 mmol of **2a**–**2i**. Yields are of isolated products.

Pleasingly, allenes with non-carbonyl substituents are also competent reaction partners. For example, allenyl phosphonate **2j** reacted with **1a** to give 3-methyleneindan-1-ol **3aj** in 64% yield (eqn 1), while allenyl phosphine oxide **2k** gave **3ak** in 70% yield (eqn 2). A phenylsulfone can also be used as the allene activating group (eqn

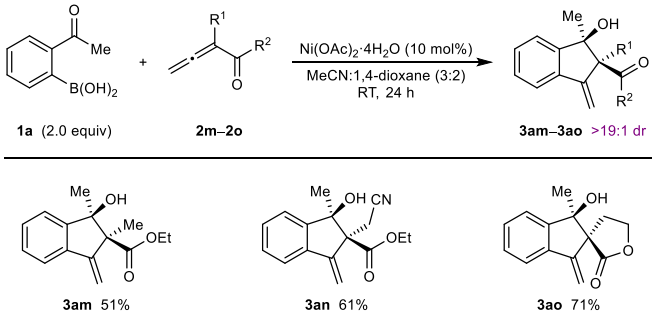


[a] Reactions were conducted with 0.30 mmol of **2j**–**2l**. Yields are of isolated products. [b] Isolated with an unknown impurity; the yield of **3al** was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

3). Although the yield of the product **3al** was more modest, this result is notable as Yu and Lu reported that allenyl sulfone **2l** did not give any product in their work.[2c]

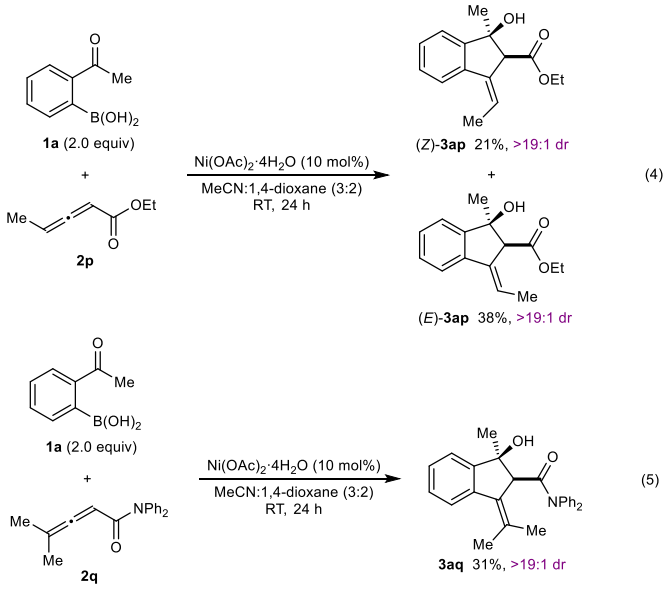
Our attention then turned to the reaction of **1a** with sterically more demanding allenes. 1,1-Disubstituted allenes were reported to be ineffective in similar annulations using palladium catalysis,[2c] but the successful use of these allenes would give products containing two adjacent quaternary stereocenters (Table 3). We were pleased to observe that allenyl esters with α-methyl or α-cyanomethyl substituents successfully gave 3-methyleneindan-1-ols **3am** and **3an** in 51% and 61% yield, respectively, as single observable diastereomers. This chemistry also enables the synthesis of spirocycles, as shown by the formation of **3ao** in 71% yield from 3-vinylidenedihydrofuran-2(3*H*)-one **2o**.

Table 3 Evaluation of 1,1-disubstituted allenes[a]



[a] Reactions were conducted with 0.30 mmol of **2m**–**2o**. Yields are of isolated products.

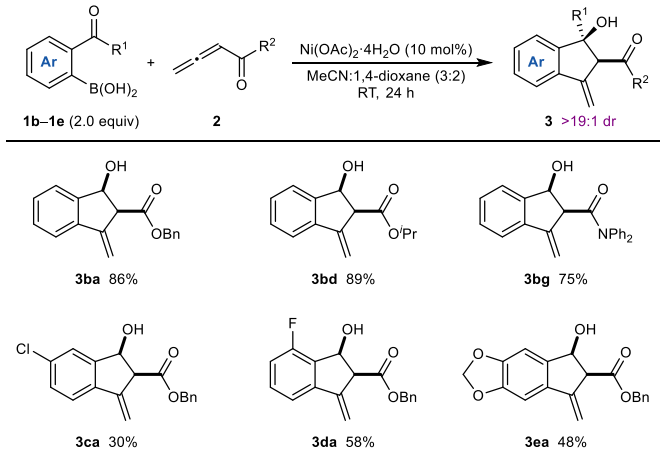
Interestingly, the 1,3-disubstituted allene **2p** reacted with **1a** to give (*Z*)-**3ap** in 21% yield and (*E*)-**3ap** in 38% yield (eqn 4). The formation of a mixture of alkene stereoisomers in this reaction suggests that *E*/*Z* isomerization of the intermediate allylnickel species **A** (see Scheme 1) by σ-π-σ interconversion and bond rotation occurs rapidly before cyclization. This outcome may also provide a clue regarding the mechanism of the cyclization itself (see Scheme 3 and the accompanying discussion, *vide infra*). In addition, the trisubstituted allene **2q** also reacted with **1a** to give **3aq**, which



contains a fully substituted exocyclic alkene, in 31% yield (eqn 5).

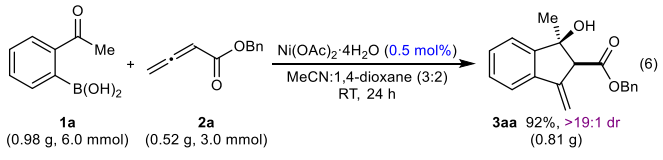
Next, variation of the 2-carbonylarylboronic acid was explored (Table 4). 2-Formylphenylboronic acid reacted smoothly with allenes **2a**, **2d**, and **2g** to give the corresponding 3-methyleneindan-1-ols **3ba**, **3bd**, and **3bg** in good yields and as a single observable diastereomers. Chloride or fluoride groups on the arylboronic acid are tolerated (**3ca** and **3da**), while 6-formylbenzo[*d*][1,3]dioxol-5-yl)boronic acid reacted with **2a** to give **3ea** in 48% yield.

Table 4 Evaluation of 2-formylarylboronic acids **8**[a]

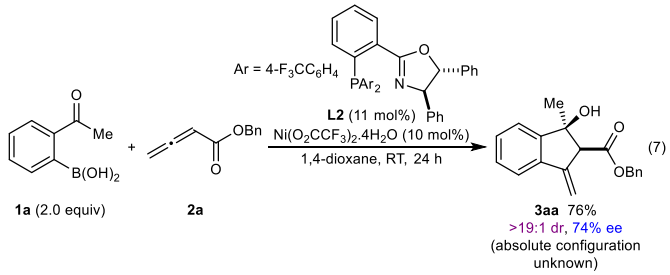


[a] Reactions were conducted with 0.30 mmol of **2**. Yields are of isolated products.

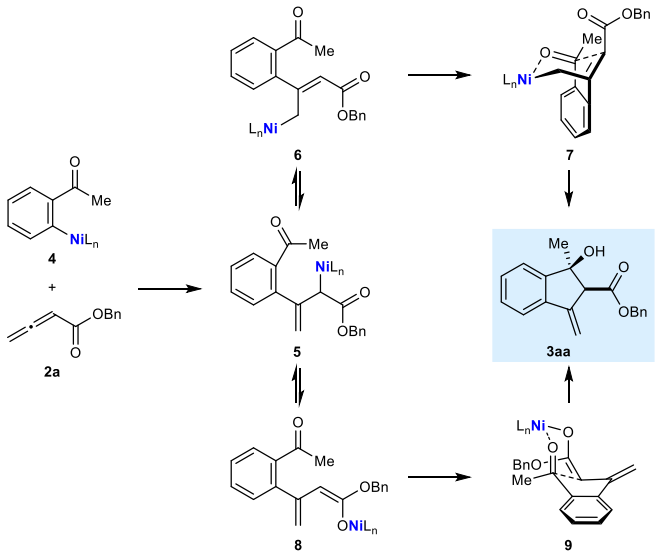
To investigate the practicality of the process, a larger-scale reaction was conducted. Notably, a reaction of **2a** (3.0 mmol) with **1a** (6.0 mmol) performed using only 0.5 mol% of $Ni(OAc)_4{\cdot}4H_2O$ gave 0.81 g of **3aa** (92% yield) (eqn 6).



Finally, we conducted preliminary studies to develop an enantioselective variant of this process.[2c] Simply adding a range of chiral phosphinooxazolines[8] that are effective in our recently developed nickel-catalyzed domino addition–cyclization reactions[4,5] led only to low enantioselectivities. However, after further investigation, we discovered that in 1,4-dioxane as the solvent, 3-methyleneindan-1-ol **3aa** can be obtained in good yield with 74% ee, using phosphinooxazoline **L2** as the ligand and $Ni(O_2CCF_3)_2{\cdot}4H_2O$ as the nickel source, (eqn 7).[9]

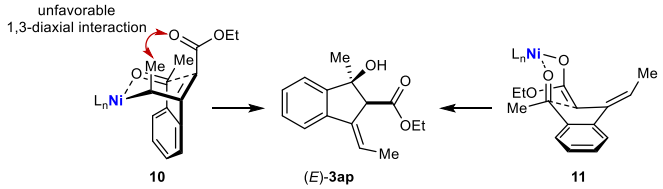


Scheme 2 presents possible models to explain the diastereochemical outcome of the reactions, using product **3aa** as a representative example. First, transmetalation of 2-acetylboronic acid with $Ni(OAc)_2{\cdot}4H_2O$ would give arylnickel species **4**. Arylnickelation of the more activated alkene of allene **2a** with **4** would then give allylnickel species **5**, which can interconvert with **6** through a σ-π-σ isomerization. The alternative geometrical isomer of **6** would possess highly unfavorable non-bonding interactions of the benzyl ester with the 2-acetylphenyl group. An intramolecular allylation of the ketone through a cyclic six-membered transition state[6c] **7** would then give 3-methyleneindan-1-ol **3aa**. Alternatively, allylnickel species **5** can interconvert with the *O*-bound nickel enolate **8**, which can undergo aldol cyclization through the cyclic six-membered transition state **9** to give **3aa**.



Scheme 2 Possible models to explain the diastereochemical outcome.

The formation of a significant quantity of (*E*)-**3ap** from the reaction between **1a** and allene **2ap** (eqn 4) may suggest that in this case, the 1,2-allylation mechanism is not operative, because this would require cyclization through transition state **10**, in which there is a highly unfavorable 1,3-diaxial interaction between the methyl group and ethyl ester. Therefore, cyclization through the *O*-bound enolate **11** appears more likely. However, whether this hypothesis is applicable to the other reactions reported in this study is not clear at the present time.



Scheme 3 Comparison of possible stereochemical models to form (*E*)-**3ap**.

In summary, we have developed nickel-catalyzed, ligand-free, and highly diastereoselective annulations between activated allenes and 2-acetylphenylboronic acid or 2-formylarylboronic acids to give 3-methyleneindan-1-ols under mild conditions. Compared with previous work,[2c] this methodology is compatible with a wider range of allenes including 1,1-disubstituted allenes and those containing a phosphonate ester, phosphine oxide, or sulfone as the activating group. Finally, preliminary results of an enantioselective reaction using a novel chiral phosphinooxazoline **L2** are reported.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Engineering and Physical Sciences Research Council [grant number EP/M506588/1] through a PhD studentship to C.C.; the European Union's Horizon 2020 research and innovation programme [grant number 702386] through a Marie Skłodowska-Curie Individual Fellowship to S.N.K.; the University of Nottingham; and GlaxoSmithKline.

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7 The relative configurations of **3aa**, **3ah**, **3aj**–**3al**, (*Z*)-**3ap**, (*E*)-**3ap**, **3aq**, **3ba**, and **3bd** were determined by NOESY analysis (see the Supplementary Information). The relative configurations of **3ai**, **3an**, and **3ao** were determined by X-ray crystallography. The relative configurations of the remaining products were assigned by analogy. CCDC 1858962–1858964.†

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9 Attempts to determine the absolute configuration of **3aa** were not successful. For details of investigations to develop an enantioselective reaction, see the Supplementary Information.

