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Nickel-Catalysed *syn*-Selective Arylnickelation and Cyclisation of Ketone/Imine-Tethered Terminal Alkynes with Arylboronic Acids

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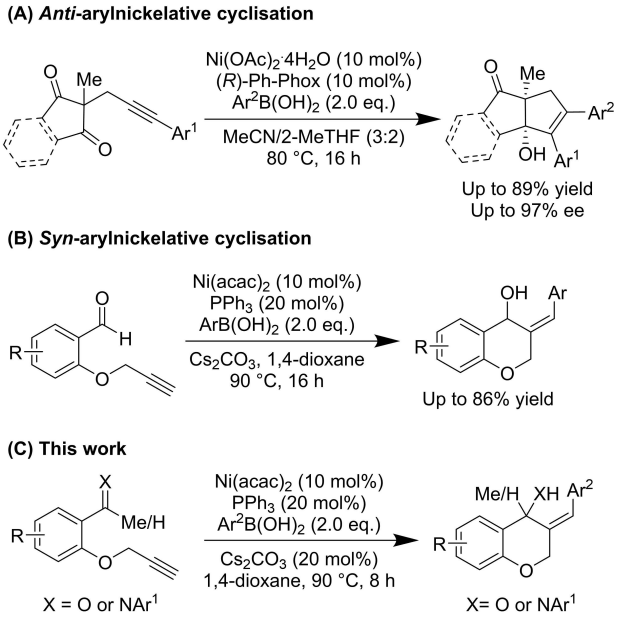
Herein we report a syn-arylnickelative cyclisation with ketone- and imine-tethered terminal alkynes (16 examples) in yields of up to 89%. The reaction proceeds via a syn-aryl nickelation of a terminal alkyne followed by cyclisation of the resulting alkenylnickel species onto the ketone or imine. The enantioselective version of this transformation has also been explored with enantioselectivities of up to 83:17 er observed.

Introduction

Aryl-metalative cyclisations of alkyne-tethered electrophiles are a step-economical manner of synthesising complex molecules that can be of use in both medicinal and synthetic organic chemistry programmes.[1–4] Among the most useful arylating reagents used in these reactions are arylboronic acids due to their ready availability, ease of handling, and stability.[5] These reactions involving arylboron reagents have been widely explored using palladium,[6–8] rhodium,[9–11] and copper catalysis.[12]

Until recently, the use of nickel catalysis employing these reagents was underexplored. Nickel lies below palladium in group 10 of the periodic table and as such can perform many of the same elementary reactions; however, it is much more abundant and inexpensive, making it an attractive option for catalysis.[13] In 2016, the Lam group reported the first enantioselective *anti*-arylnickelative cyclisation in which substrates containing an alkyne tethered to five- or six-membered 1,3-diketones were reacted with arylboronic acids to give bicyclic products in excellent yields and enantioselectivities (Scheme 1A).[14] A further example using these substrates in combination with an arylhalide instead of an arylboronic acid was later reported by Kong in 2020.[15] Since this report, the range of substrates applicable in this reaction has expanded greatly to give products such as chiral 1,4-diene-containing hetero- and carbocycles, chiral cyclopent-2-enones, and cyclic enones with a nitrile containing all carbon quaternary centre.[1,16–21] A number of examples involving intermolecular cyclisations have also been developed.[22–24]

In comparison, considerably fewer examples of *syn*-arylnickelative cyclisations have been described, with the first example reported by the Reddy group in 2018.[25] In this work substrates which consisted of a terminal alkyne tethered to an aldehyde were reacted with arylboronic acids in 1,4-dioxane at 90 °C to give arylated cyclised products in good yields (Scheme 1B). Other examples which have been reported in subsequent years



Scheme 1. *Anti-* and *syn*-arylnickelative cyclisations.

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include cyclisations onto ester electrophiles to give multi-substituted benzofurans,[26] and the synthesis of bridged tricyclo[5.2.1.0^{1,5}]decanes.[27]

This paper describes our aim to expand the work to a broader substrate scope of tethered-electrophiles, namely the less electrophilic, more sterically hindered ketones and imines (Scheme 1C), allowing for the synthesis of a more diverse range of products. Furthermore, initial work was undertaken to develop the first enantioselective *syn*-arylnickelative cyclisation with such substrates.

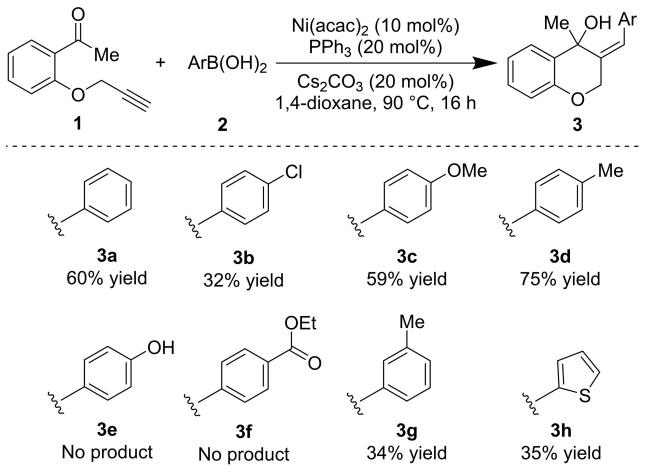
Results and Discussion

Reddy had successfully shown that *ortho*-propargyloxybenzaldehydes could be applied to the *syn*-arylnickelative cyclisation in good yields.[25] We initially began our substrate scope by applying more sterically hindered alkyne-tethered ketones to this reaction (Scheme 2). The *ortho*-propargyloxy ketone **1** was first reacted with phenylboronic acid (2 equivalents) in the presence of $Ni(acac)_2$ (10 mol%), PPh_3 (20 mol%) and Cs_2CO_3 (20 mol%) in dioxane (0.1 M) at 90 °C for 16 h, to afford the desired product **3a** in a 60% yield. Arylboronic acids with electron-withdrawing or electron-donating groups at the *para*-position were then tested in the reaction. The one containing an electron-withdrawing group (chloro) afforded **3b** with a reduction in yield (to 32%) whereas those containing electron-donating groups (methoxy or methyl) gave products **3c** and **3d** in 59% and 75% yield, respectively. Arylboronic acids containing hydroxy or ester functional groups were tested in the reaction, but neither were tolerated, with no products **3e** or **3f** being formed. Methyl substitution at the *meta*-position of the arylboronic acid led to product **3g** in a lower yield of 34% compared to the *para*-substituted analogue **3d** (75%). Finally, a thiophene-containing boronic acid was tested and this afforded product **3h** in a moderate yield of 35%, showing that heterocycles were tolerated in the reaction. The starting material and product were both stable under the reaction conditions, in all cases where a lower yield was obtained the starting material was fully consumed, with lost yield attributed to degradation of the reaction intermediate due to slow cyclisation at the rate determining step.

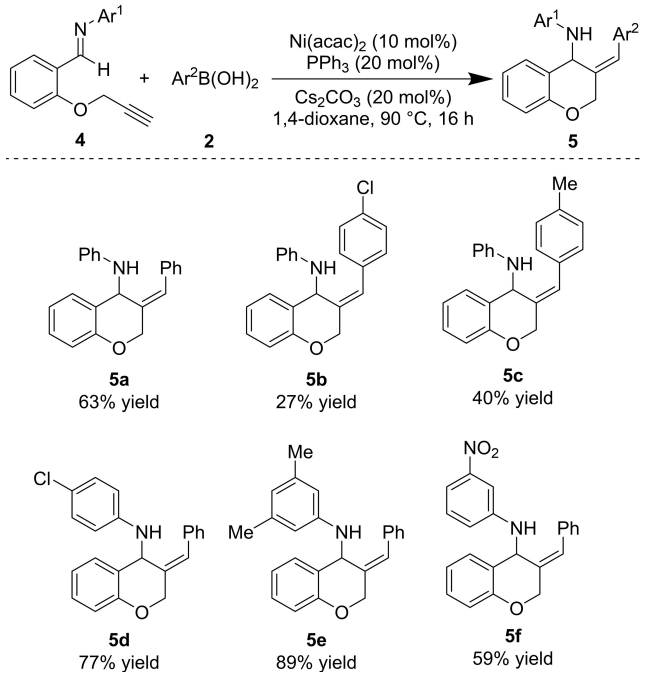
As carbonyl-containing functional groups (aldehydes, ketones and esters) have been shown to be viable electrophiles in arylnickelative cyclisations,[25] we therefore looked at applying the electronically distinct imine as an option for the tethered electrophile in this transformation (Scheme 3). An *ortho*-propargyloxy *N*-phenyl imine was first reacted with phenylboronic acid to give the product **5a** in a 63% yield, showing very similar results to what had been seen when ketone **1** was used as the substrate (product **3a**, Scheme 2). Arylboronic acids containing an electron-withdrawing (chloro) or electron-donating group (methyl) in the *para*-position led to lower yields of 27% and 40%, respectively for the products **5b** and **5c**, a trend that was also observed when the ketone substrate **1** was reacted with these arylboronic acids.

The substitution on the *N*-aryl ring (Ar^1) of the imine was next varied. A good yield was obtained when an electron-withdrawing group was present at the *para*-position as seen in the formation of **5d** in 77% yield. The 3,5-dimethyaniline-containing product **5e** was obtained in 89% yield, the highest yield seen to date in the present study. Finally, a substrate with an electron-withdrawing group (nitro) at the *meta*-position of the aryl amine afforded product **5f** in a respectable 59% yield, similar to that obtained for the formation of unsubstituted aniline **5a** (63% yield).

Substitution on the tethering aromatic ring of the *ortho*-propargyloxy *N*-phenyl imine was then investigated (Scheme 4).



Scheme 2. Scope of arylboronic acids **2** reacting with ketone **1**. Reaction conditions: ketone-tethered terminal alkyne (0.15 mmol) and arylboronic acid (0.30 mmol), in 1,4-dioxane (1.5 mL).



Scheme 3. Scope of arylboronic acids reacting with *N*-aryl imine **4**. Reaction conditions: imine-tethered terminal alkyne (0.15 mmol) and boronic acid (0.3 mmol), in 1,4-dioxane (1.5 mL).

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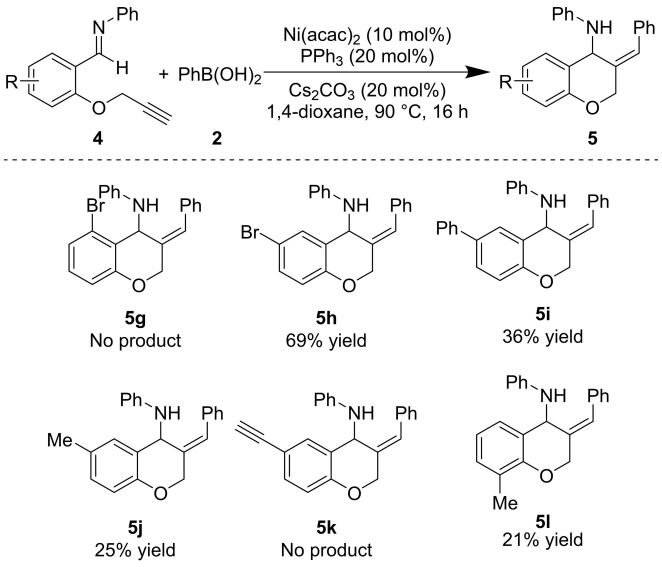
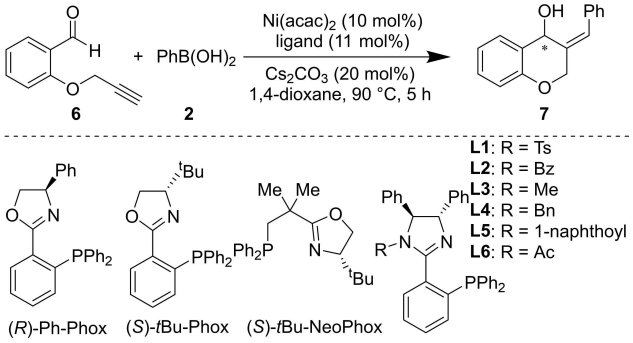


Scheme 4. Variation of substitution pattern on *o*-propargyloxy benzimines. Reaction conditions: imine-tethered terminal alkyne (0.15 mmol) and boronic acid (0.3 mmol), in 1,4-dioxane (1.5 mL).

Substitution at the 5-position was not tolerated with none of product **5g** observed when a bromo group was placed at this position; this is likely due to steric effects with a clash between the bromide and the *N*-phenyl group making formation of the ring unfavourable. Substitution at the 4-position with electron-withdrawing groups (bromo or phenyl) led to the formation of products **5h** and **5i** in 69% and 36% yield, respectively. The product containing an electron-donating group (methyl) at the 4-position was synthesised in a poor yield of 25%. No product was seen when an alkyne was present on the ring **5k**, whereas the 2-methyl-substituted substrate was tolerated as product **5l** was formed in a similar yield (21%) to the 4-methylated product **5j** (25% yield).

Finally, we envisaged that the use of a chiral ligand in the place of PPh_3 could lead to asymmetric induction in the reaction. Due to the success that had been seen by the Lam group and others in the use of chiral 'Phox' type P,N ligands in *anti*-arylnickelative cyclisation reactions,[1] we initially tested a range of 'Phox' and 'Neo-Phox' ligands in the reaction; however, no or low levels of enantioselectivity were observed (Table 1). A range of commonly used P,P and N,N ligands were also tested and although some good yields were obtained, all ligands tested failed to induce any enantioselectivity (full table in SI). We instead turned to a range of 'Phim'-type ligands **L1**–**L6**,[28–32] of which **L4** induced the best enantioselectivity (71:29 er) observed to date (entry 7). We had previously demonstrated the potential for 'Phim'-type ligands in copper-catalysed A^3 couplings and the alkynylation of quinolones.[33–35] These 'Phim'-type ligands have, to the best of our knowledge, not been applied to arylnickelative cyclisation reactions, so the results of this study demonstrate their potential as a further family of ligands to be considered when optimising these or similar reactions. A range of organic and inorganic bases were tested (full table in SI), and changing of the counterion of the base from the large caesium to the smaller potassium led to an increase in the enantioselectivity 73:27 er (entry 10). The solvent was also varied, with the polar protic 1-propanol giving the highest yield (32%) and enantioselectivity (83:17 er) seen to date (entry 11) (full table in SI).

Table 1. Optimisation of enantioselective reaction.



Entry	Ligand	SM (%)	Yield (%)[a]	Er[b]
1	(*R*)-Ph-Phox	17	20	35:65
2	(*S*)-*t*Bu-Phox	13	37	51:49
3	(*S*)-*t*Bu-NeoPhox	5	33	50:50
4	**L1**	22	37	52:48
5	**L2**	32	33	55:45
6	**L3**	0	55	55:45
7	**L4**	0	29	71:29
8	**L5**	10	26	71:29
9	**L6**	6	37	60:40
10[c]	**L4**	0	26	73:27
11[c,d]	**L4**	0	34 (32)[e]	83:17

Reaction conditions: ortho-propargyloxybenzaldehyde (0.15 mmol) and phenylboronic acid (0.3 mmol in 1,4-dioxane (1.5 mL). [a] Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b] Enantiomeric ratio determined by separation on chiral SFC UPC^2. [c] K_2CO_3 used as base. [d] 1-propanol used as solvent. [e] Isolated yield after column chromatography.

The optimised conditions were next applied to a range of ketone- and imine-containing substrates (Scheme 5). With the exception of aldehyde-containing substrate **6**, lower than expected yields were obtained when 1-propanol was used as the reaction solvent, so the solvent was switched back to 1,4-dioxane for all other substrates. Despite the large differences in both sterics and electronics across the ketone- and imine-containing substrates tested, ligand **L4** induced moderate levels of enantioselectivity in all cases (from 58:42 to 74:26). Further optimisation of reaction conditions could be undertaken to optimise the ligand chosen to the specific substrates but the initial results shown here are promising for the utility of the 'Phim'-type family of ligands in these reactions.

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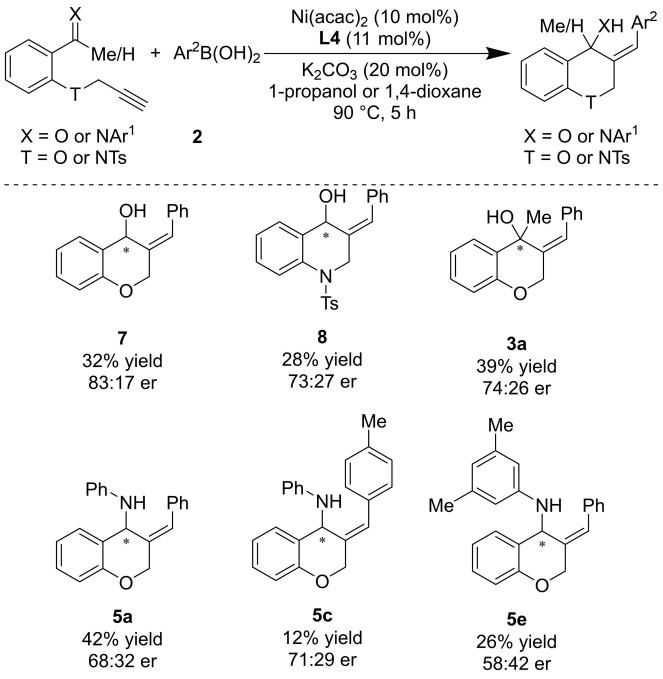

Scheme 5. Enantioselective syn-selective arylnickelation with ketone- and imine-containing substrates. Reaction conditions: substrate (0.15 mmol) and boronic acid (0.30 mmol) in propanol or 1,4-dioxane (1.5 mL).

Conclusions

In summary, the nickel-catalysed *syn*-selective arylnickelation and cyclisation of ketone/imine-tethered terminal alkynes with arylboronic acids has been developed, with 16 novel products successfully synthesised. Furthermore, preliminary studies into the development of the first enantioselective *syn*-selective arylnickelation cyclisation for aldehyde/ketone/imine-tethered terminal alkynes were conducted. The optimised conditions were applied to 6 substrates with differing steric and electronic properties, and although the yields could be improved, the optimal ligand **L4** was able to induce moderate to good levels of enantioselectivity in all cases.

Experimental Section

General Procedure for Racemic Arylnickelative Cyclisation

A flame-dried Schlenk tube was charged with a stir bar. The flask was charged with $Ni(acac)_2$ (3.9 mg, 0.015 mmol, 0.1 eq.), PPh_3 (7.9 mg, 0.03 mmol, 0.2 eq.), Cs_2CO_3 (9.8 mg, 0.03 mmol, 0.eq), *ortho*-propargylbenzimine/ketone/aldehyde (0.15 mmol, 1 eq.) and boronic acid (0.3 mmol, 2 eq.). The Schlenk tube was evacuated and backfilled with nitrogen 3 times. 1,4-Dioxane (1.5 mL. 0.1 M) was added and the reaction was stirred at room temperature for 15 min. The reaction was heated to 90 °C and left stirring for 16 h. The reaction mixture was cooled and filtered through a celite plug using CH_2Cl_2. The crude residue was purified by flash column chromatography (0–5 % EtOAc in c-Hex) to afford the pure cyclised product.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: nickel catalysis · *syn*-selective arylnickelation · tethered electrophile · domino reaction

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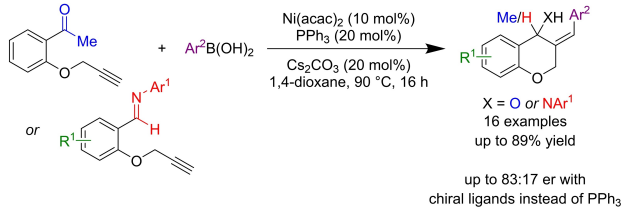

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Nickel-Catalysed *syn*-Selective Arylnickelation and Cyclisation of Ketone/Imine-Tethered Terminal Alkynes with Arylboronic Acids

Herein the substrate scope of a nickel-catalysed *syn*-selective arylnickelation and cyclisation with arylboronic acids is expanded to include ketone and imine-tethered terminal alkynes. The reaction proceeds via a *syn*-aryl nickelation of a terminal alkyne followed by cyclisation of the resulting alkenylnickel species. Along with this the first enantioselective version of the reaction has been developed using PHIM type P,N ligands.