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Enantioselective nickel-catalyzed arylative intramolecular 1,4-allylations†

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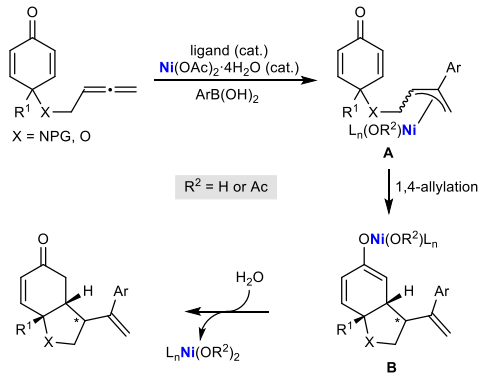
Thi Le Nhon Nguyen,‡[ab] Celia A. Incerti-Pradillos,‡[ab] William Lewis[b] and Hon Wai Lam*[ab]

The enantioselective nickel-catalyzed desymmetrization of allenyl cyclohexa-2,5-dienones by reaction with arylboronic acids is described. Nickel-catalyzed arylation of the allene gives allylnickel species, which undergo cyclization by 1,4-allylation to produce hexahydroindol-5-ones and hexahydrofuran-5-ones with three contiguous stereocenters in high diastereo- and enantioselectivities.

Catalytic enantioselective 1,4-additions of organometallic reagents to electron-deficient alkenes are important reactions for the formation of new carbon–carbon bonds.[1] Despite the tremendous diversity of known examples of such reactions,[1] the catalytic enantioselective 1,4-addition of allylic nucleophiles remains considerably underdeveloped and only a handful of examples have been described.[2] Therefore, new types of catalytic enantioselective 1,4-allylations are highly desired to increase the range of accessible products.

In light of our discovery that chiral phosphinooxazoline–nickel complexes are highly effective in promoting enantioselective *anti*-carbometallative cyclizations of alkynyl electrophiles with arylboronic acids,[3] we questioned whether these complexes could promote a catalytic enantioselective intramolecular 1,4-allylation[2g,i] of substrates containing an allene tethered to an electron-deficient alkene. Specifically, nickel-catalyzed addition of an arylboronic acid to an allenyl cyclohexa-2,5-dienone could provide an allylnickel species **A** (which could interconvert with σ-allyl isomers, Scheme 1). An enantioselective intramolecular 1,4-allylation would then likely give nickel enolate **B**, which upon protonolysis would release the Ni(II) catalyst and a *cis*-fused hexahydroindol-5-one or hexahydrobenzo-furan-5-one,[4,5,6,7] which are important structures that appear in several natural products such as runanine,[8] acutumine,[9] millingtonine,[10] and cryptocaryone[11] (Figure 1). Furthermore, the enone in these structures serves as a versatile handle for further manipulations to give octahydroindole and octahydrobenzofuran derivatives, which are present in many other natural products.



Scheme 1 Proposed arylative cyclization of allenyl cyclohexa-2,5-dienones

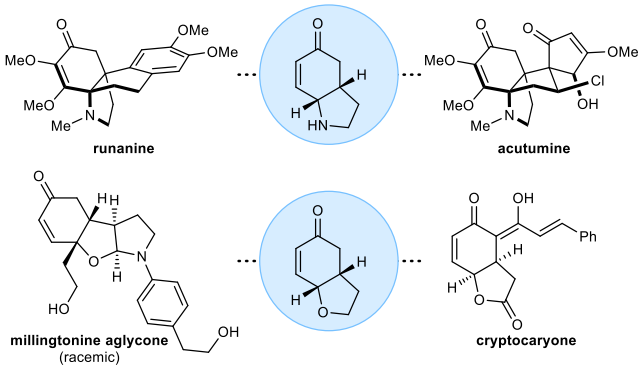


Figure 1 Hexahydrobenzofuran-5-one and hexahydroindol-5-one natural products

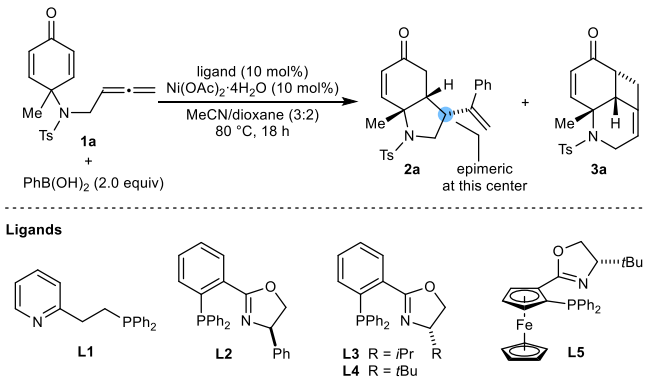
To our knowledge, however, there is only limited precedent for nickel-catalyzed 1,4-allylations, with only one reported study by Sieber and Morken.[2b] Also relevant is work by Montgomery and co-workers, who described diastereoselective nickel-catalyzed alkylative cyclizations of allenes tethered to α,β-unsaturated carbonyl compounds that give products of formal 1,4-allylation.[12] Herein, we describe the successful implementation of the strategy shown in Scheme 1, which gives

[a] The GlaxoSmithKline Carbon Neutral Laboratories for Sustainable Chemistry, University of Nottingham, Jubilee Campus, Triumph Road, Nottingham, NG7 2TU, United Kingdom
[b] School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, United Kingdom

† Electronic Supplementary Information (ESI) available: Experimental procedures, full spectroscopic data for new compounds, and crystallographic data for **2a**–**2d**, **2g**, **2h**, and **3a**. See DOI: 10.1039/x0xx00000x

‡ These authors contributed equally.

Table 1 Evaluation of reaction conditions[a]



entry	ligand	yield of **2a** (%)[b]	yield of **3a** (%)[b]	dr of **2a**	ee of **2a** (%)[c]
1	–	35	11	2.0:1	–
2	**L1**	82	9	3.6:1	–
3	**L2**	89	10	>19:1	90
4	**L3**	62	14	14:1	–91[d]
5	**L4**	33	22	5.3:1	–87[d]
6	**L5**	16	26	0.6:1[e]	–68,[d] 69[e]

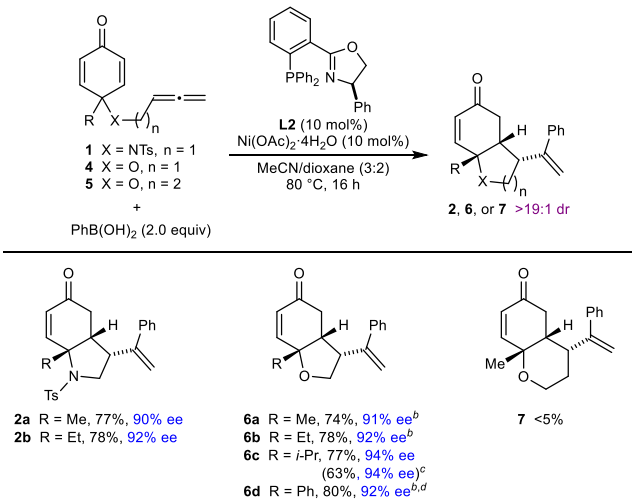
[a] Reactions were conducted with 0.10 mmol of **1a** at 0.1 M concentration. [b] Determined by ^{1}H NMR analysis of the crude reactions using 1,3,5-dimethoxybenzene as the internal standard. [c] Determined by chiral HPLC analysis. [d] The major product was the enantiomer of **2a**. [e] The major product was the diastereomer of **2a**, obtained in 69% ee.

hexahydroindol-5-ones and hexahydrofuran-5-ones with three contiguous stereocenters in high diastereo- and enantioselectivities.

This study began with the reaction of allenyl cyclohexa-2,5-dienone **1a** with $PhB(OH)_2$ (2.0 equiv) and $Ni(OAc)_2{\cdot}4H_2O$ (10 mol%) in MeCN/dioxane (3:2) at 80 °C for 18 h (Table 1, entry 1). We were pleased to observe that 6,5-bicycle **2a** was obtained in 35% ^{1}H NMR yield as a 2.0:1 ratio of diastereomers.[13] However, this reaction also gave cyclobutane **3a** in 11% ^{1}H NMR yield, resulting from a [2+2] cycloaddition.[13] Heating **1a** in MeCN/dioxane (3:2) at 80 °C for 24 h in the absence of $PhB(OH)_2$ and $Ni(OAc)_2{\cdot}4H_2O$ also gave **3a** in 44% NMR yield, which demonstrates this [2+2] cycloaddition is a thermally promoted process rather than a nickel-catalyzed reaction (see the Supplementary Information for details). The addition of 10 mol% of the *P*,*N*-ligand **L1** increased the yield of **2a** to 82% (entry 2). Furthermore, chiral phosphinooxazoline (PHOX) ligands **L2**–**L5** successfully gave enantioenriched products, though with varying levels of efficiency (entries 2–6). Of these, (*R*)-Ph-PHOX (**L2**) provided **2a** in the best balance between yield, diastereoselectivity, and enantioselectivity (entry 3), and this ligand was selected for further experiments.

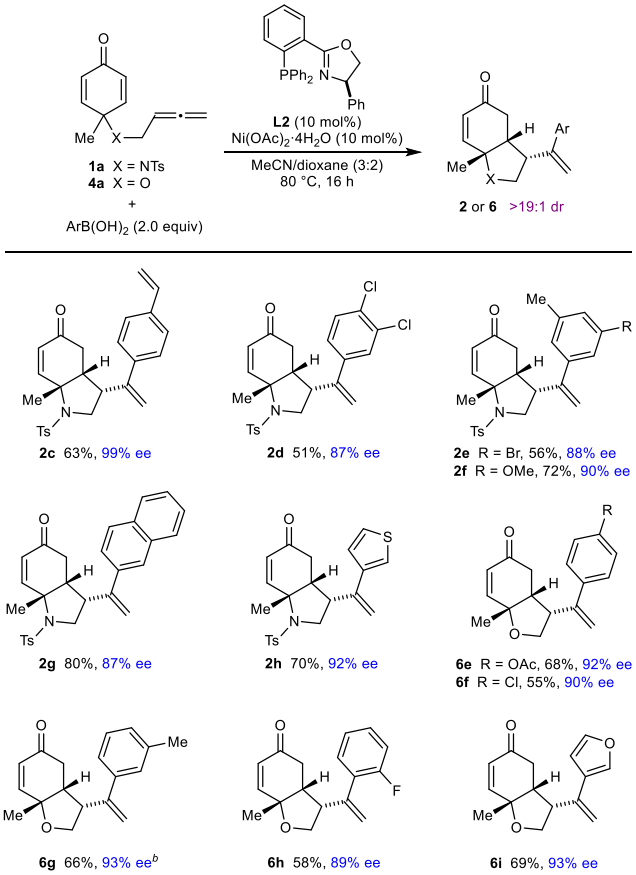
The scope of the process with respect to the allenyl substrate was examined in reactions with $PhB(OH)_2$ (Table 2). Both *N*-sulfonyl-tethered and *O*-tethered substrates reacted successfully to give 6,5-bicycles **2a**–**2b** and **6a**–**6d**, respectively, in good yields (77–87%) and high enantioselectivities (90–94% *ee*). In all cases, small quantities of cyclobutanes (either **3a** or analogous to **3a**) were also formed, but with the exception of the reactions forming **6a**, **6b**, and **6d**, these were separable by column chromatography. The substituent at the quaternary center of the substrates can be changed from methyl (**2a** and **6a**) to ethyl (**2b** and **6b**), isopropyl (**6c**), or phenyl groups (**6d**). By increasing the reaction concentration, the

Table 2 Substrate evaluation[a]



[a] Reactions were conducted with 0.30 mmol of **1**, **4**, or **5** at 0.1 M concentration. Yields are of isolated products. Enantiomeric excesses were determined by chiral HPLC analysis. [b] Products **6a**, **6b**, and **6d** were isolated together with cyclobutane side products (see the Supplementary Information for details) as inseparable mixtures in ratios of between 11:1 and 20:1. Yields have been adjusted accordingly. [c]Values in parentheses are of a reaction conducted with 2.00 mmol of **4c** at 0.4 M concentration for 42 h, using 5 mol% each of $Ni(OAc)_2{\cdot}4H_2O$ and **L2**. [d] Conducted with 0.15 mmol of **4d**.

Table 3 Boronic acid evaluation[a]

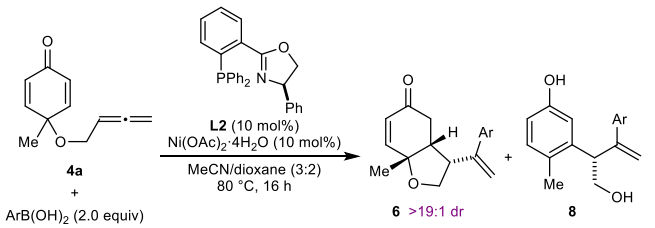


[a] Reactions were conducted with 0.30 mmol of **1a** or **4a** at 0.1 M concentration. Yields are of isolated products. Enantiomeric excesses were determined by chiral HPLC analysis. [b] Isolated together with cyclobutane **3b** (see the Supplementary Information for the structure) in a 11:1 ratio. The yield of **6g** has been adjusted accordingly.

catalyst loading can be reduced. For example, **6c** was obtained in 63% yield and 94% ee from a 2.00 mmol scale reaction conducted at 0.4 M concentration, using a 5 mol% catalyst loading. Allenyl substrate **5**, containing a longer tether between the allene and the cyclohexa-2,5-dienone, was largely unreactive and only a trace (<5%) of 6,6-bicycle **7** was observed, with the mass balance being mostly starting material.

The scope of the boronic acid was then examined using substrates **1a** and **4a**, which gave products **2c**–**2h** and **6e**–**6i** in 51–81% yield with generally high enantioselectivities (Table 3). The reaction is compatible with a variety of *para*- (**2c**, **6e**, and **6f**), *meta*- (**6g**), *ortho*- (**6h**), and disubstituted (**2d**–**2f**) arylboronic acids, and the functional group tolerance is shown by examples with vinyl (**2c**), halide (**2d**, **2e**, **6f** and **6h**), methoxy (**2f**), and acetoxy (**6e**) substituents. 2-Naphthylboronic acid (**2g**) and heteroarylboronic acids (**2h** and **6i**) are also tolerated.

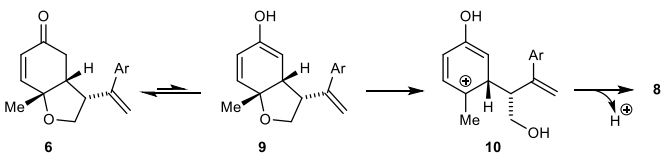
Table 4 Reactions producing phenols **8**[a]



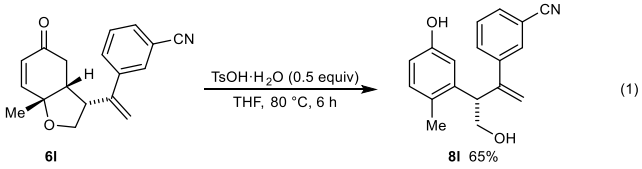
entry	Ar	6,5-bicycle	phenol
1	4-AcC_6H_4	**6j** 51%, 89% ee	**8j** 16%, 92% ee
2	4-$Me_3SiC_6H_4$	**6k** 35%, 93% ee	**8k** 14%, 94% ee
3	3-NCC_6H_4	**6l** 28%, 89% ee	**8l** 59%, 91% ee
4	3-$EtO_2CC_6H_4$	**6m** 64%, 91% ee	**8m** 22%, 91% ee

[a] Reactions were conducted with 0.30 mmol of **4a**. Yields are of isolated products. Enantiomeric excesses were determined by chiral HPLC analysis.

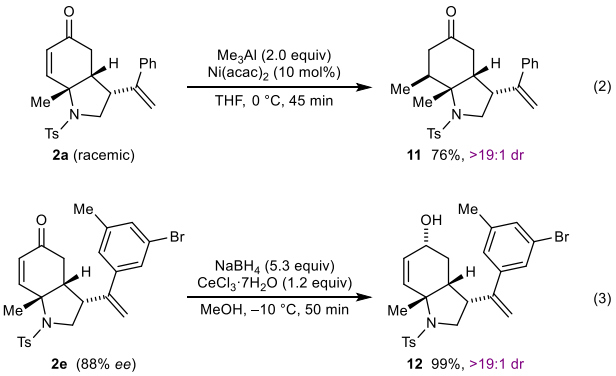
Interestingly, the reaction of **4a** with certain arylboronic acids gave 3,4-disubstituted phenols **8** in addition to the expected 6,5-bicycles (Table 4). In each case, both products were formed with high enantioselectivities (89–94% ee). Most of these arylboronic acids contain strongly electron-withdrawing substituents such as 4-acetyl (entry 1), 3-cyano (entry 3), or 3-carboethoxy groups (entry 4), but 4-trimethylsilylphenylboronic acid also resulted in phenol formation (entry 2). Phenols **8** might be formed by enolization of the ketone of **6** to give **9**, followed by ring-opening of the furan ring, which presumably is promoted by a Brønsted acid or hydrogen bond donor (Scheme 2). Proton loss from **10** then gives **8**.[14] The fact that phenols **8** are observed in appreciable quantities only when certain arylboronic acids are used may indicate that the boronic acid serves as a hydrogen bond donor to promote ring-opening.[15] Confirmation of the ability of acid to promote the formation of phenols **8** was provided by heating **6l** with $TsOH·H_2O$ (0.5 equiv) at 80 °C, which gave **8l** in 65% yield (eqn (1)).



Scheme 2 Rationale for the formation of phenols **8**



To demonstrate the synthetic utility of the products, further transformations were conducted (eqn (2) and (3)). Reaction of racemic **2a** with Me_3Al in the presence of $Ni(acac)_2$ (10 mol%) gave **11** in 76% yield as a single observable diastereomer (>19:1 d.r.), resulting from 1,4-addition to the less hindered convex face [Eq. (2)]. Furthermore, a Luche reduction of **2e** gave allylic alcohol **12** in >99% yield, also as a single observable diastereomer (eqn (3)).



In summary, we have reported the enantioselective nickel-catalyzed desymmetrization of allenyl cyclohexa-2,5-dienones by reaction with arylboronic acids. These domino addition–cyclizations add to the currently limited body of work in catalytic enantioselective intramolecular 1,4-allylations,[2g,i] and provide hexahydroindol-5-ones and hexahydrofuran-5-ones with three contiguous stereocenters in high diastereo- and enantioselectivities. Further enantioselective nucleophilic allylations triggered by nickel-catalyzed migratory insertions of allenes are under investigation in our group.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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