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Enantioselective nickel-catalyzed *anti*-arylmetallative cyclizations onto acyclic electron-deficient alkenes†

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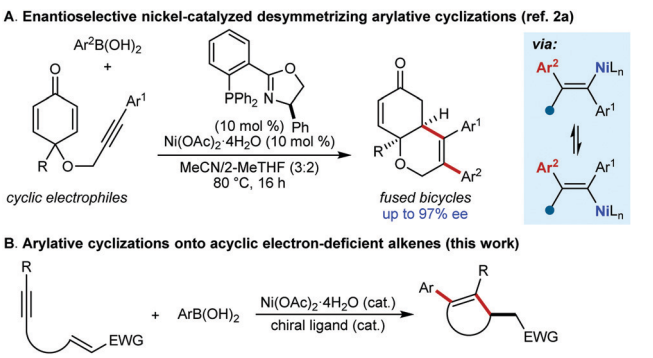
Enantioselective nickel-catalyzed reactions of (hetero)arylboronic acids or alkenylboronic acids with substrates containing an alkyne tethered to various acyclic electron-deficient alkenes are described.

The metal-catalyzed addition of an arylboron reagent to an alkyne, followed by enantioselective intramolecular nucleophilic addition of the resulting alkenylmetal species onto a tethered electrophile, is a versatile domino reaction sequence for the synthesis of diverse chiral carbo- and heterocycles.[1] We[2] and others[3] have recently described nickel-catalyzed variants of these reactions in which reversible *E*/*Z* isomerization of the intermediate alkenylnickel species enables enantioselective arylative cyclizations to proceed that would otherwise be impossible because of geometric constraints. Variants of these reactions that give achiral products,[4] and several related processes,[5–7] have also been described.

We have previously described enantioselective desymmetrizing nickel-catalyzed arylative cyclizations onto cyclohexa-2,5-dienones, which give fused bicyclic products with high diastereo- and enantioselectivities (Scheme 1A).[2a] However, the use of a broader range of acyclic electron-deficient, conjugated alkenes in cyclizations would be valuable in providing less complex, non-fused products, and would substantially increase the synthetic utility of this methodology. Herein, we demonstrate that acyclic enones, nitroalkenes, α,β-unsaturated esters, and α,β-unsaturated nitriles can be used as electrophiles in the enantioselective preparation of various non-fused chiral carbo- and heterocycles (Scheme 1B). Collectively, these results represent a substantial increase in the scope of nickel-catalyzed *anti*-carbometallative cyclizations.

This study began with the reactions of $PhB(OH)_2$ with substrates **1a–1p** (Table 1). An evaluation of conditions[8] led to the finding that heating the substrate **1**, $PhB(OH)_2$ (1.2 equiv.), and 5 mol% each of $Ni(OAc)_2{\cdot}4H_2O$ and (*S*)-*t*-Bu-NeoPHOX (**L1**)[2b,9] in TFE at 100 °C for 16–19 h gave the desired products **2** in generally good yields and high enantioselectivities.[10] In some cases (**2j**, **2o**, and **2p**), using 2.0 equivalents of $PhB(OH)_2$ and increasing the catalyst loading were required for acceptable yields. Aromatic ketones with halide (**2a** and **2b**), nitro (**2c** and **2e**), or trifluoromethyl (**2d**) substituents at various positions of the benzene are tolerated, as are 2-furyl (**2f**), 2-thienyl (**2g**), and methyl ketones (**2h** and **2k–2n**). Notably, an α,β-unsaturated aldehyde underwent arylative cyclization to give **2i** in 58% yield and >99% ee. An α-chloroketone, containing a potentially labile carbon–chlorine bond, is also tolerated (**2j**). The alkynyl group can be changed from phenyl (**2a–2j**) to 4-chlorophenyl (**2k**), 3-methylphenyl (**2l**), 2-thienyl (**2m**), and vinyl (**2n**), although **2m** was formed in lower yield and enantioselectivity. Aryl- and alkenyl-substituted alkynes are usually required for high regioselectivities in the initial arylnickelation step, presumably because the resulting alkenylnickel intermediates are better stabilized by an adjacent sp^2-hybridized group. Therefore, it was of interest to evaluate the reaction of methyl-substituted alkyne **1o**,



Scheme 1 Enantioselective nickel-catalyzed arylative cyclizations onto electron-deficient alkenes.

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† Electronic supplementary information (ESI) available: Experimental procedures, full spectroscopic data for new compounds, and crystallographic data for **2a**, **2r**, **2s**, and **2y**. CCDC 2040010–2040013. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc01166a

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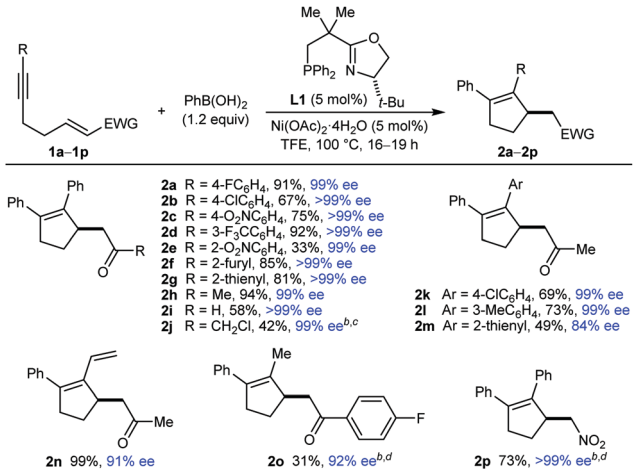
Table 1 Scope of alkynes tethered to electron-deficient alkenes[a]

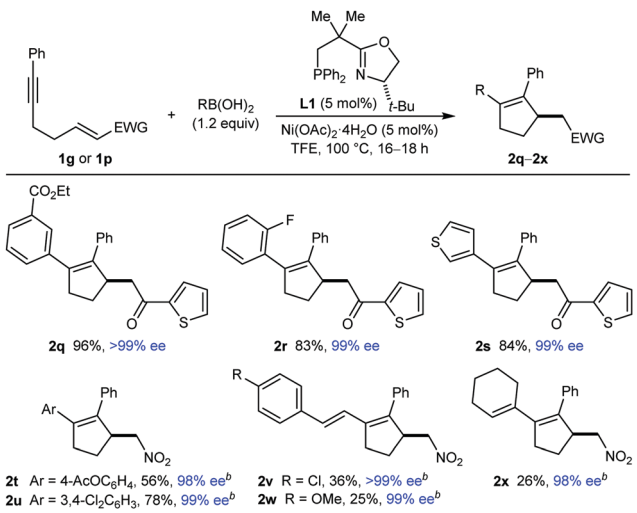


[a] Reactions were conducted using 0.30 mmol of **1** in TFE (3 mL). Yields are of isolated products. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [b] Using 2.0 equivalents of $PhB(OH)_2$. [c] Using 20 mol% each of $Ni(OAc)_2{\cdot}4H_2O$ and **L1**. [d] Using 10 mol% each of $Ni(OAc)_2{\cdot}4H_2O$ and **L1**.

which gave **2o** in 31% yield and 92% ee. This reaction also gave a mixture of other unidentified products, presumably because of low regioselectivity in the initial arylnickelation. A nitroalkene can also be used as the electrophile (**2p**).

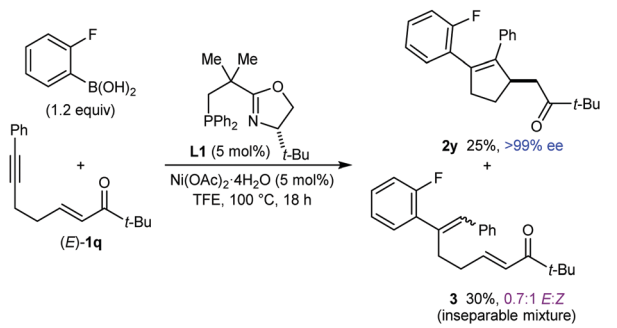
The results of evaluating different boronic acids in reactions with substrates **1g** or **1p** are shown in Table 2. Substituted phenylboronic acids with various groups at the *para* (**2t**), *meta* (**2q**), or *ortho* (**2r**) positions successfully underwent the reaction to give products with reasonable to high yields and high enantioselectivities, as did 3,4-dichlorophenylboronic acid (**2u**) and 3-thienylboronic acid (**2s**). Various alkenylboronic acids also reacted with **1p** to give products **2v–2x** in >99% ee but in low yields because of competitive protodeboronation.

Table 2 Scope of boronic acids[a]

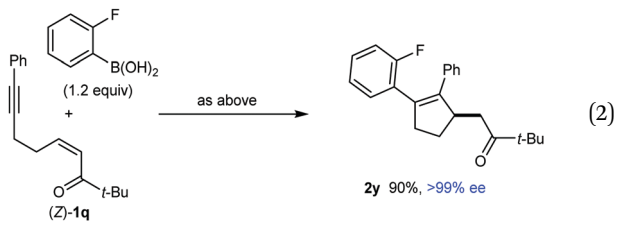


[a] See footnote *a* of Table 1. [b] Using 2.0 equivalents of boronic acid and 10 mol% each of $Ni(OAc)_2{\cdot}4H_2O$ and **L1**.

Further investigations into the scope of these reactions revealed some interesting findings. For example, the reaction of 2-fluorophenylboronic acid with substrate (*E*)-**1q**, which contains an α,β-unsaturated *t*-butyl ketone, gave the arylative cyclization product **2y** in only 25% yield but in >99% ee (eqn (1)). This reaction also gave the alkyne hydroarylation products **3** in 30% yield, which were isolated as a 0.7 : 1 mixture of inseparable *E*- and *Z*-isomers, respectively. Evidently, the steric hindrance imparted by the *t*-butyl group had a negative effect on the efficiency of arylative cyclization. Interestingly, however, the analogous reaction with the stereoisomeric substrate (*Z*)-**1q** gave **2y** in 90% yield and >99% ee (eqn (2)). The markedly different propensity of (*E*)-**1q** and (*Z*)-**1q** to undergo the desired reaction is reminiscent of our prior work in enantioselective nickel-catalyzed intramolecular allylic alkenylations, where *Z*-allylic phosphates gave arylative cyclization products but the corresponding *E*-isomers did not.[2b] The reasons for the differing results obtained from (*E*)-**1q** and (*Z*)-**1q** are not clear, but perhaps the lower thermodynamic stability of (*Z*)-**1q** is manifested in greater reactivity toward nucleophilic attack, and/or the steric requirements of the reaction are better accommodated by (*Z*)-**1q**. Moreover, the major enantiomer of **2y** is identical for both reactions (see the ESI† for tentative stereochemical models). These results contrast with several other examples of enantioselective 1,4-additions of carbon nucleophiles to electron-deficient alkenes where *E*- and *Z*-isomers of the substrates give opposite enantiomers of the products.[11] However, reactions where *E*- and *Z*-isomers give the same major enantiomers of 1,4-addition products are also known.[1j,11b]



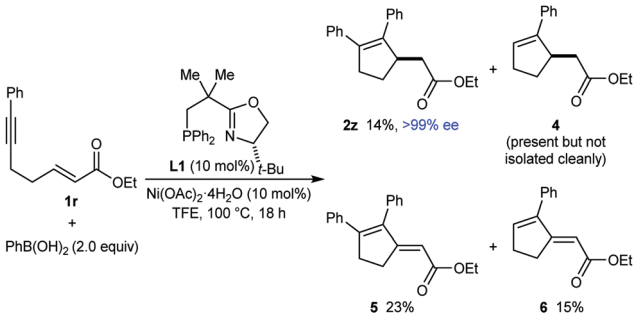
(1)



(2)

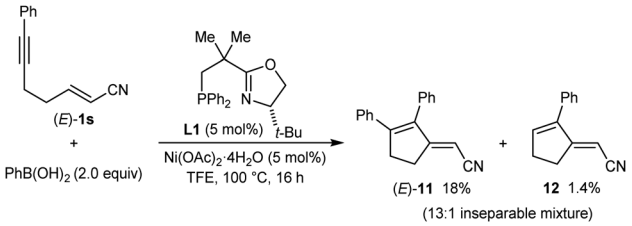
Thus far, only enones or nitroalkenes had been used as electrophiles. Interestingly, use of an α,β-unsatured ester gave other types of products (eqn (3)). Substrate **1r** reacted with $PhB(OH)_2$ (2.0 equiv.) in the presence of 10 mol% each of $Ni(OAc)_2{\cdot}4H_2O$ and (*S*)-*t*-Bu-NeoPHOX (**L1**) to give the arylative cyclization product **2z** (14%, >99% ee), conjugated dienes **5** (23% yield) and **6** (15% yield) resulting from Heck-type cyclizations,[12,13] and what appeared to be the reductive cyclization product **4**, which could not be isolated cleanly. These results can be

explained by considering the mechanism of nickel-catalyzed *anti*-carbometallative cyclizations that we have proposed previously (Scheme 2).[2,4c] Reaction of **1r** and $PhB(OH)_2$ would, after arylnickelation and reversible *E*/*Z* isomerization,[2,4c] lead to alkenylnickel species **7**. A *syn*-stereospecific migratory insertion of the alkene[2b] would then give the *C*-bound nickel enolate **8**. Protodenickelation of **8** by TFE gives the arylative cyclization product **2z**. However, the low yield of **2z** suggests that this step is slow compared with substrates containing ketones or nitro groups (Tables 1 and 2).[14] In competition with protodenickelation of **8**, bond rotation to give **8′** and stereospecific *syn*-β-hydride elimination gives diene **5** and a nickel hydride species **9**. The nickel hydride **9** can then enter analogous reaction pathways with substrate **1r** but *via* alkyne hydronickelation to give **10** and eventually, the reductive cyclization product **4** and diene **6**.

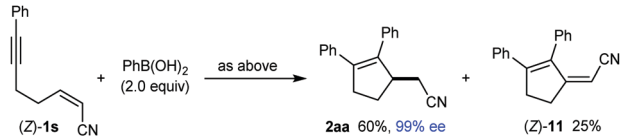


(3)

Conjugate dienes were also obtained from substrates containing an α,β-unsaturated nitrile (eqn (4) and (5)). The reaction of $PhB(OH)_2$ with (*E*)-**1s** gave an inseparable 13 : 1 mixture of dienes (*E*)-**11** (18% yield) and **12** (1.4% yield), and the remainder of the material was a mixture of unidentified products (eqn (4)). None of the desired product **2aa** was detected. In contrast, the stereoisomeric substrate (*Z*)-**1s** gave **2aa** in 60% yield and 99% ee, along with diene (*Z*)-**11** in 25% yield (eqn (5)). The observation that the *Z*-isomer of the substrate is more effective in providing the product **2aa** is similar to the results shown in eqn (1) and (2). For a mechanistic rationale of the production of different stereoisomers of dienes (*E*)-**11** and (*Z*)-**11** from (*E*)-**1s** and (*Z*)-**1s**, respectively, see the ESI.†



(4)

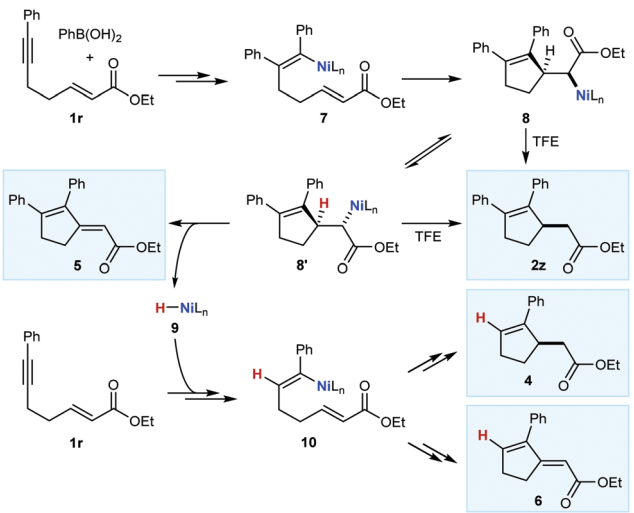


(5)

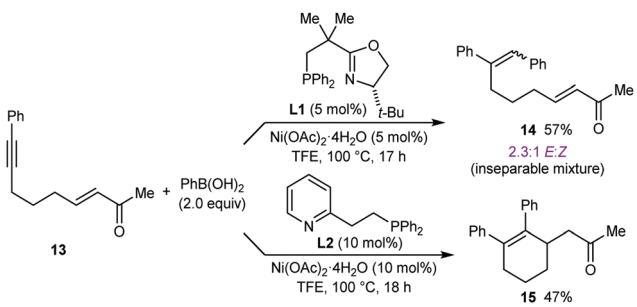
Next, the formation of six-membered rings was attempted. However, reaction of **13** (a higher homologue of substrate **1h** that successfully gave product **2h** (see Table 1)) with $PhB(OH)_2$ (2.0 equiv.) in the presence of 10 mol% each of $Ni(OAc)_2{\cdot}4H_2O$ and (*S*)-*t*-Bu-NeoPHOX (**L1**) failed to provide the desired six-membered arylative cyclization product. Instead, a 2.3 : 1 mixture of inseparable stereoisomeric alkyne hydroarylation products (*E*)-**14** and (*Z*)-**14**, respectively, was obtained in 57% yield (Scheme 3). Replacing (*S*)-*t*-Bu-NeoPHOX (**L1**) with other chiral phosphine–oxazoline ligands did not lead to any improvement.[8] However, use of the achiral ligand pyphos (**L2**) gave racemic **15** in 47% yield (Scheme 3).[15]

The reaction of $PhB(OH)_2$ with substrate **16a**, which contains a *para*-toluenesulfonamide group, gave only a complex mixture of unidentified products (Scheme 4). As with **13**, improved results were not obtained with other chiral phosphine–oxazoline ligands[8] but use of pyphos (**L2**) gave the racemic arylative cyclization product **17** in 52% yield.

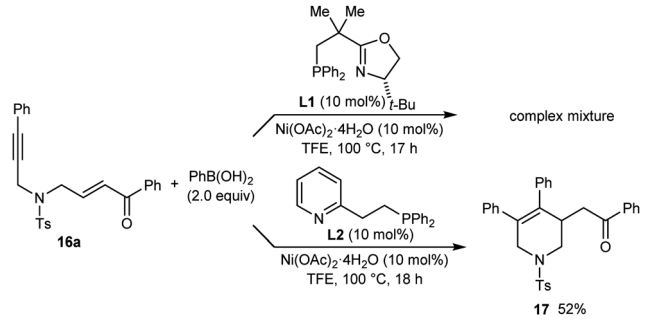
Given the results shown in Schemes 3 and 4, it was not surprising that substrate **16b** (see eqn (6)), which contains an α,β-unsaturated ester rather than an α,β-unsaturated ketone, did not provide the desired arylative cyclization product when it was reacted with $PhB(OH)_2$ using **L1** as the chiral ligand. However, unlike for substrates **13** and **16a**, it was interesting to observe that (*S*)-*t*-Bu-PHOX (**L3**) was an effective chiral ligand in the arylative cyclization of **16b**, which reacted smoothly with $PhB(OH)_2$ (2.0 equiv.) in the presence of 10 mol% each of $Ni(OAc)_2{\cdot}4H_2O$ and **L3** to give tetrahydropyridine



Scheme 2 Mechanistic rationale of the formation of **2z** and **4**–**6**.

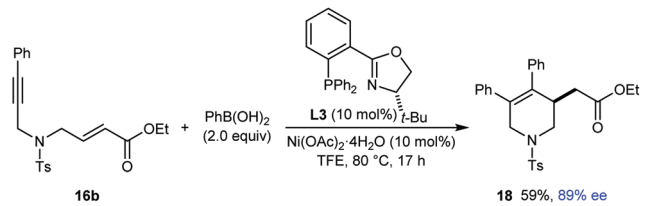


Scheme 3



Scheme 4

18 in 59% yield and 89% ee (eqn (6)).



(6)

In summary, we have reported enantioselective nickel-catalyzed *anti*-carbometallative cyclizations of (hetero)arylboronic acids and alkenylboronic acids with acyclic substrates containing an alkyne tethered to an enone, nitroalkene, α,β-unsaturated ester, or α,β-unsaturated nitrile. The products are various non-fused chiral carbo- and heterocycles, and the enantioselectivities are excellent in most cases (often ≥99% ee). These results represent a substantial increase in the scope over our previous work.[2] Interesting findings comparing the efficiencies of *E*/*Z* stereoisomers of certain substrates, and the isolation of products resulting from β-hydride eliminations and reductive cyclizations have also been described (eqn (1)–(5)).[16]

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Conflicts of interest

There are no conflicts to declare.

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14 A possible reason is that protodenickelation proceeds faster via the *O*-bound, rather than the *C*-bound nickel enolate, and ketone-derived enolates are more likely to exist as the *O*-bound form compared with ester-derived enolates. Similarly, protodenickelation of nickel nitronates is likely to be more rapid than ester-derived nickel enolates because of a higher ratio of *O*- *vs.* *C*-bound forms.

15 Product **15** contained an inseparable impurity and therefore the yield was calculated by ^{1}H NMR analysis using an internal standard.

16 The research data associated with this publication can be found at:http://dx.doi.org/10.17639/nott.7109.