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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 We² and others³ 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 conditions⁸ led to the finding that heating the substrate 1, $PhB(OH)_2$ (1.2 equiv.), and 5 mol% each of Ni(OAc)2·4H2O 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 sp²-hybridized group. Therefore, it was of interest to evaluate the reaction of methyl-substituted alkyne 10,



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

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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)₂·4H₂O and L1. ^{*d*} Using 10 mol% each of Ni(OAc)₂·4H₂O and L1.

which gave **20** 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 acids⁴



^{*a*} See footnote *a* of Table 1. ^{*b*} Using 2.0 equivalents of boronic acid and 10 mol% each of Ni(OAc)₂·4H₂O and L1.

Further investigations into the scope of these reactions revealed some interesting findings. For example, the reaction of 2fluorophenylboronic acid with substrate (E)-1q, which contains an α , β -unsaturated *t*-butyl ketone, gave the arylative cyclization product **2v** 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}



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)₂·4H₂O 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

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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**.



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



Scheme 2 Mechanistic rationale of the formation of 2z and 4-6

(Z)-11 from (E)-1s and (Z)-1s, respectively, see the ESI.†



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)₂·4H₂O and (*S*)-*t*-Bu-NeoPHOX (**L1**) failed to provide the desired sixmembered 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 ligands⁸ 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)₂·4H₂O and L3 to give tetrahydropyridine





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



In summary, we have reported enantioselective nickelcatalyzed *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 $\geq 99\%$ 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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- 15 Product 15 contained an inseparable impurity and therefore the yield was calculated by $^1{\rm H}$ 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.