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N-Heterocyclic Carbene Ligand-Controlled Regioselectivity for Nickel-Catalyzed Hydroarylation of Vinylarenes with Benzothiazoles

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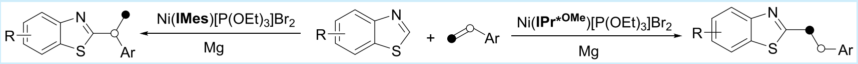
S Supporting Information



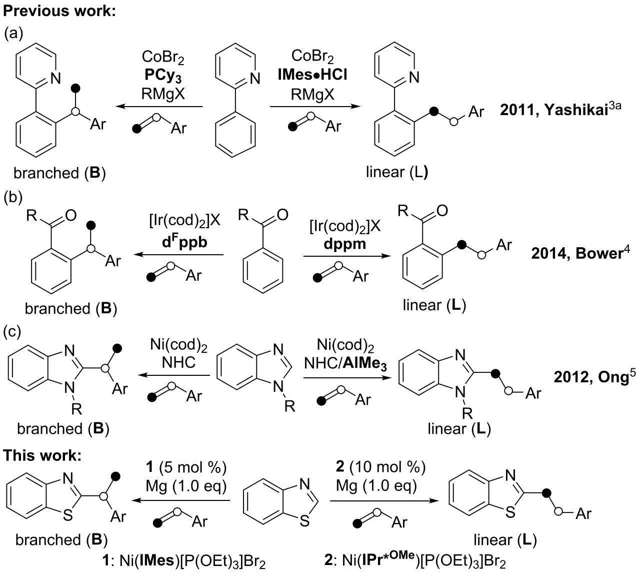
ABSTRACT: A facile regioselective switch for nickel-catalyzed hydroarylation of vinylarenes with benzothiazoles has been developed, which relies on the simple structural variation of novel Ni(II) complexes of the type Ni(NHC)[P(OR)$_3$]Br$_2$. Using magnesium turnings as the reductant, Ni(IMes)[P(OEt)$_3$]Br$_2$ afforded branched products, while Ni(IPr$^{*\mathrm{OMe}}$)[P(OEt)$_3$]Br$_2$ created steric demand to afford linear products. This work also provides a rare example of the rational design of heteroleptic Ni(II) complexes that display the required air stability, reactivity, and regioselectivity via synergism between NHC and phosphite ligands.

In the last two decades, transition-metal-catalyzed alkylation of aromatic C−H bonds with alkenes, also known as hydroarylation of alkenes, has developed rapidly as among the most atom-economical and versatile protocols for the construction of functionalized aromatic rings.[1] For example, the hydroarylation of vinylarenes can offer either 1,1-(branched)- or 1,2-(linear)-diarylethyl structural motifs, which are found in many medicinally active molecules and natural products.[2] A central challenge in this field is the development of simple and accessible strategies for the highly regioselctive control of this transformation since the regioselectivity of most current methodologies is achieved by a relatively rigid substrate dependence strategy, which limited their synthetic applications to special molecules.[1d]

In 2011, Yashikai reported the first example of a regioselective switch in the cobalt-catalyzed hydroarylation of styrenes with 2-arylpyridines, wherein the selectivity for the branched or linear product was controlled by adding PCy$_3$ or IMes·HCl [1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride], respectively, as ancillary ligands (Scheme 1a).[3a] The author also extended the substrate scope to arylimines.[3c,d] Similarly, Bower discovered that adding a bulky biphoshine ligand could significantly affect the iridium-catalyzed hydroarylation of vinylarenes with *N*,*N*-diethylbenzamides (Scheme 1b).[4] Ong described using AlMe$_3$ in the nickel-catalyzed addition of benzimidazoles to styrenes to switch from branched selectivity to linear selectivity (Scheme 1c).[5] Nevertheless, these strategies still have inherent deficiencies regarding synthetic applications because hazardous organometallic reagents (RMgBr[3] and AlMe$_3$[5]) and/or poisonous and expensive phosphine ligands[3,4] are employed.

Since the pioneering work by Cavell,[6] the development of nickel-catalyzed hydroarylations of vinylarenes with heteroarenes[5,7] or fluoroarenes[8] has received increasing research attention. However, to our knowledge, the nickel source employed in these reports has remained restricted to Ni(COD)$_2$, used in combination with ligands including phosphines and N-heterocyclic carbenes (NHCs). Although the direct use of Ni(COD)$_2$ is common in catalysis, this zerovalent nickel source has inherent drawbacks, including being highly air sensitive, difficult to handle, and costly to synthesize.[9] Therefore, it is highly desired to develop a solution to those deficiencies mentioned above.

Scheme 1. Regioselectivity-Switchable Hydroarylation of Vinylarenes



As a continuation of our investigations on the development of nickel-based catalysis of NHCs,[10] we now report the first divalent nickel-based example of a novel class of heteroleptic

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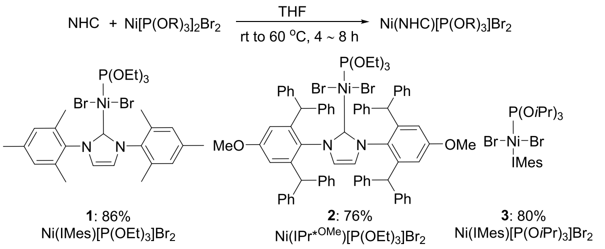
complexes featuring an NHC ligand and a phosphite ligand. Their catalysis for the hydroarylation of vinylarenes with benzothiazoles using stoichiometric amounts of magnesium turnings as the reductant is also reported. The present work shows that a new switching of branched/linear regioselectivity is easily accessible via the rational structural design of well-defined heteroleptic Ni(II) complexes.

To date, heteroleptic Ni(II) complexes incorporating NHC and phosphine ligands are well-known;[11] however, their analogues incorporating phosphate ligand, a typical class of labile ligands that is much cheaper and less toxic than phosphine ligands, has remained unexplored.[12]

We found that target complexes of the type Ni(NHC)[P(OR)$_3$]Br$_2$ could be synthesized by reacting available Ni[P(OR)$_3$]$_2$Br$_2$ with 1 equiv of *in-situ*-generated NHC ligand. As steric hindrance from an NHC ligand might strongly influence the regioselectivity of the reaction,[13] we selected less bulky IMes and very bulky 1,3-bis(2,6-bis(diphenylmethyl)-4-methoxyphenyl)imidazol-2-ylidene (IPr*^{OMe})[14] to synthesize the new Ni(II) complexes. As shown in Scheme 2, the synthetic procedure used afforded heteroleptic Ni(II) complexes **1** and **2** in high yields. However, the reaction involving the IPr*^{OMe} ligand required an elevated reaction temperature and a prolonged reaction time to achieve the desired yield. This methodology was also applied to other phosphite ligands, i.e. P(O*i*Pr)$_3$, affording the desired Ni(II) complex **3** in 80% yield. Complexes **1**−**3** were obtained as air-stable red (**1** and **3**) or pink (**2**) microcrystalline solids. Notably, their solutions also showed considerable stability, with no coloration observed after 2 days in air. This stability was better than that of Ni(NHC)(PR$_3$)X$_2$, which showed a color change in solution several minutes after exposure to air.[10c]

Scheme 2. Synthesis of Heteroleptic Ni(II) Complexes 1−3



The structures of complexes **1**−**3** were unambiguously determined by single-crystal X-ray diffraction (Figure 1). Their structures are similar to each other, wherein each nickel atom adopts a slightly distorted square planar geometry with a *trans* arrangement of the NHC ligand and the P(OR)$_3$ ligand, which was similar to the structures of Ni(NHC)(PR$_3$)X$_2$[10c] and Pd(NHC)[P(OR)$_3$]X$_2$[15] reported previously. As expected, detailed structural analysis clearly showed the differences in steric hindrance. For example, complex **2** bearing the IPr*^{OMe} ligand has a longer Ni−C$_{carbene}$ bond than complex **1**, mostly due to the higher steric bulk of IPr*^{OMe} compared with IMes (percent buried volume: 40.2%V$_{Bur}$ for **2** and 34.9%V$_{Bur}$ for **1**).[16] Meanwhile, complex **1** bearing the smaller P(OEt)$_3$ ligand has a slightly shorter Ni−P bond compared with complex **3** [Tolman cone angle (θ): 109° for P(OEt)$_3$ and 130° for P(O*i*Pr)$_3$].[15] However, no clear trend in the Ni−Br bond length was observed for complexes **1**−**3**.

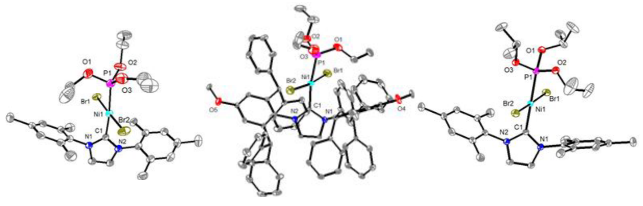
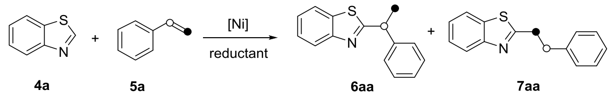


Figure 1. Molecular structures of **1** (left), **2** (middle), and **3** (right). Hydrogens are omitted for clarity.

The catalytic performances of complexes **1**−**3** and related nickel complexes were then explored in the addition of benzothiazole (**4a**) to styrene (**5a**). Benzothiazole and its derivatives, which are among the most attractive heterocyclic skeletons, have rarely been applied in the hydroarylation of vinylarenes.[7c] To our delight, the initial optimization experiments showed switchable regiocontrol of this addition through judicious selection of the heteroleptic Ni(II) complex incorporating different NHC liagnds. As shown in Table 1, in the presence of reductive magnesium turnings (1 equiv),[10d] complex **1** containing the comparatively small IMes ligand afforded a 93% yield of the hydroarylation products with excellent regioselectivity favoring branched isomer **6aa** (**6aa**/**7aa** = 98:2, entry 1). Notably, using complex **2** bearing the very bulky IPr*^{OMe} ligand completely switched the regioselectivity to favor linear isomer **7aa** (**6aa**/**7aa** = 1:99, entry 2). The effect of Ni(II) complex variation was further explored using **3**, modified from **1** by replacing P(OEt)$_3$ with P(O*i*Pr)$_3$, which slightly decreased the yield to 80% with branched selectivity (**6aa**/**7aa** = 98:2, entry 3). These results showed that the hydroarylations of styrene to the corresponding branched and linear products were competing processes and that the regioselectivity could be controlled switchably through modification of the NHC ligand.

Table 1. Optimization of Reaction Conditions[a]

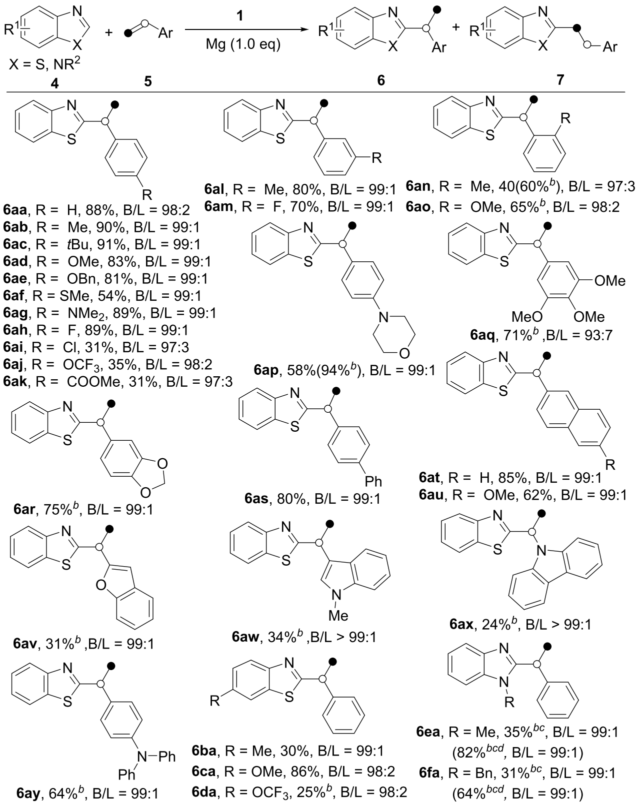


entry	[Ni] (mol %)	reductant	yield (%)	6aa:7aa
1	**1** (5)	Mg	93(88[c])	98:2
2[b]	**2** (10)	Mg	88(83[c])	1:99
3	**3** (5)	Mg	80	98:2
4	**1** (5)	Mn	56	98:2
5	**1** (5)	Zn	<5	-
6[b]	**2** (10)	Mn	6	3:97
7[b]	**2** (10)	Zn	trace	-
8	**1** (5)	KOMe	trace	-
9[b]	**2** (10)	LiO*t*Bu	trace	-
10	Ni(IMes)$_2$Br$_2$ (5)	Mg	trace	-
11	Ni[P(OEt)$_3$]$_2$Br$_2$ (5)	Mg	trace	-
12	Ni(IMes)$_2$Br$_2$/P(OEt)$_3$ (5/5)	Mg	51	99:1
13	Ni[P(OEt)$_3$]$_2$Br$_2$/IMes·HCl (5/5)	Mg	<5	-
14	Ni(COD)$_2$/IMes/P(OEt)$_3$ (5/5/5)	-	90	98:2
15[b]	Ni(COD)$_2$/IPr*^{OMe}/P(OEt)$_3$ (10/10/10)	-	18	3:97

[a]Conditions: **4a** (0.5 mmol), **5a** (0.75 mmol), [Ni] (5 mol %), reductant (0.5 mmol), THF (1.5 mL), 60 °C, 48 h, under Ar. GC yield using *n*-hexadecane as internal standard, and **6aa**/**7aa** ratios were determined by GC analysis of crudes. [b][Ni] (10 mol %), **5a** (1.0 mmol), 100 °C, 60 h. [c]Isolated yield.

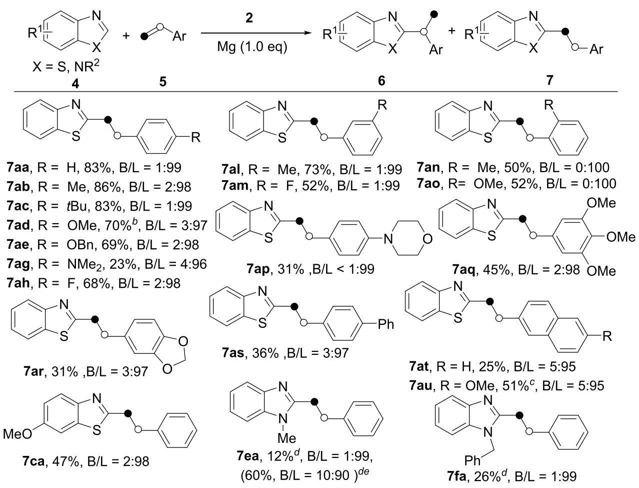
Notably, both the NHC ligand and phosphite ligand were necessary to obtain high yields for both regioisomers, with the absence of one resulting in either a much lower yield or no reaction (entries 10−12). Moreover, a mixture of Ni[P(OEt)$_3$]$_2$Br$_2$ and an imidazolium salt, i.e., IMes·HCl, exhibited almost no catalytic activity (entry 13). Replacing magnesium turnings with widely used manganese powder or zinc dust shut down reactivity (entries 4−7). Using KOMe and LiO*t*Bu also led to no reaction (entries 8−9). A mixture of Ni(COD)$_2$, IMes, and P(OEt)$_3$ in a 1:1:1 molar ratio gave a result very similar to that of **1** (entry 14), but the desired product was obtained in only 18% yield using a 1:1:1 (molar ratio) mixture of Ni(COD)$_2$, IPr*^{OMe}, and P(OEt)$_3$ (entry 15).

Scheme 3. Substrate Scope Catalyzed by 1[a]



[a] Reaction conditions: **1** (5 mol %), **4** (0.5 mmol), **5** (0.75 mmol), Mg (0.5 mmol), THF (1.5 mL), 60 °C, 48 h, under Ar, isolated yield. B/L ratios were determined by GC analysis of crudes or ^{1}H NMR. B: branched, L: linear. [b] **1** (10 mol %). [c] Toluene (1.5 mL) in place of THF, 130 °C. [d] KOMe (0.625 mmol) in place of Mg.

Scheme 4. Substrate Scope Catalyzed by 2[a]



[a] Reaction conditions: **2** (10 mol %), **4** (0.5 mmol), **5** (1.0 mmol), Mg (0.5 mmol), THF (1.5 mL), 100 °C, 60 h, under Ar, isolated yield. B/L ratios were determined by GC analysis of crudes or ^{1}H NMR. [b] **2** (20 mol %). [c] **2** (15 mol %). [d] Toluene (1.5 mL) in place of THF, 130 °C. [e] LiO*t*Bu (0.625 mmol) in place of Mg.

This switchable regiocontrol showed broad generality, with a variety of 2-alkylated benzothiazoles easily synthesized from vinylarenes and benzothiazoles (Schemes 3 and 4). In the presence of a **1**/Mg catalytic system, a variety of styrenes bearing both electron-donating and electron-withdrawing substituents reacted successfully with **4a** to give good yields (31%−91%) and branched selectivity (≥98:2) (**6aa**−**6aj**). In particular, methoxy, chlorine, and fluorine substituents were well-tolerated, despite related Ni(II) complexes of the type Ni(NHC)(PR$_3$)X$_2$ having been reported to be capable of Ar−O, Ar−Cl, and Ar−F bond activation.[10c,d] Notably, an ester group survived (**6ak**). Sterically hindered 2-methyl- and 2-methoxy-substituted styrenes also reacted smoothly when subjected to a higher loading of **1**, affording products **6an** and **6ao** in 60% and 65% yields, respectively, with high levels of branched selectivity (≥97:3). Furthermore, effective structural units in pharmaceuticals, **6ap**, **6aq**, and **6ar**, were obtained in 94%, 71%, and 75% yields with high branched selectivity (≥93:7), respectively, using 10 mol % loading of **1**. The introduction of polyaromatic substitution did not affect the regioselectivity of the reaction (**6as**−**6au**). The present protocol was also applicable to 2-vinylbenzofuran, 3-vinylindole, 9-vinylcarbazole, and *N*,*N*-diphenyl-4-vinylaniline, affording the branched adducts **6av**−**6ay** in yields from 31% to 64%. Several 6-substituted benzothiazoles also are suitable substrates, affording products **6ba**−**6da** in 25%−86% yield with branched selectivity (≥98:2). The present scope was further extended to the reaction of other heterocyclic compounds such as *N*-methylbenzimidazole and *N*-benzylbenzimidazole, affording products **6ea** and **6fa** with high regioselectivity (99:1), but in obviously decreased yields. Nevertheless, the use of KOMe instead of magnesium turnings is of benefit to increase the yields of **6ea** and **6fa**.[14b] In this way, a 20 mmol scale reaction of **5a** with **4a** gave similar yield to the smaller scale experiment, producing **6aa** in 85% yield with branched selectivity (99:1).

The most anticipated application of this generality is that replacing **1** with **2** completely switches the selectivity to the linear product, as shown in Scheme 4, albeit with an average reduced rate compared with the reaction catalyzed by **1**. Interestingly, 2-vinylnapthalenes smoothly participated in the hydroarylation in both reaction modes, affording branched and linear products with high selectivity, despite their switchable regiocontrol being difficult to achieve using the Ni(COD)$_2$/AlMe$_3$[5] or CoBr$_2$/IMes·HCl systems[3a] reported previously.

Although an exact mechanism of this reaction requires further investigation, from our current experimental investigations (Schemes S1 and S2) and literature precedent,[3a,5,7] we inferred that the reaction proceeded through initial *in situ* generation of heteroleptic Ni(0) species, which then catalyzed hydroarylation of the vinylarene through a catalytic cycle involving the following steps: (i) oxidative addition of a C$_{Ar}$−H bond to the Ni(0) center to form a heteroleptic nickel hydride;[17] (ii) reversible coordination of the vinylarene[18] and subsequent insertion into a Ni−H bond to give organonickel intermediates; and (iii) reductive elimination occurred to afford a branched product or a linear product (Schemes S3). Using ^{1}H NMR spectroscopy, nickel hydrides are evident, with signals attributed to nickel hydride hydrogen resonances observed as sharp singlets at −16.65 ppm (using **1**) and −11.33 ppm (using **2**), respectively. The presence of the very bulky IPr*^{OMe} ligand at the nickel center caused sterically induced linear selectivity,[14b] while branched selectivity is well-documented as an electronic preference for benzylnickel species.[7]

In summary, we have synthesized a novel kind of heteroleptic Ni(II) complex of the type $Ni(NHC)[P(OR)_3]Br_2$ (**1**−**3**) and reported their application as the first Ni(II)-based precatalysts for regioselectively-switchable hydroarylation of vinylarenes with benzothiazoles in the presence of stoichiometric amounts of magnesium turnings. The NHC-controlled regioselective switch of the present mode is very rare in hydroarylations reported thus far, which afforded a new practical protocol for the synthesis of a wide variety of 2-alkylated benzothiazoles. The study also shows the potential of synergism between an NHC ligand and a phosphite ligand for the development of nickel catalysis. Further fine-tuning of their catalytic performances by surveying well-matched pairs of $NHC/P(OR)_3$ ligands, extension of this method to other substrates, and a detailed mechanistic study are underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01645.

> Detailed experimental procedures, characterization data for complexes **1**−**3**, structural data for **1**−**3**, and details pertaining to the characterization of the products (PDF)

Accession Codes

CCDC 1545851, 1586771, and 1891606 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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