Communication

Highly Enantioselective Nickel-Catalyzed Intramolecular Hydroal-kenylation of N- and O-Tethered 1,6-Dienes to Form Six-Membered Heterocycles

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Highly Enantioselective Nickel-Catalyzed Intramolecular Hydroalkenylation of N- and O-Tethered 1,6-Dienes to Form Six-Membered Heterocycles

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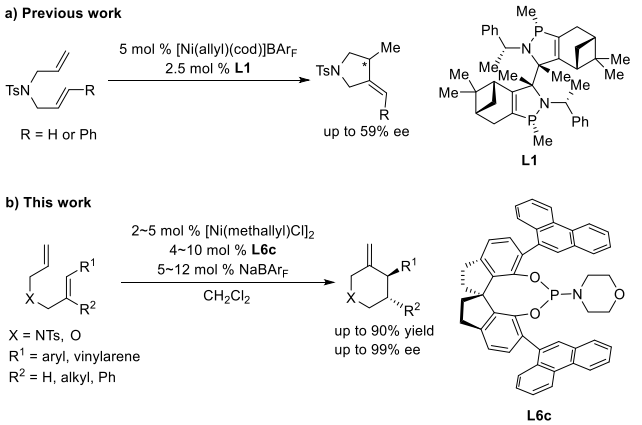
Supporting Information

Abstract: A highly enantioselective nickel-catalyzed intramolecular hydroalkenylation of N- or O-tethered 1,6-dienes was developed by using monodentate chiral spiro phosphoramidite ligands. The reaction provides an efficient and straightforward method for preparing very useful six-membered N- and O-heterocycles with high regioselectivity as well as excellent stereoselectivity from easily accessible starting materials under mild reaction conditions. The chiral spiro nickel catalyst developed in this study represents one of the few catalysts for highly enantioselective cyclization of unconjugated dienes.

Chiral N- and O-heterocyclic moieties are ubiquitous in natural products, pharmaceuticals, and agrochemicals,[1] and the development of efficient methods for their construction has attracted considerable attention in organic synthesis. Transition-metal-catalyzed enantioselective cyclization of N- and O-tethered unsaturated substrates is a straightforward, 100% atom-economical approach to chiral N- and O-heterocycles. Enantioselective cyclizations of N- and O-tethered enynes and allenynes have been achieved with chiral transition metal catalysts.[2] In contrast, enantioselective cyclizations of N- and O-tethered dienes are rare.[3] Leitner and co-workers[4] explored intramolecular hydroalkenylations of N-tethered 1,6-dienes using a nickel complex with chiral phosphineamine ligand **L1** as a catalyst; however, five-membered-ring N-heterocyclic products were obtained with moderate enantioselectivities (up to 59% ee, Scheme 1a). Herein, we report a highly enantioselective intramolecular hydroalkenylation of N- and O-tethered 1,6-dienes mediated by a nickel catalyst modified with monodentate chiral spiro phosphorus ligands; this reaction provides six-membered-ring N- and O-heterocycles with excellent regioselectivity and enantioselectivity (Scheme 1b). Some of the reaction products, for example, 3-substituted-4-arylpiperidines and 3-substituted-4-aryltetra hydropyrans, are

Scheme 1. Nickel-Catalyzed Intramolecular Hydroalkenylation of N- or O-tethered 1,6-Dienes. BAr_F- = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.



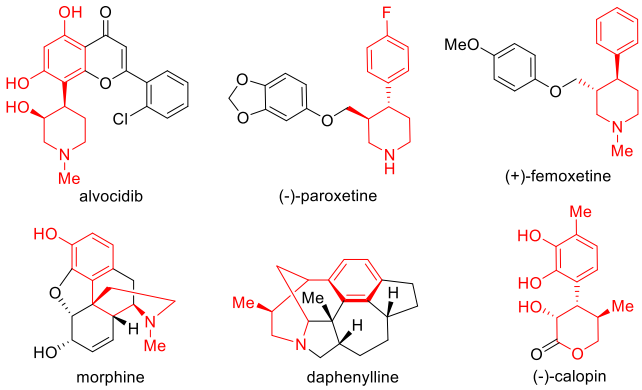
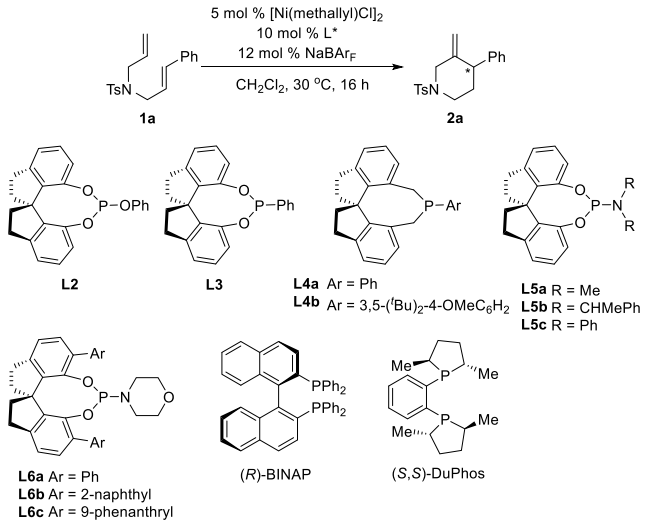


Figure 1. Selected chiral drugs and natural products with 3-substituted-4-arylpiperidine and 3-substituted-4-aryltetrahydropyran as core structures.

core structures of many chiral drugs and natural products, including the anticancer drug alvocidib,[5] the antidepressants

(–)-paroxetine and (+)-femoxetine,[6] and the natural products morphine, daphenylline,[7] and (–)-calopin[8] (Figure 1).

Table 1. Enantioselective Nickel-Catalyzed Intramolecular Hydroalkenylation of N-Tethered 1,6-Diene 1a: Optimization of the Reaction Conditions.[a]



entry	L*	conv. (%)	yield (%)[b]	ee (%)[c]
1	(S_a)-**L2**	27	10	ND[d]
2	(S_a)-**L3**	18	8	ND
3	(S_a)-**L4a**	>95	73	92
4	(S_a)-**L4b**	>95	75	95
5	(S_a)-**L5a**	78	39	13
6	(S_a,*R*,*R*)-**L5b**	<5	<5	ND
7	(R_a,*R*,*R*)-**L5b**	<5	<5	ND
8	(S_a)-**L5c**	85	27	75
9	(S_a)-**L6a**	>95	51	89
10	(S_a)-**L6b**	>95	51	95
11	(S_a)-**L6c**	>95	69	99
12	(*R*)-BINAP	<5	<5	ND
13	(*S*,*S*)-DuPhos	<5	<5	ND
14[e]	(S_a)-**L6c**	>95	68	99
15[f]	(S_a)-**L6c**	62	42	99
16[g]	(S_a)-**L6c**	>95	61	97

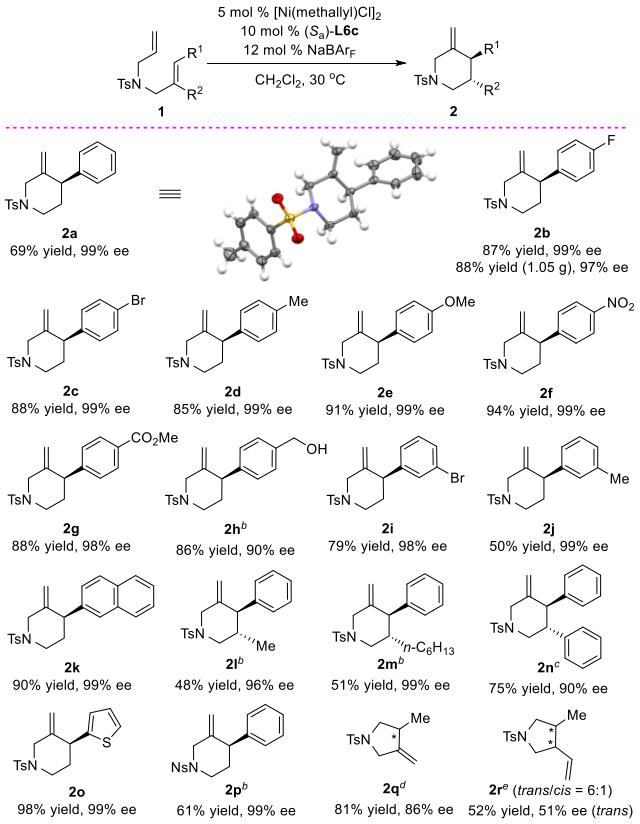
[a] Reaction conditions: $[Ni(methallyl)Cl]_2$ (0.0050 mmol), ligand (0.010 mmol), $NaBAr_F$ (0.012 mmol), **1a** (0.10 mmol), in 1.5 mL CH_2Cl_2, at 30 °C, 16 h. [b] Isolate yield. [c] The ee values were determined by HPLC using IC-3 column. [d] Not determined. [e] Replaced $[Ni(methallyl)Cl]_2$ with $[Ni(allyl)Br]_2$. [f] Performed with 2 mol % catalyst, at 30 °C, 48 h. [g] Performed at gram-scale: $[Ni(methallyl)Cl]_2$ (0.24 mmol), (S_a)-**L6c** (0.49 mmol), $NaBAr_F$ (0.58 mmol), **1a** (4.9 mmol), in 20 mL solvent, at 30 °C, 48 h.

We began by investigating the cyclization of N-tethered 1,6-diene **1a**. The reactions were performed in CH_2Cl_2 at room temperature in the presence of a nickel catalyst prepared in situ from 5 mol % $[Ni(methallyl)Cl]_2$, 10 mol % monodentate phosphorus ligand, and 12 mol % $NaBAr_F$. First, we evaluated various monodentate chiral spiro phosphorus ligands developed in our laboratory.[9] Although phosphite **L2**, phosphonite **L3**, and phosphoramidite **L5** gave low conversions, reactions carried out with phosphine **L4** and 6,6′-diaryl-substituted phosphoramidite **L6** proceeded smoothly and gave six-membered-ring N-heterocyclic product **2a** in good yield with excellent enantioselectivity (Table 1, entries 1–11). (S_a)-**L6c**, which has a 6,6′-di-9-phenanthryl group, afforded the highest enantioselectivity (99% ee, entry 11). The regioselectivity was excellent: no five-membered-ring product was detected. The only side reaction was migration of the terminal double bond of the diene to afford *N*-cinnamyl-4-methyl-*N*-(prop-1-en-1-yl)benzenesulfonamide (<5%). Bidentate phosphine ligands, such as BINAP and DuPhos, were inactive under the tested reaction conditions (entries 12 and 13). Using ligand (S_a)-**L6c**, we systematically optimized the reaction conditions. In addition to $[Ni(methallyl)Cl]_2$, $[Ni(allyl)Br]_2$ was also a suitable catalyst precursor (entry 14). $NaBAr_F$ played a crucial role: the use of additives containing different anions markedly lowered the catalyst activity (Table S1). The bulky, noncoordinative BAr_F ion may have prevented deactivation of the catalyst. Chlorinated solvents and toluene were suitable for the reaction, with dichloromethane giving the highest enantioselectivity (Table S1). Lower catalyst loading resulted in a decreased yield but with retained excellent enantioselectivity (entry 15). The nickel catalyst degraded before getting full conversion. The reaction could be performed on a gram scale without decreasing the yield or enantioselectivity (entry 16).

Under the optimal reaction conditions (Table 1, entry 11), we evaluated the substrate scope of this nickel-catalyzed intramolecular hydroalkenylation of N-tethered 1,6-diene substrates **1** (Scheme 2). Substrates in which R^2 was H and R^1 was a *para*- or *meta*-substituted aryl group (**2b–2k**) smoothly underwent the cyclization to give the corresponding six-membered-ring N-heterocycles in moderate to good yields (50–90%) with excellent enantioselectivities (98–99% ee). Functional groups, including halogen (**1b**, **1c**, **1i**), -OMe (**1e**), $-NO_2$ (**1f**), $-CO_2Me$ (**1g**), and -OH (**1h**) groups were compatible to this reaction. In contrast, the functional groups with strong coordinative nature (e.g. $-NMe_2$, -CN) fully prevented the reaction. X-ray diffraction analysis of a single crystal of **2a** revealed that its absolute configuration was *R*.[10] A gram-scale reaction of **2b** gave essentially the same outcome as that of the small-scale reaction. The catalyst was sensitive to the steric bulk of the substrate, and only a trace amount of the cyclization product was isolated when R^1 was an *ortho*-substituted aryl group (data not shown). Moreover, the reaction is highly sensitive to the configuration of the olefin because *E*-**1a** cannot afford the desired product under standard reaction conditions. To our delight, 1,6-diene (**1l**, **1m** and **1n**), which bears a trisubstituted olefin moiety, also underwent the cyclization reaction to give corresponding products (**2l, 2m and 2n**), which has two chiral centers, as a single anti-isomer. The substrate with a thienyl ring (**1o**) smoothly afforded the desired product **2o** in high yield (98%) with excellent enantioselectivity (99% ee). The substrate with N-Ns (**1p**) gave satisfactory results while the one with N-Boc was inactive for this reaction. The six-membered-ring selectivity of this cyclization reaction rests mainly on the nature of the R^1 substituent of the substrate.

When R¹ was H or Me as well as R² was H, five-membered-ring N-heterocyclic products **2q** and **2r** were isolated in moderate to good yields and enantioselectivities.

Scheme 2. Enantioselective Nickel-Catalyzed Intramolecular Hydroalkenylation of N-Tethered 1,6-Dienes.[a]



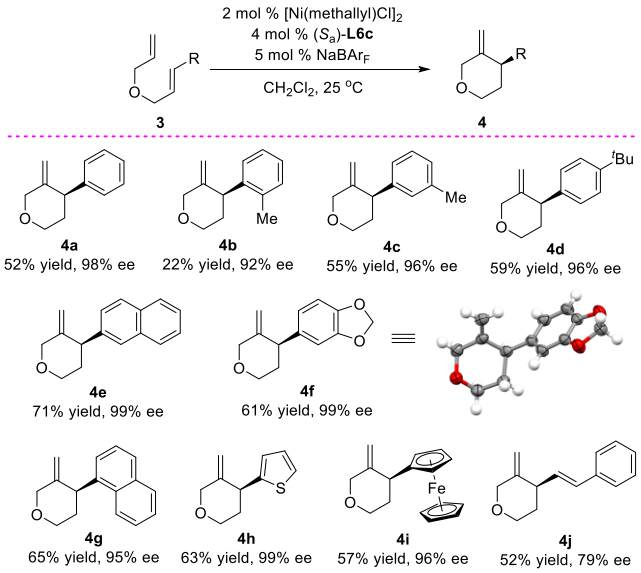
[a] Reaction conditions: [Ni(methallyl)Cl]$_2$ (0.013 mmol), (S_a)-**L6c** (0.026 mmol), NaBAr$_F$ (0.030 mmol), **1** (0.25 mmol), in 1.5 mL CH_2Cl_2, at 30 °C, 16 h. The isolated yields are given. [b] Performed using 10 mol % catalyst at 45 °C, 24 h. [c] Performed with 10 mol % catalyst with **L4b**, at 30 °C, 24 h. [d] Performed with 5 mol % catalyst, at 10 °C, 28 h. [e] Performed with 5 mol % catalyst, at -10 °C, 48 h.

Chiral spiro nickel catalyst Ni/(S_a)-**L6c** (4 mol %) also efficiently catalyzed intramolecular hydroalkenylations of O-tethered 1,6-dienes **3** in moderate to good yield and generally excellent enantioselectivity (Scheme 3). In addition to substituted phenyl groups, the R group of **3** could also be 1-naphthyl (**3g**), 2-naphthyl (**3e**), benzodioxole (**3f**), thienyl (**3h**), ferrocenyl (**3i**), or cinnamenyl (**3j**). The substrate (**3b**) with an *ortho*-substituent exhibited very modest yield but still with high enantioselectivity (92% ee). The structure and absolute configuration of product (*R*)-**4f** were confirmed by X-ray diffraction analysis of a single crystal. The major side-reactions we detected are terminal carbon-carbon double bond isomerization and oligomerization of 1,6-dienes (see Figure S1).[11]

To demonstrate the synthetic utility of this reaction, we performed several transformations of the products (Scheme 4). Product **2g** was oxidized to ketone **5** with ruthenium(III) chloride and sodium periodate in high yield with retained ee (Scheme 4a). Compound **5** is a typical 4-aryl piperidin-3-one, which is a very useful building block in organic synthesis.[12]

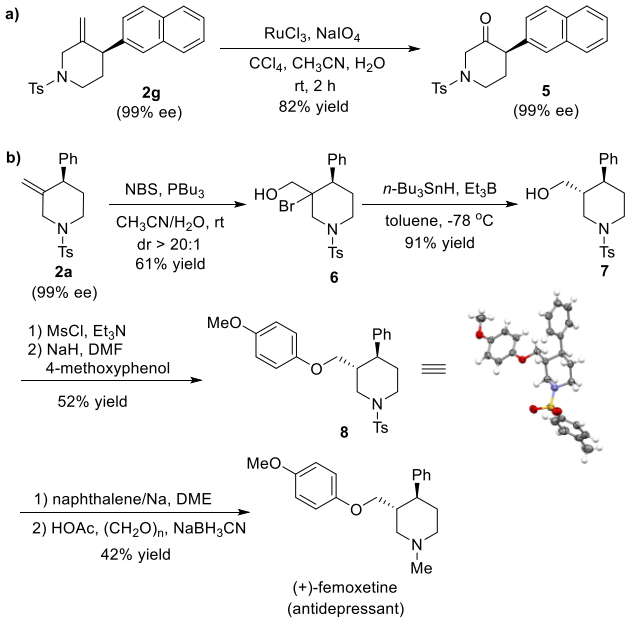
From product **2a**, the antidepressant (+)-femoxetine could be readily synthesized (Scheme 4b). Bromohydroxylation of the exocyclic olefin of **2a** gave bromo alcohol **6**, which underwent radical debromination to form **7** by means of a procedure developed by Hong and co-workers.[13] Introduction of a *para*-methoxyphenol moiety afforded **8**,[14] and methylation of the N atom of the ring[15] produced (+)-femoxetine. The structure and absolute configuration of **8** were confirmed by single-crystal X-ray diffraction analysis.

Scheme 3. Enantioselective Nickel-Catalyzed Intramolecular Hydroalkenylation of O-Tethered 1,6-Dienes.[a]



[a] Reaction conditions: [Ni(methallyl)Cl]$_2$ (0.020 mmol), (S_a)-**L6c** (0.020 mmol), NaBAr$_F$ (0.025 mmol), **3** (0.50 mmol), in 1.5 mL CH_2Cl_2, at 25 °C, 12 h.

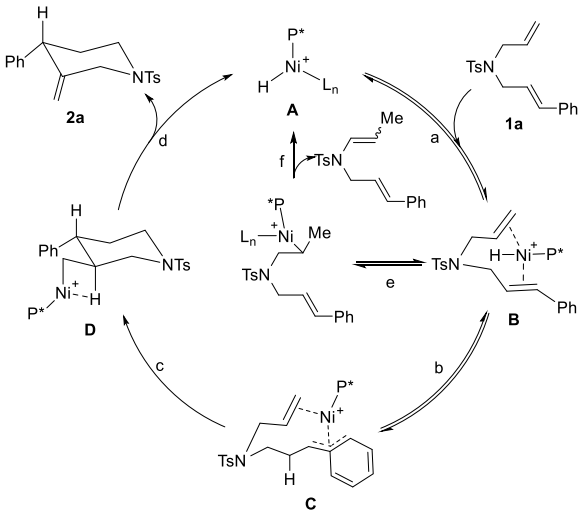
Scheme 4. Transformations of the Products.



We put forward the mechanism shown in Scheme 5 on the basis of our observations and literature results.[4b,16] The cata-

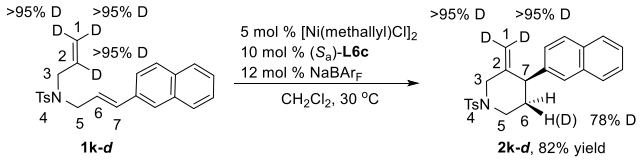
lytic cycle starts with cationic Ni(II)-hydride **A**,[17] which coordinates with the 1,6-diene to form intermediate **B**. After a migratory insertion of the Ni–H into the double bond of the cinnamic moiety of **1a**, π-allyl-Ni intermediate **C** is generated. Cyclization of **C** forms alkyl-nickel intermediate **D**. Finally, β-hydride elimination from **D** gives product **2a** and regenerates Ni(II)-hydride **A**. The phenyl group of **1a** induces hydride migration to the β-position to form relatively stable allylic nickel species **C**, which ensures the regioselectivity of the reaction.

Scheme 5. Proposed Mechanism.



A deuterium-labeling study using the diene **1K-*d*** showed that 78% of the deuterium label was incorporated into the 6-position of **2K-*d*** and the deuterium atom and the naphthalene ring of the **2K-*d*** are in a *cis*-configuration (Scheme 6). These results could be well rationalized by the above mechanism and implies that the migratory insertion of Ni-H into cinnamyl most likely passes through an inner-sphere coplanar four-member-ring transition state (step b). The loss of 22% D might attribute to the generation of Ni-H species through the side reactions of isomerization (steps e-f) or oligomerization.

Scheme 6. Deuterium-Labeling Experiments.



In summary, we developed a highly enantioselective nickel-catalyzed intramolecular hydroalkenylation of N- and O-tethered 1,6-dienes mediated by a nickel catalyst bearing monodentate chiral spiro phosphoramidite ligands. The cyclization reaction provides a mild, efficient, straightforward method for preparing six-membered-ring N- and O-heterocycles, which are core structures in number of bioactive compounds, with high regioselectivity and excellent stereoselectivity. The catalyst developed in this study has high potential for application in other cyclization reactions, which are under investigation in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:
Crystallographic information for compound **2a** (CIF)
Crystallographic information for compound **4f** (CIF)
Crystallographic information for compound **8** (CIF)

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Notes

Notes The authors declare no competing financial interest. Metrical parameters for the structures are available free of charge from the Cambridge Crystallographic Data Centre under reference numbers CCDC-1527598, 1527599 and 1540871.

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