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New *N*-Heterocyclic Carbene Ligand and Its Application in Asymmetric Nickel-Catalyzed Aldehyde/Alkyne Reductive Couplings

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Allylic alcohols are integral subunits of a variety of biologically interesting natural products as well as key building blocks for a number of important synthetic transformations. Among the numerous strategies for the preparation of allylic alcohols, the reductive coupling of aldehydes and alkynes in either an inter- or intramolecular sense arguably provides the most direct access to this important substructure from simple precursors.^{1,2} Whereas several asymmetric approaches to the reductive coupling of aldehydes and alkynes have been reported,³ our recent studies involving the use of achiral *N*-heterocyclic carbene complexes of nickel illustrated several important features including broad scope with both internal and terminal alkynes, direct incorporation of a silyl protecting group, and the ability to tune alkyne regioselection in macrocyclizations based on ligand sterics.⁴ In order to capitalize upon these advantages, we have now examined the asymmetric coupling of aldehydes and alkynes using chiral *N*-heterocyclic carbene complexes.

Pioneering studies from Grubbs illustrated that *N*-heterocyclic carbenes derived from C-2 symmetric diamines and mono-*ortho*-substituted aryl halides were excellent participants in asymmetric ring-closing metathesis reactions.⁵ Members of this structural class of *N*-heterocyclic carbenes appeared to be promising candidates for asymmetric nickel-catalyzed reductive couplings. We thus examined the reductive coupling of benzaldehyde and 1-phenylpropyne under a variety of conditions to provide a lead ligand structure for further optimization. The known *N*-heterocyclic carbene ligands, generated *in situ* from **1a** and **1b** in THF with KO-*t*-Bu, allowed the production of the desired protected allylic alcohol **2a** in modest yield and poor enantioselectivity (Table 1). New ligands **1c** and **1d**, which incorporate an *ortho*-phenyl or *ortho*-cyclohexyl substituent, were then prepared from the commercially available aryl bromides. A reaction involving ligand **1c** afforded product **2a** with slightly improved enantioselectivity, whereas a reaction with ligand **1d** proceeded with significantly improved enantioselectivity, affording compound **2a** in 76% ee in 60% yield. Despite the encouraging enantioselectivity with ligand **1d**, examination of additional starting material combinations illustrated that yields were often poor to modest. Given the requirement of steric hindrance to stabilize free *N*-heterocyclic carbenes (by preventing dimerization), we next considered *ortho,ortho*-disubstituted carbene ligands. Ligand **1e** was thus prepared, which did indeed allow improved chemical yields but with low enantioselectivities. Recognizing that *ortho,ortho*-disubstitution was optimal from the standpoint of chemical yield, whereas steric differentiation of the two *ortho* substituents was optimal from the standpoint of enantioselectivity, we next prepared ligand **1f**. Under the same conditions described for the above experiments, chemical yields in couplings of benzaldehyde and 1-phenylpropyne

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Supporting Information Available: Full experimental details and copies of NMR spectral data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

improved to 98% with lower catalyst loading (2 mol%) in 78% ee. Whereas ligand **1f** was primarily designed for enantioselectivity optimization, the catalytic activity of the nickel catalyst derived from this ligand surprisingly exceeded that of the commonly employed IMes and IPr *N*-heterocyclic carbene ligands in catalytic aldehyde/alkyne reductive couplings. We therefore anticipate that this new ligand may be useful in various metal-catalyzed^{5,6} or organocatalytic⁷ processes that rely on *N*-heterocyclic carbene species.

Upon identifying the excellent catalytic activity and promising enantioselectivity in a reaction with the catalyst derived from ligand **1f**, we sought to explore its generality across a range of substrates. As illustrated (Table 2), the yields and enantioselectivities are relatively uniform across a broad range of substrates. Key functional groups cleanly tolerated in the procedure include aromatic as well as branched and unbranched aldehydes, internal alkynes that either possess or lack an aromatic substituent, terminal alkynes, and unprotected alcohols, wherein the trialkylsilyl group is regioselectively installed on the newly formed hydroxyl. Regioselection of alkyne insertion is high with the exception of internal alkynes that possess two aliphatic substituents (entries 4 and 11). Notably, the regioselectivity in one of these cases was found to undergo reversal with ligand **1d** (compare entries 11 and 12). Therefore, ligand **1d** may be useful in some applications due to this complementary regioselection. The reversal of regioselectivity is consistent with the steric-based model for regioselectivity reversal proposed in macrocyclizations involving achiral ligands.^{4b}

Given that macrocyclizations of ynal substrates provide an important entry to substructures found in many bioactive natural products, this new procedure was applied in an asymmetric macrocyclization of ynal **3** (eq 1). In this example, 14-membered macrocycle **4a** and 13-membered macrocycle **4b** were produced in 76% combined yield as an 86:14 mixture of regioisomers (79% ee for (*S*)-**4a** and 42% ee for (*S*)-**4b**). Notably, the regioselection is reversed in comparison to intermolecular examples (Table 2, entries 4 and 11), illustrating that ring size is a factor in determining regioselectivity.

In analogy to the proposal from Grubbs in asymmetric ring-closing metathesis reactions involving members of the ligand class **1**,⁵ we propose that the reaction proceeds via generation of a three coordinate complex **5** (Scheme 1).⁸ Tilting of the *N*-aryl ring of **5** relative to the imidazolidine ring would position the *ortho*-cyclohexyl substituent *anti* to the backbone phenyl group and distal to nickel as depicted. This orientation would then position the *ortho*-methyl substituent *syn* to the backbone phenyl group and proximal to nickel. It is the *ortho*-methyl substituent that thus dictates the selectivity of aldehyde binding according to this model. Oxidative cyclization of structure **5** to metallacycle **6** would then lead to the formation of **2**, which is the major enantiomer observed.⁹

In summary, an efficient approach to synthesis of allylic alcohols involving the catalytic asymmetric coupling of aldehydes and alkynes has been developed. A new chiral *N*-heterocyclic carbene ligand was prepared that provides improved reaction efficiencies and enantioselectivities compared with known, structurally-related *N*-heterocyclic carbene ligands. Although prior studies established good to excellent enantioselectivities with specific substrate combinations,³ the simple experimental protocol (fast reactions at rt with a stable reducing agent) provides significant preparative advantages of this new procedure, and the range of participating substrates is the broadest of any single method to date. The development of new generations of ligands, synthetic applications, and mechanistic studies are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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9. Absolute stereochemistry of twelve of the fourteen examples (Table 1 and eq 1) were established by Mosher's ester analysis. See supporting information for details

Scheme 1.
Model for Enantioselection.

Table 1
Examination of Ligand Structure.^a

$\text{Ph}-\text{CHO} + \text{Me}-\text{C}\equiv\text{C}-\text{Ph} \xrightarrow[\text{THF, 25 } ^\circ\text{C}]{\text{Et}_3\text{SiH (2.0 equiv), 1, KO-}t\text{-Bu, Ni(COD)}_2 \text{ (0.1 equiv each)}} \text{Ph}-\text{CH}(\text{OSiEt}_3)-\text{C}(\text{Me})=\text{CH}-\text{Ph}$ <p>(1.0 equiv) (1.2 equiv) 2a</p>		
$\mathbf{1} = \text{Ar}-\text{N}^+\text{C}(\text{Ph})_2\text{N}-\text{Ar} \text{ BF}_4^-$		
<p>Ar =</p> <p>1a, 50% (27% ee)</p>	<p>1b, 50% (29% ee)</p>	<p>1c, 40% (45% ee)</p>
<p>1d, 60% (72% ee)</p>	<p>1e, 79% (30% ee)</p>	<p>1f, 98% (78% ee)^b</p>

^bThis entry employed 2 mol % of **1f**, KO-*t*-Bu, and Ni(COD)₂.

^aBelow each structure in the Table is the given the compound number of the imidazolium salt, % yield for the production of **2** using the ligand, and the % ee (in parentheses) of compound **2** produced with the ligand.

Table 2

Scope of Asymmetric Couplings.

Entry	$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1\text{C}-\text{H} \end{array} + \begin{array}{c} \text{R}^3 \\ \diagup \\ \text{R}^2-\text{C}\equiv\text{C} \end{array}$			$\xrightarrow[\text{THF, 25 }^\circ\text{C}]{\begin{array}{c} \text{Et}_3\text{SiH (2.0 equiv)} \\ \mathbf{1f}, \text{KO-}i\text{-Bu, Ni(COD)}_2 \\ \text{(0.1 equiv each)} \end{array}}$		$\begin{array}{c} \text{OSiEt}_3 \\ \\ \text{R}^1-\text{CH}-\text{C}(\text{R}^2)=\text{C}(\text{R}^3) \\ \mathbf{2} \end{array}$	% Yield (% ee) ^d	Regioselect.
	R ¹	R ²	R ³					
1	Ph	Me	Ph			98 (78) ^b		10:1
2	Ph	Et	Et			82 (70)		--
3	<i>i</i> -Pr	Me	Ph			86 (70)		>19:1
4	<i>i</i> -Pr	(CH ₂) ₃ Ph	Me			86 (75)		3:1
5	Cy	Et	Et			84 (85) ^c		--
6	(CH ₂) ₂ Ph	Et	Et			75 (78)		--
7	Cy	Me	Ph			78 (81)		>19:1
8	Cy	H	<i>n</i> -hex			64 (65)		>19:1
9	<i>n</i> -hex	Me	Ph			70 (73)		10:1
10	Cy	(CH ₂) ₄ OH	Ph			99 (79)		9:1
11	Cy	<i>n</i> -pent	Me			79 (76)		3:1 ^e
12	Cy	Me	<i>n</i> -pent			47 (79) ^d		6:1

^a % Ee is given for the major regioisomer.

^b 2 Mol% of **1f**, Ni(COD)₂, and KO-*i*-Bu were used.

^c Ligand (*S,S*)-**1f**, was used, and the enantiomer of the configuration shown for product **2** was obtained.

^d Ligand **1d** was used.

^e Minor regioisomer of entry 11 is of the (*S*) configuration produced in 76% ee.