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NHC Ligands Tailored for Simultaneous Regio- and Enantiocontrol in Nickel-Catalyzed Reductive Couplings

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KEYWORDS regioselective, enantioselective, N-heterocyclic carbene, allylic alcohol, computation

ABSTRACT: An exceptionally hindered class of enantiopure NHC ligands has been developed. While racemic forms had previously been utilized, a scalable and practical route to the enantiopure form of this ligand class is described utilizing a Buchwald-Hartwig *N*,*N*-diarylation in a highly sterically demanding environment. Using this newly accessible ligand class, nickel-catalyzed enantioselective reductive coupling reactions of aldehydes and alkynes have been developed. These studies illustrate that the newly available NHC ligands are well suited for simultaneous control of regio- and enantioselectivity, even in cases with internal alkynes possessing only very subtle steric differences between two aliphatic substituents. The steric demand of the new ligand class enables a complementary regiochemical outcome compared with previously described enantioselective processes. Using this method, a number of allylic alcohol derivatives were efficiently obtained with high regioselectivity (up to >95:5) and high enantioselectivity (up to 94% ee). The reaction conditions can also be extended to the reaction of aldehydes and allenes, providing silyl-protected allylic alcohol derivatives possessing a terminal methylene substituent. Computational studies have explained the origin of the exceptional steric demand of this ligand class, the basis for enantioselectivity, and the cooperative relationship of the aldehyde, alkyne, and ligand in influencing enantioselectivity.

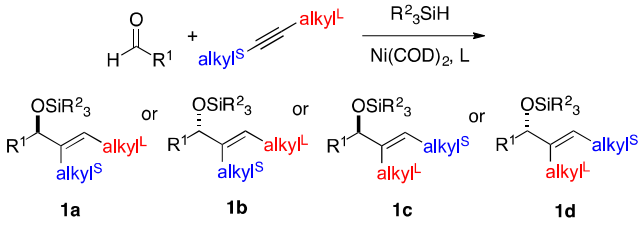
Introduction

Tremendous strides have been made in the development of regioselective and enantioselective C-C bond-forming processes. However, the optimization of ligand structures becomes complex when high levels of both enantioselectivity and regioselectivity are desired with a substrate class that does not possess electronic or steric biases or directing groups that effectively control regiochemistry. Ligand changes that enable high degrees of regioselectivity for a challenging substrate class often compromise the ability to simultaneously tune enantioselectivity. Similarly, the most broadly useful classes of chiral ligands are typically not amenable to modifications that enable access to elusive regiochemical outcomes.

Recent advances in regiodivergent processes have focused on several strategies, including tuning steric interactions between substrates and ligands, turning on and off directing effects, or changing catalyst class altogether to enable a fundamental change in mechanism.[1] Recent studies from our laboratory have focused on the ligand steric control strategy by developing classes of *N*-heterocyclic carbene (NHC) ligands that enable regiodivergence (access to either regioisomer from a common substrate) in catalytic reductive coupling processes.[1-3] The high levels of regiodivergence that are now possible have not yet been paired with an effective strategy for enabling enantioselectivity. Numerous important advances in enantiocontrol in reductive couplings have been illustrated in cases where regioselectivity is governed by substrate control.[4] In these cases, access to only one of the two possible regioisomers is typically possible, and more commonly, mixtures are obtained. Therefore, the ability to tune regioselectivity through catalyst control while obtaining high levels of enantioselectivity remains as an unsolved problem in this class of reactions.

In the reductive coupling of aldehydes and alkynes to prepare allylic alcohols, a benchmark challenge in regiocontrol is presented by internal alkynes that possess two different alkyl substituents. This class of alkynes leads to the unselective production of two possible regioisomers in nearly all catalytic bond-forming processes of internal alkynes.[5] The previous advances in enantioselective aldehyde-alkyne reductive couplings with internal alkynes that lack conjugation or directing functionality are typically unselective or favor the production of products **1a** and **1b** where the least hindered alkyne terminus ($alkyl^S$) undergoes addition to the aldehyde (Scheme 1).[4h-j] However, the products **1c** and **1d** derived from highly regioselective coupling at the more hindered alkyne terminus ($alkyl^L$) can only be accessed in racemic form using current methods.[2a-c] Building on the insights provided by our previous efforts in establishing racemic regiodivergent processes,[2,6] in this study, we have now focused on the development of processes that enable the highly selective production of the more hindered allylic alcohol regioisomers **1c** and **1d**, while simultaneously providing high levels of enantioselectivity.

Scheme 1. Challenge of Simultaneous Regio- and Enantiocontrol.

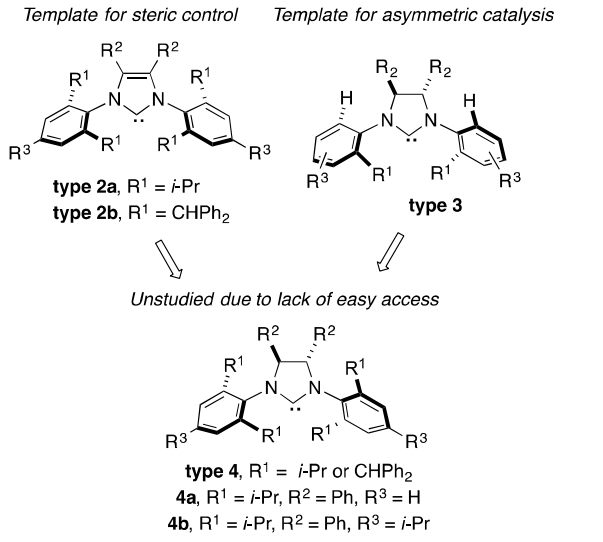


Results and Discussion

Design of a Ligand Class to Exert Regio- and Enantiocontrol

The most robust classes of NHC ligands in exerting steric control in catalytic processes are those that possess branched 2,6-disubstitution within an *N,N*-diaryl imidazolium framework. For example, the IPr and IPr*OMe classes of ligands **2a** and **2b** have been widely exploited in a vast array of catalytic processes that are governed by ligand steric control.[1-2] Towards the goal of achieving enantioselectivity, multiple types of chiral NHC ligands exist for catalytic asymmetric processes.[4,7] While many of these possess chirality within the *N*-substituent, these ligand classes designed for enantioselectivity typically lack a steric environment that is well positioned for regiocontrol. Installation of backbone chirality within the imidazolidine core enables a variety of *N*-aryl substituents to be utilized in ligand framework **3**,[7,8] but none of the previously utilized chiral ligands of this class possess secondary branching of both substituents at the *ortho* positions. The ligand class **4** that possesses C-2 backbone chirality and *N*-aryl substituents that possess a bulky 2,6-disubstitution pattern seems an obvious choice, but this ligand type has only been exploited in racemic form in catalytic processes.

Scheme 2. NHC templates for steric control and asymmetric catalysis.



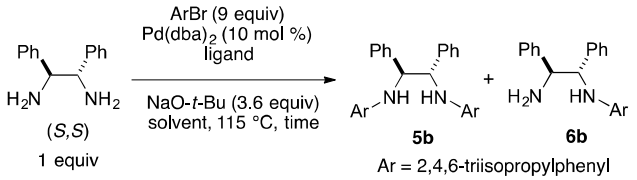
Chiral ligands of the type **4** have rarely been obtained in enantiopure form, and never by a route that avoids multistep synthesis including a resolution.[9] The obvious synthetic route involving *N,N*-diarylation of a commercially available enantiopure diamine has not been previously been accomplished due to the low yields of the two-directional Buchwald-Hartwig coupling in an extremely sterically demanding environment. The original strategy to this ligand class from Sigman, involving a pinacol coupling of *N*-aryl imines followed by separation of rac- and meso isomers of the resulting diamine,[9a] has been employed to prepare racemic ligand **4a**. This ligand provided unique regiochemical outcomes in several different contexts in our own laboratory,[2] and these promising outcomes motivated us to better explore the synthesis and utility of the enantiopure ligand class.

Ligand Synthesis and Optimization

Initial studies in aldehyde-alkyne reductive couplings were conducted with ligand **4a** (Scheme 2) obtained in enantiopure form by preparative chiral SFC chromatography.[10] Given the promise of preliminary results in asymmetric couplings, the more straightforward route involving palladium-catalyzed C-N couplings was then explored. Considering the low cost of 1-bromo-2,4,6-triisopropylbenzene, we opted to explore this substrate in the synthesis of ligand **4b** (Scheme 2). Under a variety of standard conditions for Buchwald-Hartwig amination, low yields of product **5b** were obtained. For example, employing BINAP as ligand at 115 °C in neat bromoarene, only 17% of the desired diarylated product **5b** was obtained, with monoarylated product **6b** being the major product obtained in 47% yield (Table 1, entry 1). Similarly, a number of NHC ligands (IMes, SIMes, SIPr, and IPr*OMe) in combination with $Pd(dba)_2$ failed to produce significant yields of the desired diarylated product **5** (see supporting information).[11] The unsaturated bulky ligand IPr, however, provided some level of improvement and was thus selected for further optimization (Table 1).

Using IPr as ligand in toluene at 115 °C afforded the desired bis-arylation product **5b** in 17% NMR yield together with 12% NMR yield of the monoarylated product **6b** (Table 1, entry 2). Other structurally related NHC ligands (IPr^{Cl} and IPr^{Me}) were then evaluated (Table 1, entries 3-4). Promising results were obtained with the IPr^{Me} ligand,[12] with which the reaction afforded product **5b** in 73% NMR yield with no observation of the mono-arylated product. It was then found that increased amounts of the NHC ligands improved yields further. As illustrated (Table 1, entries 4-6), when a 1:1 ratio of IPr^{Me}•HCl to $Pd(dba)_2$ was used, the NMR yield of **5b** decreased to 12%, and the major product of the reactions is the monoarylated compound **6b**. On the contrary, when the ratio of IPr^{Me}/Pd was increased to 3:1, the NMR yield of **5b** rose to 93% after stirring the reaction at 115 °C for 60 hours (Table 1, entry 6). Reducing the reaction time to 20 hours decreased the NMR yield of **5b** to 77% (Table 1, entry 7). While dioxane as solvent lowered the chemical yield (Table 1, entry 8), further study showed that more polar solvent α,α,α-trifluorotoluene was the optimal solvent for the reaction. With this solvent, the NMR yield of the reaction rose to 94% (Table 1, entry 9). Although all previous studies used a large excess of the aryl bromide reactant (9 equiv), the same level of the reaction yield was observed when the amount of the bromide was reduced to 3 equiv (Table 1, entry 10). A lower yield of product **5b** (77%) was obtained after decreasing the reaction temperature to 90 °C (Table 1, entry 11). Therefore, the optimized conditions from entry 10 were selected for the preparation of a range of new ligand motifs.

Table 1. Optimization of the *N,N*-diarylation reaction.

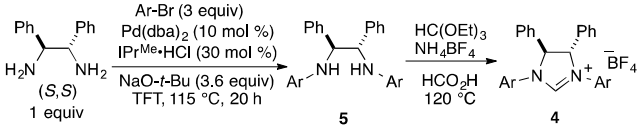


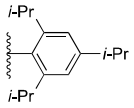
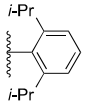
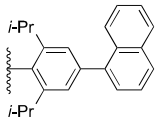
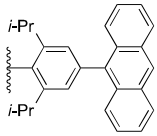
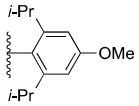
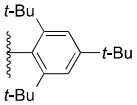
entry	ligand (mol %)[a]	solvent	time (h)	**5b** yield (%)[b]	**6b** yield (%)[b]
1	BINAP (24)	neat	20	17	47
2	IPr•HCl (20)	PhMe	60	17	12
3	IPr^{Cl}•HCl (20)	PhMe	60	16	39
4	IPr^{Me}•HCl (20)	PhMe	60	73	--[c]
5	IPr^{Me}•HCl (10)	PhMe	60	12	56
6	IPr^{Me}•HCl (30)	PhMe	60	93	--[c]
7	IPr^{Me}•HCl (30)	PhMe	20	77	--[c]
8	IPr^{Me}•HCl (30)	dioxane	20	49	--[c]
9	IPr^{Me}•HCl (30)	$C_6H_5CF_3$	20	94	--[c]
10[d]	IPr^{Me}•HCl (30)	$C_6H_5CF_3$	20	93	--[c]
11[d,e]	IPr^{Me}•HCl (30)	$C_6H_5CF_3$	20	77	--[c]

[a]Ligand scaffolds are shown in Scheme 2. IPr = ligand **2a**, R^1 = *i*-Pr, R^2, R^3 = H; IPr^{Cl} = ligand **2a**, R^1 = *i*-Pr, R^2 = Cl, R^3 = H; IPr^{Me} = ligand **2a**, R^1 = *i*-Pr, R^2 = Me, R^3 = H. [b]NMR yields with dibromomethane as the internal standard. [c]Not observed. [d]3 equiv of bromide was used. [e]Reaction was conducted at 90 °C.

Using the optimized conditions, the synthesis of a range of bulky NHC salts was carried out (Table 2). The reaction of 1,2-diphenylethane-1,2-diamine with 1-bromo-2,4,6-triisopropylbenzene was conducted on a 10 mmol scale, which furnished product **5b** in 78% isolated yield. Employing previously reported conditions, the subsequent cyclization reaction of **5b** produced its corresponding NHC salt **4b** in 79% yield (Table 2, entry 1). The initially explored NHC salt **4a**, previously utilized in exploratory studies as material obtained by chiral chromatography, was also successfully synthesized under these conditions (Table 2, entry 2). Incorporating 1-naphthyl and 9-anthracenyl at the *para*-position of the bromoarenes decreases the yields for the diarylation reaction, and diamine **5c** and **5d** were obtained in 39% and 36% yield respectively. No monoarylated product was observed in either case. Compared to the synthesis of ligands **4a** and **4b**, NHC salts **4c** and **4d** were obtained in lower yields (Table 2, entries 3-4). The decrease in preparative efficiency may result from the extended conjugation of the *N*-aryl moiety in compounds **5c** and **5d**, which decreased the nucleophilicity of the nitrogen towards the cyclization reaction. Increasing the electron density on the bromide reactant by introducing a para-methoxy group resulted in no formation of arylated products (Table 2, entry 5). We were also unable to apply these reaction conditions to the reaction of 1-bromo-2,4,6-tri(*tert*-butyl)benzene, suggesting that 2,6-diisopropyl substitution marks the limit of steric hindrance tolerated by this procedure. (Table 2, entry 6).

Table 2. Application of the diarylation reaction conditions in the synthesis of chiral bulky NHC ligands



entry	Ar	yield of **5a-d**	yield of **4a-d**
1		**5b**, 78%[a]	**4b**, 79%
2		**5a**, 73%	**4a**, 97%
3		**5c**, 39%	**4c**, 55%
4		**5d**, 36%	**4d**, 57%
5		not observed	
6		not observed	

[a]10 mmol scale.

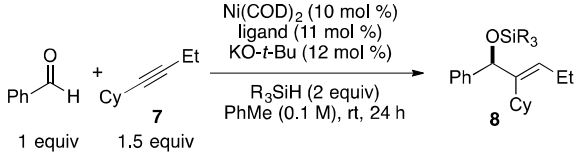
Regio- and Enantioselective Reductive Couplings

With the new classes of chiral ligands in hand, the asymmetric reductive coupling of aldehydes and alkynes was explored (Table 3). As highlighted above, the control of regiochemistry in additions of internal alkynes that bear aliphatic substituents of similar size are exceptionally challenging in virtually all classes of catalytic reactions. For this reason, our initial explorations focused on alkyne **7**, which possesses cyclohexyl and ethyl groups that must be differentiated during the coupling process. With this substrate, the catalyst must be able to distinguish a secondary from a tertiary propargylic substitution pattern in order to exert regiocontrol in the formation of product **8**. While processes involving the influence of directing functionality are typically employed to obtain highly regioselective outcomes with this substitution pattern,[2e,13] non-directed processes involving internal alkynes of this type are exceedingly rare.

In initial explorations of regio- and enantioselective couplings with Et_3SiH as the reducing reagent and tetrahydrofuran as the solvent, the nickel(0) catalyst of ligand **4b** produced the desired regioisomer with high regioselectivity and excellent

enantioselectivity (82% ee) but in low yield (Table 3, entry 1). It was then found that toluene was a superior solvent for this reaction, which improved the reaction yield to 62% and enantioselectivity to 92% ee (Table 3, entry 2). Further optimization showed that *t*-BuMe$_2$SiH was the best reducing agent for the reaction. With this silane, high reaction yield (80% yield) was obtained and the high enantioselectivity (92% ee) was maintained (Table 3, entry 3). The reaction mediated with bulky (*i*-Pr)$_3$SiH afforded only trace amounts of the reductive coupling product (Table 3, entry 4). This is likely due to inefficiencies of the bulky silane to participate in an effective σ–bond metathesis with the metallacycle intermediate.[1a,14] In addition to **4b**, other ligands **4a**, **4c**, and **4d** were also tested, and slightly decreased enantioselectivity was observed for all cases (Table 3, entries 5-7). Next, the possibility of decreasing the catalyst loading was examined. Although the level of enantioselectivity was maintained by reducing the active catalyst loading to 5 mol %, the reaction yield decreased to 47% (Table 3, entry 8). A slight decrease in the enantioselectivity was observed after reducing the catalyst loading to 2 mol % (Table 3, entry 9). Therefore, the optimal conditions for the reductive coupling reaction (Table 3, entry 3) involves the use of 10 mol % active catalyst loading (10 mol % Ni(COD)$_2$ and 11 mol % ligand **4b**), toluene as the reaction solvent and *t*-BuMe$_2$SiH as the reducing reagent, with no slow addition of the substrates being required.[15] The absolute configuration of the product **8** was determined by Mosher ester analysis[16] of the corresponding alcohol generated by TBAF deprotection, and an assignment as the *S*-configuration was made (see supporting information).

Table 3. Optimization of the reductive coupling reaction with bulky NHC ligands

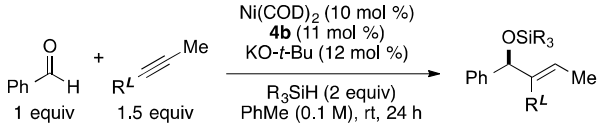


entry	ligand	solvent	R_3	rr[a]	yield[b] (%)	ee[c] (%)
1	**4b**	THF	Et_3	>95:5	28	82
2	**4b**	PhMe	Et_3	>95:5	62	92
3	**4b**	PhMe	*t*-BuMe$_2$	>95:5	80	92
4	**4b**	PhMe	(*i*-Pr)$_3$	-	<5	-
5	**4a**	PhMe	*t*-BuMe$_2$	>95:5	65	86
6	**4c**	PhMe	*t*-BuMe$_2$	>95:5	53	81
7	**4d**	PhMe	*t*-BuMe$_2$	>95:5	85	84
8[d]	**4b**	PhMe	*t*-BuMe$_2$	>95:5	47	91
9[e]	**4b**	PhMe	*t*-BuMe$_2$	>95:5	46	87

[a]Ratio of regioisomer. [b]Isolated yield. [c]Determined by Supercritical Fluid Chromatography (SFC) analysis of the correspond alcohols generated by *n*-Bu$_4$NF deprotection. [d]5 mol % catalyst loading; 72 hours. [e]2 mol % catalyst loading; 72 hours.

Compared to the excellent enantioselectivity obtained with the alkyne having an ethyl group as the small substituent, the reaction of prop-1-yn-1-ylcyclohexane provided the TBS protected allylic alcohol in 79% yield with >95:5 regioselectivity but only 28% ee (Table 4, entry 1). Similar results were obtained from the reaction of 2-hexyne (Table 4, entry 2). The role of silane structure and temperature was explored, but these changes failed to improve the reaction enantioselectivity (Table 4, entries 3-6). Comparing the data in Tables 3 and 4, this outcome clearly demonstrates that the small substituent of the alkyne strongly influences enantioselectivity. The origin of this effect is discussed in a computational analysis below.

Table 4. Couplings involving methyl-substituted alkynes



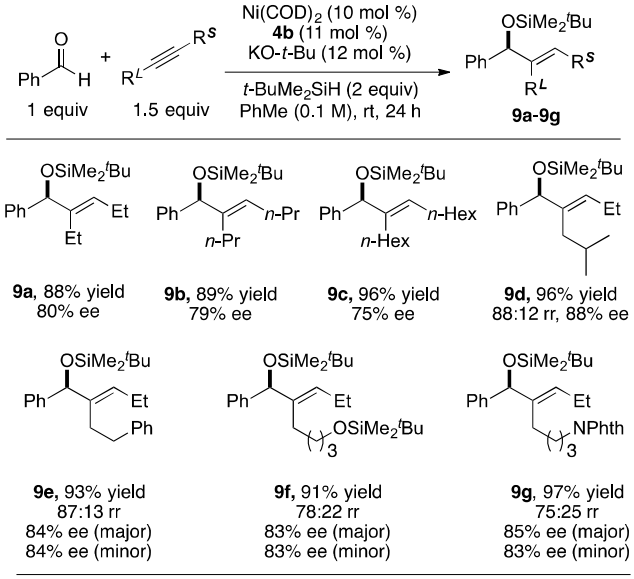
entry	R^L	R_3	temp (°C)	rr	yield (%)	ee (%)
1	Cy	*t*-BuMe$_2$	rt	>95:5	79	28
2	*n*-Pr	*t*-BuMe$_2$	rt	>95:5	83	36
3	*n*-Pr	(*i*-Pr)$_3$	rt	>95:5	74	11
4	*n*-Pr	*t*-BuMe$_2$	50	>95:5	78	38
5	*n*-Pr	*t*-BuMe$_2$	-20	>95:5	74	33
6	*n*-Pr	*t*-BuMe$_2$	-78	>95:5	70	32

With the understanding that substituents larger than methyl are essential as the small, distal substituent, the scope of enantioselective and regioselective couplings was explored with a range of aldehyde-alkyne combinations (Table 5). To first focus on enantioselectivity, the reactions of symmetrical alkynes were examined to probe the influence of the length of the alkyl chain on the enantioselectivity. Compared to the reaction of **7**, the removal of the propargylic branched substituent of the alkyne produced the silyl protected allylic alcohols in high yield with slightly decreased enantioselectivity (compounds **9a-9c**). Compared to the results of the reaction with unbranched alkynes, improved enantioselectivity was observed for the reaction of the alkyne having homopropargylic branched substituent (compound **9d**). Good regioselectivity (88:12) was also obtained. Alkynes with phenyl, silyloxy, and phthalimido groups were tolerated under the reaction conditions. Compounds **9e-9g** were all obtained with high enantioselectivity, and the enantioselectivity of the minor regioisomers was also determined, which is the same level as that of the major regioisomers. The absolute configurations of the silyl-protected allylic alcohols were assumed to be the same as compound **8** by analogy.

The scope for the aldehyde was found to be quite broad (Table 6). Both electron-rich and electron-poor aldehydes were tolerated under the reaction conditions, and compounds **10a-10c**, possessing para-methoxy, fluoro, and methyl ester substituents were all formed with >90% ee. For the synthesis of compounds **10a** and **10c**, 20 mol % catalyst loading was required to ensure full conversion. In addition to benzaldehyde derivatives, naphthalenyl and heteroaryl aldehydes were also tolerated, and compounds **10d**, **10e**, **10f** and **10g** were obtained with 90%, 84%, 89% and 90% ee respectively. The reactivity of aliphatic aldehydes was also evaluated. To facilitate the analysis of enantioselectivity, the alkyne having a phenethyl substituent was employed. Both linear and α-branched aldehydes, such as octanal and cyclohexyl carboxaldehyde, reacted with the alkyne under the standard conditions to furnish products **10h** and **10i** with moderate regioselectivity and good en-

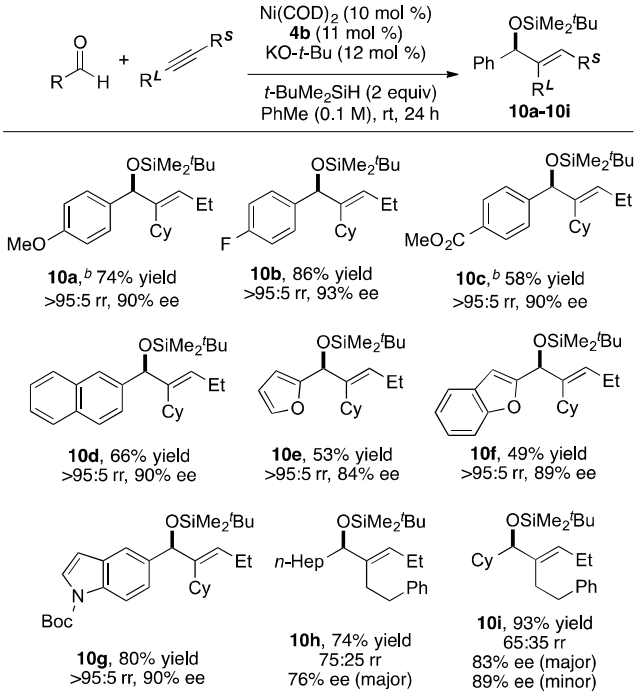
antioselectivity. The decrease of the regioselectivity of **10i** compared to **10h** illustrates that increasing steric interactions between the aldehyde substituent and the large group on the alkyne compromises the normal regiochemistry preference for the more hindered regioisomer.

Table 5. Exploration of alkyne scope[a]



[a]Enantioselectivity was determined by SFC analysis of the corresponding alcohols generated by *n*-Bu_4NF deprotection.

Table 6. Exploration of aldehyde scope[a]

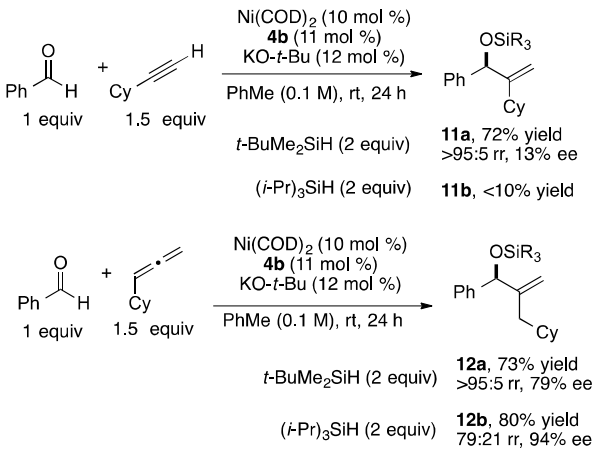


[a]Enantioselectivity was determined by SFC analysis. [b]20 mol % $Ni(COD)_2$ and **4b** were used.

As expected, based on the above observations that groups larger than methyl are required as the small alkyne substituent for high enantioselectivity, the reaction of a terminal alkyne afforded the terminal methylene product **11a** with low enantioselectivity (Scheme 3). Compared to reactions of internal alkynes, the slow addition of the solution of the reactants benzaldehyde, cyclohexylacetylene and *tert*-butyldimethylsilane in toluene is necessary for the reaction of terminal alkynes to achieve good yield with minimal alkyne trimerization. As seen in the reactions of compound **7** and of prop-1-yn-1-ylcyclohexane, $(i\text{-Pr})_3SiH$ was ineffective in producing the branched terminal alkyne, affording a very low yield of the product **11b**.

As an alternative, the terminal methylene product can be synthesized by the reaction of aldehydes with allenes (Scheme 3). The nickel-catalyzed reductive coupling reaction of aldehydes and allenes were previously developed by Jamison.[17] While excellent chirality transfer utilizing enantiopure allenes was exploited in that study, highly enantioselective variants using achiral allenes have not been developed. Employing the reaction conditions developed above for the reaction of aldehydes and alkynes, the reaction of benzaldehyde and cyclohexylallene using *t*-$BuMe_2SiH$ as reductant provided the product **12a** in promising yield (73%) and enantioselectivity (79% ee). The absolute stereochemistry was determined to be of the *S*-configuration through Mosher ester analysis of the corresponding alcohol generated by TBAF deprotection of **12a**. In this instance, the use of the bulkier silane *i*-Pr_3SiH afforded considerably improved results, with product **12b** being obtained with high enantioselectivity (94% ee), albeit with lower regioselectivity (79:21).

Scheme 3. Comparison of terminal alkynes and allenes

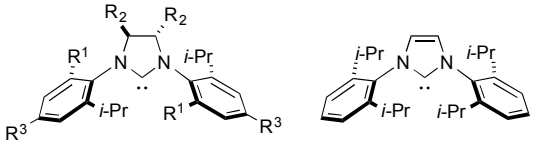


Computational Evaluation

A number of key mechanistic questions emerge from the above experimental data. First, ligands **4a** and **4b** demonstrated unique regiochemical control in the enantioselective couplings examined in this study as well as in the racemic reactions in previous studies.[2a] While the steric bulk of the 2,6-disubstitution pattern of the ligand *N*-aryl group is well documented as a key factor in ligand sterics of the widely used IPr and SIPr ligands,[18] the identical 2,6-diisopropylphenyl substituent of ligands **4a** and **4b** exerts a regiochemical influence consistent with a much greater degree of steric demand. To reveal the effects of backbone substitution on the steric properties of the NHC ligands, we calculated the percent buried volumes ($\%V_{bur}$, Table 7) of a series of ligands using structures

optimized with density functional theory (DFT).[19] Percent buried volume describes the percentage of space occupied by the NHC ligand within the first coordination sphere that is 3.5 Å from the metal center.[20] Both **4a** and **4b** have greater $\%V_{bur}$ than SIPr and IPr, indicating an increased steric demand of the C2 symmetric ligands. Since the backbone phenyl substituents of **4a** and **4b** are outside of the first coordination sphere, they indirectly influence the steric properties of these NHC ligands by controlling the conformation of the *N*-aryl groups and placing the *ortho*-isopropyl groups closer to the metal center. This illustrates that the modification of backbone substitution and stereochemistry as an effective approach to increasing the steric demand of NHC ligands, in addition to the more commonly employed alteration of the size of the *N*-aryl group.[18b]

Table 7. Percent buried volumes ($\%V_{bur}$) of NHC ligands.



4b, R^1 = *i*-Pr, R^2 = Ph, R^3 = *i*-Pr
4a, R^1 = *i*-Pr, R^2 = Ph, R^3 = H
SIPr, R^1 = *i*-Pr, R^2 = H, R^3 = H
3a, R^1 = H, R^2 = Ph, R^3 = H

IPr

ligand	$\%V_{bur}$
4b	37.5
4a	37.5
SIPr	36.1
3a	31.6
IPr	31.6

Furthermore, the above experimental study demonstrates that the small alkyne substituents, which are positioned as the distal substituent with respect to the bond-forming process in aldehyde-alkyne couplings, play a significant role in determining the reaction enantioselectivity. This feature is illustrated by the simple change of an ethyl to a methyl substituent (compare Tables 3 and 4), which results in enantioselectivities dropping from 92% to 28% *ee* under otherwise identical conditions in couplings of benzaldehyde with cyclohexyl acetylene derivatives. Coupling with cyclohexylacetylene further reduced the enantioselectivity to 13% *ee* (Scheme 3). We performed DFT calculations of the oxidative cyclization transition states to investigate the origin of enantioselectivity and the effects of the alkyne substituents.[21] We first investigated the reaction of alkyne **7** and benzaldehyde using ligand **4b** (Figure 1a). The transition state that eventually leads to the (*S*)-product (**TS1**) is 2.6 kcal/mol more stable than the transition state that gives the (*R*)-product (**TS2**), in agreement with the high level of enantioselectivity for the (*S*)-product in experiment. Considering the chiral center on the NHC backbone is more than 6 Å away from the prochiral aldehyde, the level of enantiocontrol is remarkable. This remote chiral induction operates through the conformational change of the *N*-2,4,6-triisopropylphenyl groups on the C2 symmetric ligand. In the disfavored transition state **TS2**, the highlighted *N*-2,4,6-triisopropylphenyl group is significantly tilted towards the benzaldehyde and causes unfavorable steric clashes between the *o*rtho-isopropyl group on the NHC ligand and the phenyl group on the benzaldehyde. This tilted *N*-aryl conformation is induced by the phenyl substituent on the NHC backbone as well as the distal ethyl group on the alkyne. In the favored transition state **TS1**, the *N*-aryl group is almost perfectly horizontal. Thus, the steric clashes between the NHC ligand and the aldehyde are diminished.[22] The cooperative effects of the NHC backbone and the distal alkyne substituent on enantioselectivity are confirmed by examining the TS structures with a terminal alkyne, cyclohexylacetylene, and the same NHC ligand **4b** (Figure 1b). With the distal ethyl group replaced with a hydrogen, the *N*-aryl group is not tilted in either transition state. Thus, the level of chiral induction is diminished.

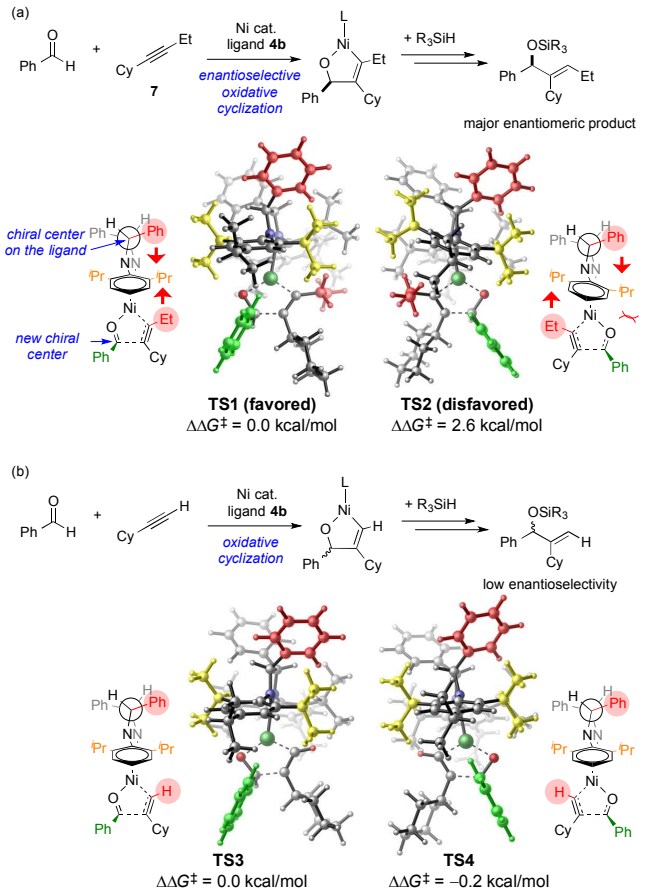


Figure 1. Remote chiral induction by the C2 symmetric ligand 4b in the oxidative cyclization transition states. Energies are computed at the M06/SDD–6-311+G(d,p)/SMD (toluene) level of theory with geometries optimized at the B3LYP/LANL2DZ–6-31G(d) level. The 4-*i*-Pr group of ligand **4b** is omitted for clarity in the Chemdraw structures.

To obtain a better understanding of the steric environment of the C2-symmetric ligand, we created the 2D steric contour plot of ligand **4b** in the oxidative cyclization transition states **TS1** and **TS2** (Figure 2). Following previously reported procedure,[23-24] the ligand steric contour was derived from the van der Waals surface of the NHC ligand and color-coded based on the distance from the substrate – red and yellow indicate regions on the ligand surface that are closer to the half-space containing the substrate, while blue and green indicate regions that are more distant from the substrate. In **TS1**, the alkyne and the nickel catalyst attack the (*Si*)-face of the benzalde-

hyde, placing the phenyl group in the less sterically encumbered quadrant (**II**) and the hydrogen in the occupied quadrant (**III**). In contrast, in the disfavored (*Re*)-face attack (**TS2**), the phenyl group is positioned in the occupied quadrant (**III**), leading to much more significant steric repulsions with the NHC ligand. The ligand contour plots highlight the conformational change of the *N*-2,4,6-triisopropylphenyl groups induced by the backbone phenyl substituents that are positioned in quadrants **I** and **III**. The distal ethyl substituent on the alkyne is positioned in quadrant **IV** and accentuates the rotation of the *N*-triisopropylphenyl group towards the substrate in the occupied quadrant **III**. As a result, quadrant **III** becomes highly encumbered, leading to the unfavorable steric repulsion with benzaldehyde in **TS2**. In accordance with the analysis in Figure 1, these results again indicate that the enantioselectivity is influenced by the cooperative effects of the chiral NHC backbone and the distal alkyne substituent.

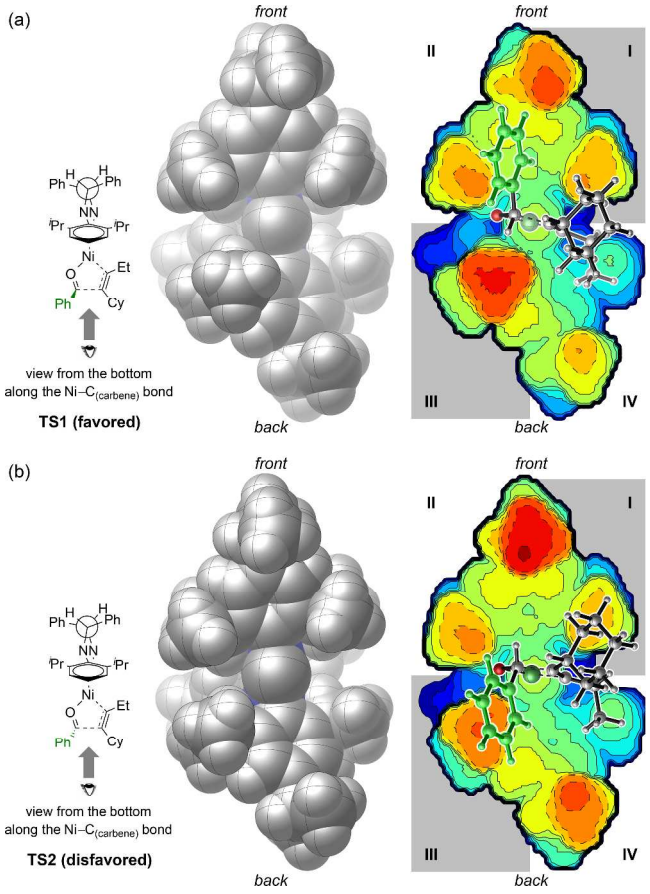


Figure 2. van der Waals surface and steric contour plot of ligand 4b in the oxidative cyclization transition states TS1 and TS2. The geometries of the benzaldehyde and the alkyne are overlaid onto the contour plots. Red and yellow in the contour plots indicate regions that are occupied by the NHC ligand. The 4-*i*-Pr group of ligand **4b** is omitted for clarity.

Conclusions

In conclusion, an effective synthesis of a novel class of enantiopure NHC ligands with exceptional steric demand has been developed. The catalytic reactivity of these ligands was evaluated in the Ni-catalyzed asymmetric reductive coupling reactions of aldehydes and alkynes. This study has identified ligands that are able to distinguish electronically and sterically similar alkyne substituents in a highly regioselective manner while also inducing high levels of enantioselectivity in the process. Computational studies have elucidated the origin of the substantial steric influence exerted by the ligand class explored. Additionally, the origin of enantioselectivity is explained, including the significant role that alkyne sterics play in influencing the ligand-aldehyde interactions. Future work will focus on employing these ligands in other organic transformations and developing other NHC ligands designed to simultaneously control enantioselectivity and regioselectivity.

ASSOCIATED CONTENT

Supporting Information

Experimental details, copies of spectra, computational details and Cartesian coordinates of optimized geometries This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) In comparison to the optimum results with ligand **4b** (Table 3, entry 3), a previously reported ligand variation possessing a 2,4-dicyclohexyl-6-methyl substituent (reference 4h) was less effective. Using this previously reported ligand, couplings of benzaldehyde with alkyne **7** proceeded in reduced chemical yield (52%), modestly reduced regioselectivity (92:8), and substantially lower ee (62%). Alternatively, reactions with ligands with *ortho*-monosubstituted N-aryl substituents (type **3**, Scheme 1) proceeded in low yield favoring the opposite regioisomer from that described in Table 3. For a computational study describing the origin of regioselectivity reversal in the absence of ortho substituents on the N-aryl group, see reference 6.

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(19) The $\%V_{bur}$ of ligands **4a**, **4b**, **3a**, IPr and SIPr were calculated using the web-based Samb*V*ca 2.0 program (https://www.molnac.unisa.it/OMtools/sambvca2.0/index.html Ref (24a), based on the geometries of $(NHC)Ir(CO)_2Cl$, which were optimized using the BP86 functional and a mixed basis set of SDD for Ir and 6-31G(d) for other atoms. The default parameters in Samb*V*ca 2.0 were used as suggested by Cavallo: sphere radius: 3.5 Å, distance from the center of the sphere: 2.1 Å, mesh spacing: 0.1 Å, H atoms omitted, atom radii: Bondi radii scaled by 1.17.

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(21) Previous mechanistic studies indicated the oxidative cyclization of the alkyne and the aldehyde is the rate-determining step in reactions with sterically less hindered silanes, while this step may be reversible in reactions with more sterically demanding silanes (see Ref. 2b; for a detailed computational study on the steric effects of silane on the rate-determining step, see Ref. 14e). The identical *ee* obtained with two different silanes in Table 3, entries 2 and 3 is consistent with the oxidative cyclization being enantioselectivity-determining. However, the decrease of *ee* with TIPSH in Table 4 (entries 2 *versus* 3) suggests that metallacycle formation becomes reversible and is no longer enantioselectivity-determining under these conditions. In the DFT calculations, we considered the enantioselectivity in the oxidative cyclization step, which is expected to determine the *ee* in reactions with sterically less hindered silanes.

(22) It should be noted that the steric interactions between the terminal Et group and the NHC ligand are comparable in **TS1** and **TS2**. In both transition states, one of the *N*-2,4,6-triisopropylphenyl groups is tilted to avoid the steric repulsion with the terminal Et group. In

TS2, the tilted *N*-aryl group (highlighted and pointing out-of-the-paper in Figure 1a) is on the same side with the phenyl group on the aldehyde. In **TS1**, the tilted *N*-aryl group (not highlighted and pointing into the paper in Figure 1a) is on the opposite side, and thus does not cause steric repulsions with the aldehyde.

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SYNOPSIS TOC (Word Style “SN_Synopsis_TOC”).