Organic LETTERS

Letter

pubs.acs.org/OrgLett

Chiral *N*-Heterocyclic Carbene Ligand Enabled Nickel(0)-Catalyzed Enantioselective Three-Component Couplings as Direct Access to Silylated Indanols

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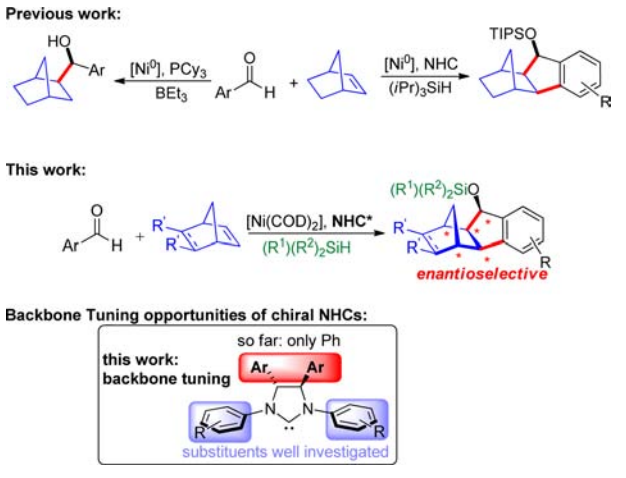
Supporting Information

ABSTRACT: An enantioselective nickel(0)-catalyzed reductive three-component coupling between aromatic aldehydes, norbornenes, and silanes affords directly silyl-protected indanol derivatives. A new bulky chiral C_2-symmetric NHC (NHC = *N*-heterocyclic carbene) ligand basing on the 1,2-di(napthalen-1-yl)ethylene diamine backbone allows accessing the annulated products as single diastereoisomers in high enantioselectivity.

Metal-catalyzed multicomponent reactions in which several components are assembled in a single transformation have emerged as a powerful tool for molecular complexity.[1] Among them, nickel-catalyzed reductive couplings between aldehydes and alkynes providing access to allylic alcohols have been well investigated.[2] Besides the development of intra- and intermolecular transformations, the alkyne coupling partner could be replaced by allenes,[3] 1,3-dienes,[4] terminal olefins,[5] and methylenecyclopropanes.[6] Norbornene was recently used as a coupling partner together with borane reductants and phosphine ligands by Fukuzawa, giving disubstituted carbinols (Scheme 1).[7] Replacing the phosphine with an NHC (NHC = *N*-heterocyclic carbene) ligand altered the reaction outcome, and silylated indanols were obtained in the presence of triisopropyl silane.[8] The reaction was proposed to occur through an aromatic *ortho*-C−H activation. This significant response to ligand tuning makes the transformation highly attractive to showcase the abilities of new ligand scaffolds. Despite the direct generation of four stereocenters in this transformation, a challenging but very valuable enantioselective process could not be realized so far.

Scheme 1. Divergent Pathways of Nickel-Catalyzed Reductive Couplings and Tuning Opportunities of Chiral NHC Ligands



In contrast to the growing number of publications describing the use and influence of NHCs in nickel-catalyzed reductive couplings,[9] only scarce examples of enantioselective reductive couplings with chiral NHCs as ligand have been reported so far.[10−12] In part, these shortcomings may be attributed to the limited choice of powerful chiral NHC ligands. For instance, the influence of the flanking aryl groups on the selectivity has been described for Grubbs' chiral imidazolidin-2-ylidene derivative,[13] whereas modifications of chiral diaryl ethylenediamine backbone have been so far largely neglected.[14,15]

The relevance of the indanol scaffold as a structural motif in natural products[16] and the attractive rapid assembly of an enantioenriched versatile building block make an efficient catalytic asymmetric transformation highly desirable. Herein, we report an enantio- and diastereoselective nickel(0)-catalyzed three-component coupling of aromatic aldehydes, norbornenes, and silanes. The use of a new chiral NHC ligand allows access to enantioenriched silyl-protected indanols in high selectivity. We started our investigations by evaluating a variety of different established chiral NHC-scaffolds (Figure 1) using available benzaldehyde, norbornene, and triisopropylsilane for the model transformation (Table 1). Kündig ligand **L1**,[17] C_1-symmetric **L2** developed by us,[12a] and Glorius' IBiox **L3**[18] furnished **3aa** in low yields and selectivity (entries 1−3). In contrast, Grubbs' C_2-symmetric imidazolidin-2-ylidene **L4**[13] gave silylated indanol **3aa** in almost quantitative yield, with exclusive diastereoselectivity and promising enantioselectivity of 71.5:28.5 (entry 4). Installation of *o*-isopropyl groups at the flanking aryl substituents on the nitrogen atom increased the selectivity to 86:14 (entry 5).

Received: May 23, 2016
Published: June 21, 2016

DOI: 10.1021/acs.orglett.6b01492
Org. Lett. 2016, 18, 3242−3245

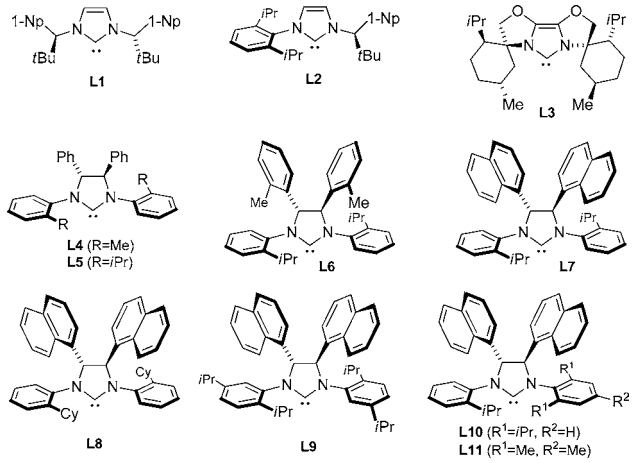
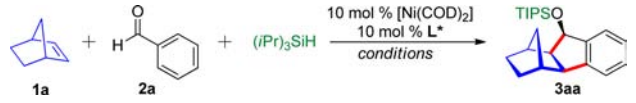


Figure 1. Chiral NHC ligands **L*** used in this study.

Table 1. Optimization of the Enantioselective Three-Component Coupling[a]



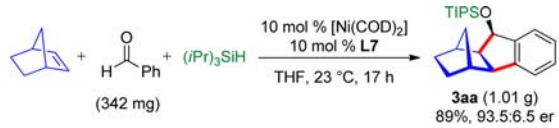
entry	L*	solvent	3aa (%)[b]	er[c]
1	**L1**	THF	5	74:26
2	**L2**	THF	41	61:39
3	**L3**	THF	0	
4	**L4**	THF	99	71.5:28.5
5	**L5**	THF	53	86:14
6	**L6**	THF	55	80:5:19.5
7	**L7**	THF	74	93:7
8	**L8**	THF	89	91:9
9	**L9**	THF	13	84:16
10	**L10**	THF	<5	
11	**L11**	THF	57	91:9
12	**L7**	dioxane	51	93:7
13	**L7**	Et_2O	56	84:16
14	**L7**	hexane	39	87:13
15	**L7**	toluene	92	82:18
16[d]	**L7**	THF	96	93.5:6.5

[a]Conditions: 0.10 mmol benzaldehyde, 0.20 mmol norbornene, 0.20 mmol triisopropylsilane, 10.0 μmol [$Ni(COD)_2$], 10.0 μmol **L***, 0.3 M in solvent at 23 °C for 17 h. [b]Isolated yields. [c]Determined by HPLC with a chiral stationary phase with the free indanol. [d]At 1.0 M.

We found that replacement of the 1,2-diphenylethylene diamine backbone with other diaryl- or dialkyl ethylenediamines strongly influenced the reaction outcome. To our surprise, despite the convenient availability of enantiopure 1,2-diarylethylene diamines,[19] no NHCs besides the ones featuring the parent 1,2-diphenylethylene diamine backbone are known. From the tested diamines, the best compromise between reactivity and selectivity was achieved with **L7**, possessing the 1,2-di(napthalen-1-yl)ethylene diamine scaffold, substantially increasing the selectivity with respect to the parent phenyl substituted one (entry 7). Evaluation of the flanking nitrogen substituent confirmed the *ortho*-isopropylphenyl group as best performer (entries 7–9). Related C_1-symmetric ligands **L10** and **L11** proved to be less suited (entries 10–11). Bulkier **L10** completely shut down the reaction, and **L11** was slightly inferior to the related C_2-symmetric ligands. **L7** was further evaluated under different conditions. For instance, the use of other ethereal or saturated hydrocarbon solvents resulted in a sharp drop of the reactivity (entries 12–14). Toluene afforded **3aa** in excellent yield, albeit with reduced enantioselectivity (entry 15). Increasing the concentration of the reaction to 1.0 molar increased the reactivity and provided **3aa** in a nearly quantitative chemical yield and with 93.5:6.5 er (entry 16).

With the aforementioned reactions conditions, we then explored the generality of the enantioselective nickel-catalyzed three-component coupling (Table 2). First, a range of *p*-substituted electron-rich and electron-deficient aryl aldehydes were tested (entries 1–6). Electron-neutral or -rich substituents provided the products in high yields and selectivities. Electron-poor substituents reduced the yields but provided consistently high enantioselectivities. A methyl substituent in the *meta*-position of the aldehyde steered the aromatic C–H activation with a selectivity of 9:1 toward the less hindered *ortho* C–H group (entry 7). The *ortho*-tolyl aldehyde largely reduced the reactivity for the annulation, producing noncyclized product **3ia′** in moderate yield and 92.5:7.5 er and very little indanol **3ia** (entry 8). A constraining 3,5-dimethyl substitution is tolerated, although a drop in yield and selectivity was observed (entry 9). For piperonal, functionalization of the more hindered *ortho*-C–H bond was favored (4.6:1, entry 10). Such behavior was already observed earlier,[20] suggesting coordination and stabilization involving the oxygen atom. We next examined different norbornene acceptors. With methylenealkoxy-substituted derivatives **1b** and **1c**, we observed an influence of the *exo*/*endo* isomer for the reactivity (entries 11–12). Whereas both provided the annulated products in high enantioselectivity, *exo*-norbornene **1b** displayed a substantially higher reactivity. Performing the reaction with benzonorbornadiene furnished the desired annulated products **3ad** with good enantioselectivity (entry 13). Unstrained alkenes like cyclopentene failed to react under these reaction conditions. Moreover, the transformation works also with a range of additional silanes (entries 14–16), maintaining similar enantioselectivities and the yields. In this respect, the most common and versatile silyl protecting groups with variable stabilities such as TES (**5**), TBS (**6**), and TBDPS (**7**) were conveniently introduced.

The scalability of the transformation was tested, furnishing annulated indanol **3aa** in gram-scale amounts (eq 1). In terms of yield and enantioselectivity, the reaction performs well and reliably.



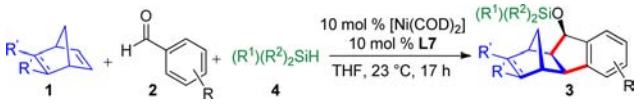
(1)

The absolute configuration of indanols **3** was unambiguously determined by X-ray crystallographic analysis.[21] Compound **3aa** was smoothly desilylated with TBAF and subsequently converted to its *p*-bromobenzoate derivative **8** (Scheme 2). The enantiomeric ratio of **8** was further upgraded by crystallization, and the configuration of the stereogenic center C1 bearing the hydroxyl group was determined to be (*R*).

The following mechanistic pathway for the nickel-catalyzed enantioselective three component coupling is suggested (Scheme 3).[8] Coordination of the aldehyde and norbornene to the low-valent NHC–Ni^0 complex with the aryl group of the aldehyde placed away from the methylene bridge avoiding steric congestion, two orientations are possible (**I-a** and **I-b**). The

DOI: 10.1021/acs.orglett.6b01492
Org. Lett. 2016, 18, 3242–3245

Table 2. Scope of the Nickel-Catalyzed Enantioselective Three-Component Coupling[a]

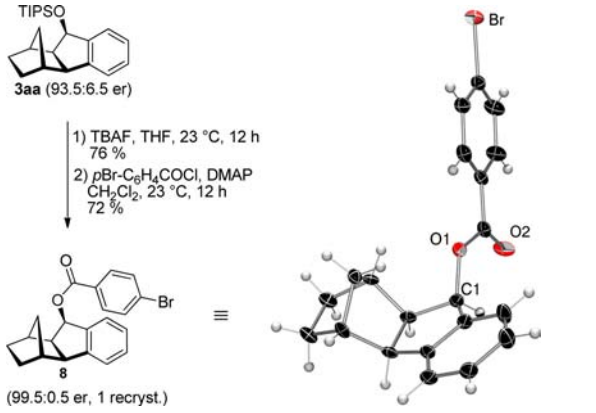


entry	3	(%)[b]	er[c]
1	**3ba** (R=Me)	93	92.5:7.5
2	**3ca** (R=*t*Bu)	84	94:6
3[d]	**3da** (R=OMe)	81	93:7
4	**3ea** (R=F)	88	94:6
5	**3fa** (R=CF_3)	38	95.5:4.5
6	**3ga** (R=CO_2Me)	49	94.5:5.5
7	**3ha**	82	94:6
8	**3ia'**	40 (2.6:1)	95:5
	3ia		92.5:7.5
9	**3ja**	52	84.5:15.5
10	**3ka**	99 (4.6:1 rs)	93:7
11	**3ab**	75	95:5
12	**3ac**	25	95.5:4.5
13	**3ad**	85 (6.7:1)	93:7
	3ad'		98:2
14	**5** (Si=TES)	74	93:7
15	**6** (Si=TBS)	70	94:6
16	**7** (Si=TBDPS)	84	93.5:6.5

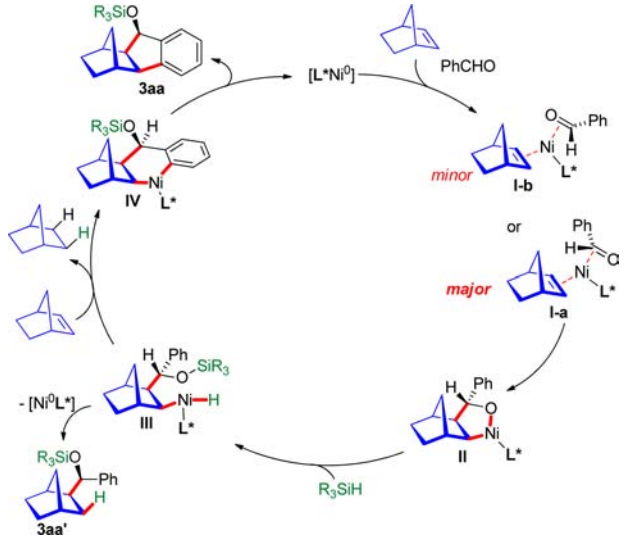
[a]Conditions: 0.10 mmol **2**, 0.20 mmol **1**, 0.20 mmol **4**, 10.0 μmol [Ni(COD)$_2$], 10.0 μmol **L7**, 1.0 M at 23 °C for 17 h. [b]Isolated yields. [c]Determined by HPLC with a chiral stationary phase with the free indanol. [d]With 20.0 μmol [Ni(COD)$_2$] and 20.0 μmol **L7**.

flanking bulky arene groups of the chiral NHC lead to a preferred orientation of **I-a**. The enantio-determining oxidative cyclization forms oxanickelacycle **II**. Subsequently, the silane reacts with the nickel alkoxide forming nickel-hydride **III**. At this stage, a straight reductive elimination would form noncyclized product **3aa'**, which is observed in some instances.[9] Alternatively, another

Scheme 2. Determination of the Absolute Configuration of Indanol 3aa



Scheme 3. Suggested Mechanism for the Enantioselective Three-Component Coupling



molecule of norbornene involves a hydrometalation; a subsequent C(sp^2)–H activation proceeds, and the release of norbornane forms cyclometalated species **IV**. This is in agreement with the experimental findings that less than two equivalents of olefin reduce the yield of **3aa** and the observation of formed norbornane. The excess of norbornene acts as a hydrogen acceptor, similarly to the role of an alkyne in other transformations.[20a,22] Finally, reductive elimination closes the catalytic cycle, delivering silyl indanol ether **3aa** and regenerating the Ni^0 species. However, an alternative mechanism involving the formation of a dimeric nickel(I) hydride from an oxidative addition of the NHC–Ni^0 complex into the Si–H bond, followed by a comproportionation cannot be ruled out.[23] The higher enantioselectivities for the carbinol products suggest that the major and minor diastereoisomers of nickel-hydride **III** might have different rates for the C–H activation and reductive elimination steps. Alternatively, a scenario involving different mechanisms can be invoked.

In summary, we reported an enantio- and diastereoselective nickel(0)-catalyzed three-component coupling of aldehydes, norbornenes, and silanes giving direct access to chiral silyl-protected indanols. We have introduced a new chiral C_2-symmetric NHC ligand deriving from 1,2-di(napthalen-1-

DOI: 10.1021/acs.orglett.6b01492
Org. Lett. 2016, 18, 3242–3245

yl)ethylene diamine, providing high selectivities in this transformation. This NHC/Ni catalyst system underscores the high potential of chiral NHCs in asymmetric nickel(0) catalysis and should enable further enantioselective transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01492.

Experimental procedures and analytical and spectral data for all new compounds (PDF)
X-ray data for **8** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is supported by the Swiss National Science Foundation (no. 155967). We thank Dr. R. Scopelliti for X-ray crystallographic analysis of **8**.

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DOI: 10.1021/acs.orglett.6b01492
Org. Lett. 2016, 18, 3242−3245