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Ni-Catalyzed Asymmetric Reductive Arylalkylation of Unactivated Alkenes

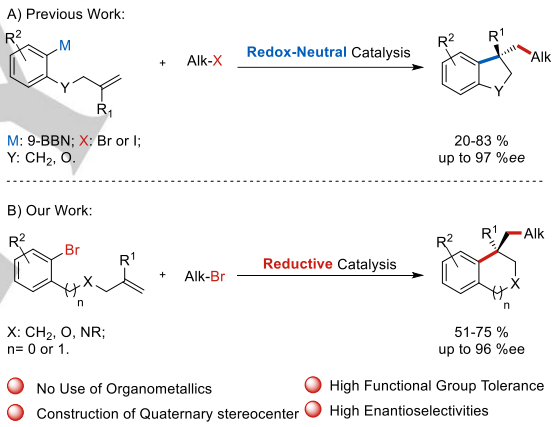
Youxiang Jin[a], and Chuan Wang*[a]

Dedication ((optional))

Abstract: In this protocol we developed an asymmetric reductive dicarbofunctionalization of unactivated alkenes. Under the catalysis of Ni-BOX system, various aryl bromides incorporating a pendant olefinic unit were successfully reacted with an array of primary alkyl bromides in the presence of Zn as reductant, furnishing a series of benzene-fused cyclic compounds bearing a quaternary stereocenter in high enantioselectivities. Notably, this reaction avoids of the use of pre-generated organometallics and demonstrates high tolerance of sensitive functionalities. The preliminary mechanistic investigations reveal that this Ni-catalyzed reaction proceeds as a cascade consisting of migratory insertion and cross-coupling with a Ni-(I)-mediated intramolecular 5-*exo* cyclization as the enantio-determining step.

Asymmetric difunctionalizations of unactivated alkenes are among the most important reactions in organic synthesis, as diverse optically active compounds can be accessed in one single step using simple olefins as precursors. Transition-metal catalysis has proven to be a powerful tool for dicarbofunctionalizations of unactivated alkenes including diarylation, dialkylation as well as arylalkylation, and tremendous advances have been achieved recently using both redox-neutral[1-3] and reductive strategies[4]. However, asymmetric versions of these reactions are still rare. In the field of diarylation, Sigman et al. developed a Pd-catalyzed enantioselective diphenylation of 1,3-dienes,[3c] while Brown and his co-worker reported a Cu-promoted asymmetric diarylation of pendant olefins tethered on aryl boronates.[2d] Recently, Liu et al. achieved Cu-catalyzed enantioselective dicarbofuntionalizations of styrenes involving the installation of a CF_3-moeity.[3d,j] Furthermore, Fu et al. accomplished an enantioselective variant of two-component arylalkylation.[2b] In this Ni-catalyzed reaction, arylboranes incorporating a terminal olefinic unit were reacted with unactivated alkyl halides, affording various benzofurans and indanes in high enantioselectivities (Scheme 1A). However, all the aforementioned asymmetric dicarbofunctionalizations of unactivated olefins require the use of pre-generated organometallics as coupling partners, which is less desirable in the viewpoint of both step-economy and functionality tolerance.

On the other side, the reductive strategy of dicarbofunctionalizations of C−C double bonds allows the incorporation of two carbo-moieties directly from aryl or alkyl halides in assistance of a reducing agent and thus eliminates the additional step of preparation of sensitive organometallics as well as the related issue of functional group compatibility. Despite rapid progresses in this area, the asymmetric version of reductive dicarbofunctionalization of unactivated olefins remains still elusive.[5,6] Very recently, our group reported a racemic version of Ni-catalyzed reductive arylalkylation of unactivated alkenes tethered to aryl bromides.[4i] In this context, we report a significant advance of our method to have identified a chiral ligand in the highly enantioselective variant, enabling the efficient synthesis of various benzene-fused cyclic compounds with the construction of a challenging quaternary stereogenic center[7] (Scheme 1B).



Scheme 1. Redox-Neutral (A) and Reductive Strategy (B) for Asymmetric Arylalkylation

For optimization of the reaction conditions, we used the bromobenzene **1a** incorporating a terminal olefinic unit and 4-bromobutyl acetate (**2a**) as standard substrates (Table 1). Initially, an array of chiral ligands were tested for this reaction. When chiral phosphine ligands including DIOP **L1**, SEGphos **L2** and PHOX **L3** were utilized, no desired reaction occurred (entries 1-3). In the case of PyBox **L4**, only a trace of arylalkylated product **3a** was formed (entry 4), while the reaction employing BOX **L5** failed to deliver the target compound **3a** (entry 5). In all the cases above-mentioned, recovery of substrate **1a** and formation of some by-products **3a-1**-**3a-4** were observed. In contrast, the reaction using Pyrox **L6** as ligand afforded the desired product **3a** in a moderate yield and enantioselectivity (entry 6). In this case, the dimer **3a-1** was delivered as a by-product with a 42 % GC-yield. Encouraged by this result, a series of Pyrox ligands **L7**-**9** and structurally related BOX ligands **L10**-**11** were investigated for this Ni-catalyzed reaction (entries 7-11). In the most cases, similar

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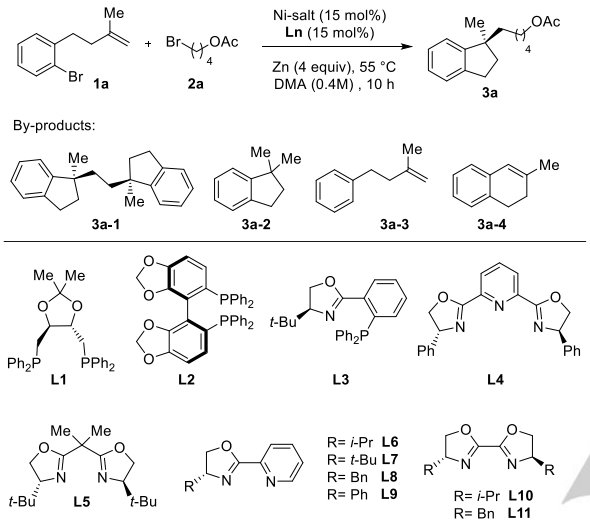
product profiles were obtained with the dimer **3a**-**1** and the reductive Heck product **3a**-**2** as the major by-products. To our delight, the facial selectivity could be elevated to an excellent level through employing BOX **L11** as ligand (entry 11). Of note is that the corresponding dimer **3a**-**1** was also afforded in a high diastereomeric ratio (dr=97:3). Next, a brief screening of Ni-salts, temperature, solvents and reductants provided the best outcome in the reaction using $NiBr_2$(dme) with Zn-powder in DMA at 40 ˚C (entry 12).[8]

Table 1. Ligands, Solvents, Ni-Salts and Temperature Screening[a]



Entry	Ligand	Ni-salt	Yield [%][b]	*ee* [%][c]
1	**L1**	$NiBr_2$	0	-
2	**L2**	$NiBr_2$	0	-
3	**L3**	$NiBr_2$	0	-
4	**L4**	$NiBr_2$	trace	n.d.[d]
5	**L5**	$NiBr_2$	0	-
6	**L6**	$NiBr_2$	55	58
7	**L7**	$NiBr_2$	3	n.d.
8	**L8**	$NiBr_2$	43	66
9	**L9**	$NiBr_2$	53	39
10	**L10**	$NiBr_2$	29	86
11	**L11**	$NiBr_2$	53	94
12[e]	**L11**	**$NiBr_2$(dme)**	**64 (69**[f]**)**	**94**

[a] Unless otherwise specified, reactions were performed on a 0.2 mmol scale of the aryl bromide **1a** using 2.0 equiv 4-bromobutyl acetate (**2a**), 15 mol % Ni-salt and 15 mol% ligand in 0.5 mL solvent at 55 ℃ for 10 h. [b] GC-yields. [c] Determined by HPLC-analysis on chiral stationary phase. [d] Not determined. [e] Reaction temperature: 40 ˚C. [f] Yield of the isolated product.

With the optimum reaction conditions in hand, we started to evaluate the substrate scope of this Ni-catalyzed asymmetric reductive arylalkylation (Table 2). First, the influence of geminal substitution of the pendant olefin of the aryl bromides **1** was explored. To our delight, all the reactions using geminal disubstituted alkenes proceeded smoothly, furnishing the corresponding products **3a**-**h** containing a quaternary stereocenter in moderate to good yields and high to excellent enantioselectivities. When monosubstituted alkenes were used as substrates, no desired products were delivered due to the high tendency to undergo β-H-elimination. Next, the permutation of substitution of on the phenyl ring (**3i**-**m** and **3x**) was carried out and it turned out that both electron-donating and –withdrawing groups were well tolerated. Furthermore, our method is also applicable to preparation of highly enantioenriched indolines **3n** and **3o**. Unfortunately, only low enantiomeric excesses could be achieved for synthesis of the six-membered ring products **3p** and **3q**. Subsequently, we continued to examine the substrate spectrum by varying the structure of the alkyl bromides **2**. In all the cases of linear alkyl bromides, the products **3r**-**z** were obtained with satisfactory to good efficiency and in high to excellent enantioselectivities. It is noteworthy that this Ni-catalyzed reaction demonstrated high compatibility of a broad range of functional moieties, such as alcohol (**3s**), acetal (**3t**), boronate (**3u**), cyanide (**3w**), imide (**3x**) and ester (**3x** and **3y**). Moreover, our method was also successfully implemented in the reaction employing structurally complex alkyl bromides as precursors (**3z** and **3aa**) derivatized from menthol and estrone, respectively. In the case of bulkier (bromomethyl)cyclohexane as reactant, the reaction also furnished the product **3ab** in a moderataly good yield and high enantioselectivity. In addition, a 5-mmol-scale reaction using the aryl bromide **1a** as substrate and *ent*-**L11** as ligand was conducted, providing the product *ent*-**3a** in a similar yield. One limitation of our method was observed in the use of secondary and tertiary bromides as coupling partners, which failed to deliver the desired products under the standard conditions.[9]

In order to demonstrate the utility of this developed method, some derivatizations of the arylalkylation product *ent*-**3a** were accomplished to achieve diverse chiral scaffolds bearing a quaternary stereogenic center (Scheme 2). First, the benzylic position of the compound *ent*-**3a** was successfully oxidized through the Ru-catalyzed oxidation, providing a chiral indanone **4** in an excellent yield.[10] The subsequent *m*-CPBA-mediated Baeyer-Villiger oxidation led to an efficient synthesis of a chiral chromanone **5**. Furthermore, the arylalkylation product *ent*-**3a** was reacted with tosylhydrazine and the afforded hydrazone **6** was then subjected to a Pd-catalyzed cross-coupling reaction, furnishing a chiral indene **7** in a good yield.[11]

A series of control experiments were carried out to shed a light on the mechanism of this Ni-catalyzed asymmetric reductive dicarbofunctionalization. First, we performed stoichiometric reactions between Zn and both bromide precursors under the standard reaction conditions. After quenching with water, no debrominated products were formed in either case.[12] These results indicate that the reaction pathway involving organozinc compounds is less likely.

It is known that aryl Ni(II) species can undergo migratory insertion to activated C−C double bonds.[5] We wonder whether the same process can occur on the unactivated olefinic unit. To verify this, we performed the stoichiometric reaction of $Ni(COD)_2$ with the pendant alkene **1a** and quenched it with water (Table 3, entry 1). Surprisingly, the expected reductive Heck product **3a**-**2** was afforded only in a trace amount. Instead, a Heck product **3a**-**4** was obtained in a moderate yield, implying that the aryl Ni(II) intermediate generated via oxidative addition favors 6-*endo* cyclization followed by β-H elimination in the case of unactivated alkenes. Next, a similar stoichiometric reaction was performed in

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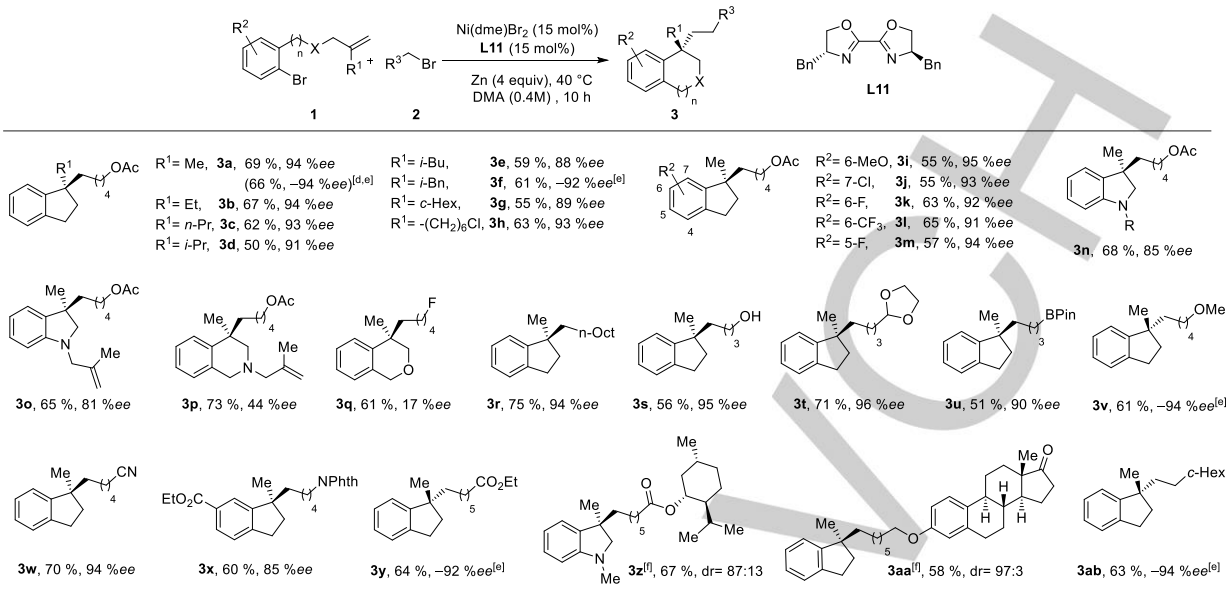
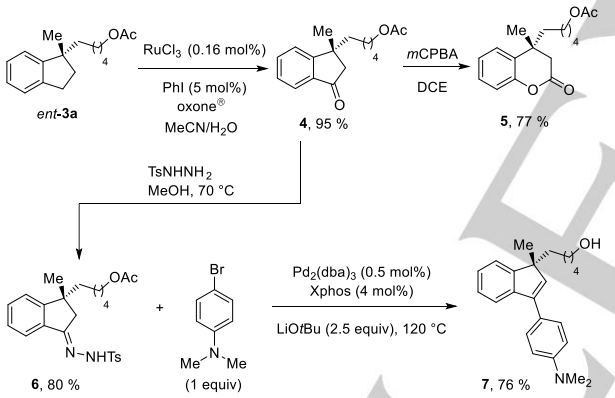
Table 2. Evaluation of the Substrate Scope[a-c],[13]



[a] Unless otherwise specified, reactions were performed on a 0.4 mmol scale of the aryl bromides **1** using 2.0 equiv alkyl bromides **2**, 15 mol % $NiBr_2$(dme) and 15 mol% ligand **L11** in 1.0 mL DMA at 40 ℃ for 10 h. [b] Yields of the isolated products. [c] The *ee* or dr were determined by HPLC-analysis on chiral stationary phase. [d] Reaction was performed on a 5-mmol-scale of the aryl bromide **1a**. [e] Reactions were performed using the enantiomer of the ligand **L11**. [f] Enantiopure precursors were employed.

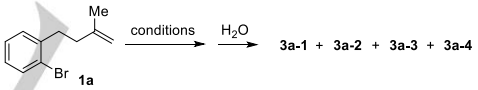


Scheme 2. Derivatizations of the Arylalkylation Product *ent*-**3a**.

the presence of Zn (entry 2). In this case, reductive Heck reaction turned out to be the major reaction. Furthermore, replacing $Ni(COD)_2$ by $Ni(dme)Br_2$ in the stoichiometric reaction gave a similar product profile, wherein only a small amount of **3a**-**4** was formed (entry 3). These results suggest that the aryl Ni(II) intermediate probably undergoes first Zn-mediated reduction to a Ni(I) species, which performs preferentially the 5-*exo* cyclization

Subsequently, we assumed that the reaction between cyclized Ni-intermediate **8** and alkyl bromides **2** would lead to the formation of the final products. Therefore, the sequential stoichiometric reaction by adding the alkyl bromide **2a** at the second stage was carried out (Scheme 3A). Indeed, the arylalkylation product **3a** was furnished in a moderate yield and excellent enantioselectivity, proving that our presumed pathway is feasible. Moreover, we employed the alkene **1g** as precursor in the stoichiometric reaction (Scheme 3B). After quenching with water, the hyroarylation product **3g**-**1** was yielded in a similar enantiomeric excess as compound **3g** in Table 1, implying the Ni-mediated migratory insertion is the enantio-determining step.[14]

Table 3. Stoichiometric Reactions [a],[b]



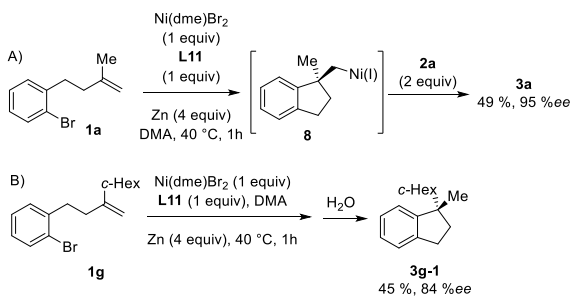
Condition A: $Ni(COD)_2$ (1 equiv), **L11** (1 equiv), DMA, 40 °C, 1h

Condition B: $Ni(COD)_2$ (1 equiv), **L11** (1 equiv), DMA, Zn (4 equiv), 40 °C, 1h

Condition B: $Ni(dme)Br_2$ (1 equiv), **L11** (1 equiv), DMA, Zn (4 equiv), 40 °C, 1h

Entry	Conditions	Yield **3a**-**1** [%]	Yield **3a**-**2** [%]	Yield **3a**-**3** [%]	Yield **3a**-**4** [%]
1	A	17	5	<5	56
2	B	9	61	<5	22
3	C	9	78	<5	4

[a] Unless otherwise specified, reactions were performed on a 0.2 mmol scale of the aryl bromide **1a** using 100 mol % Ni-salt and 100 mol% ligand **L11** in 0.5 mL DMA at 40 ℃ for 1 h. [b] GC-yields.



Scheme 3. Sequential Stoichiometric Reactions.

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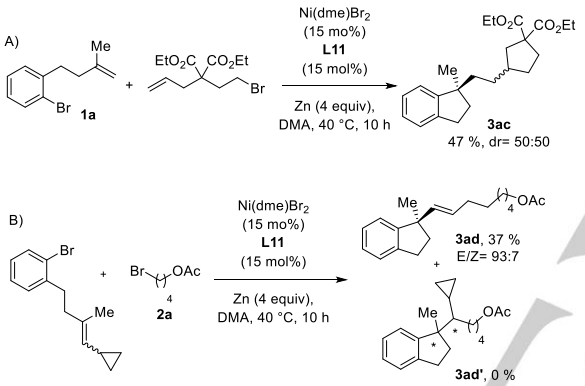
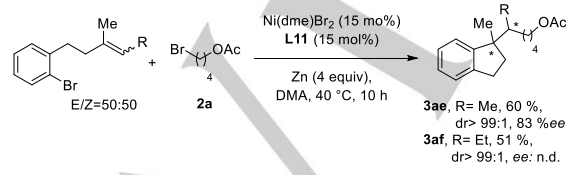
It is well-known that alkyl halides can form radicals with Ni-catalyst.[15,16] Thus we conducted the reaction using the alkyl bromide with a terminal olefinic unit (Scheme 4A). In this case, a double cyclized product **3ac** was obtained with a diastereomeric ratio of 50:50. Relying on the result that the intramolecular arylation process provides high enantioselectivity, we conclude that the cyclization of the alkyl bromide must proceed with no enantiocontrol, which is characteristic for radical-mediated ring-closure. Next, a trisubstituted olefin containing a cyclopropyl group was employed in the radical clock reaction, affording the ring opening product **3ad** in a moderate yield (Scheme 4B). In contrast, the formation of unrearranged product **3ad'** was not observed. To interpret this result, we presume that the ring opening of cyclopropane is likely initiated by a radical, which is generated through homolytic Ni-Alkyl bond cleavage of the Ni(I)-species after the formation of indane ring. However, non-radical cyclopropane ring opening via a migratory insertion/β-C elimination cascade could not be rule out in this case.



Scheme 4. Radical Clock Reactions.

Subsequently, we utilized two trisubstituted olefins with an E/Z ratio of 50:50 as substrates in the Ni-catalyzed arylalkylation reaction (Scheme 5). If the homolytic Ni-carbon bond cleavage does not exist, the products **3ae** and **3af** are supposed to have similar diastereomeric ratios as their alkene precursors. Actually, they were both furnished in complete diastereoselectivities, which supports our assumption.



Scheme 5. Asymmetric Arylalkylation Using a Trisubstituted Alkene.

In conclusion, we developed a Ni-catalyzed asymmetric two-component reductive arylalkylation of unactivated alkenes tethered to aryl bromides with primary alkyl bromides, offering an entry to approach diverse chiral benzene-fused cyclic compounds bearing a quaternary stereocenter in highly enantioselective manner. Remarkably, this new method is bestowed with better step-economy and high tolerance of a wide range of functionalities through circumventing the use of pre-generated organometallics. In the plausible reaction mechanism, a Ni(I)-mediated 5-*exo* cyclization turns out to be the enantio-determining step, and the following cage-bound oxidative addition with alkyl bromides and reductive elimination provides the dicarbofunctionalization products.

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Keywords: Dicarbofunctionalization • Reductive Coupling • Asymmetric Ni-Catalysis •Unactivated Alkenes • Quaternary Stereocenter

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Layout 2:

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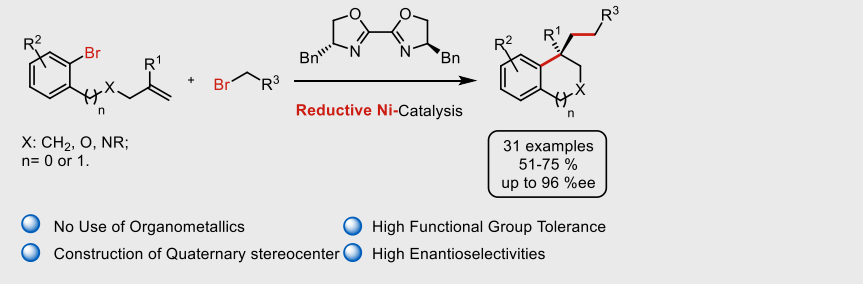

A Ni-catalyzed asymmetric arylalkylation of tethered unactivated alkenes has been developed, providing an entry to benzene-fused cyclic compounds containing a quaternary stereocenter in highly enantioselective manner.

*Youxiang Jing, Chuan Wang **

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Ni-Catalyzed Asymmetric Reductive Arylalkylation of Unactivated Alkenes