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Ni-catalysed reductive arylalkylation of unactivated alkenes†

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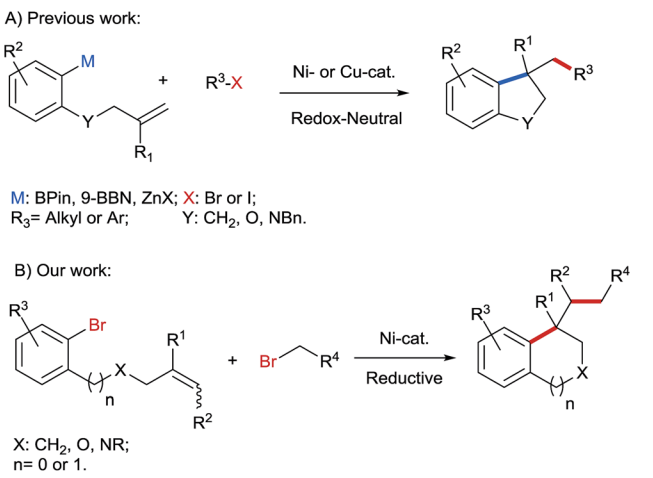
In this protocol Ni-catalysed reductive arylalkylation of unactivated alkenes tethered to aryl bromides with primary alkyl bromides has been accomplished, providing a new path to construct diverse benzene-fused carbo- and heterocyclic cores including indanes, tetrahydroisoquinolines, indolines and isochromanes. Notably, this new method circumvents the pregeneration of organometallics and demonstrates high tolerance to a wide range of functional groups. The preliminary mechanistic investigations suggest a reaction pathway with an intermediate reduction.

Introduction

In recent years, transition-metal catalyzed dicarbofunctionalisation of unactivated alkenes has gained increasing interest in the organic community, because simple olefin precursors can be converted into structurally more complex molecules in one single step with the formation of two C–C bonds. Significant progress has been achieved in this area using both redox-neutral[1–3] and reductive strategies.[4,5] For instance, aryl organometallics containing a pendant olefinic unit were successfully reacted with diverse alkyl or aryl halides as electrophiles under redox-neutral conditions to construct a series of carbo- and heterocyclic cores, such as indanes, dihydrobenzofurans and indolines (Scheme 1A).[2b–d] However, the use of pregenerated organometallics is less desirable from the viewpoint of step economy and functional group tolerance. In contrast, through reductive dicarbofunctionalisation two different alkyl or aryl electrophiles can be directly installed across the C–C double bonds under mild reaction conditions. Although a few examples of reductive dicarbofunctionalisation have been reported,[4,5] application of this reductive strategy in a two-component reaction to prepare benzene-fused cyclic compounds is still elusive. In this protocol we report Ni-catalyzed reductive arylalkylation of tethered olefins with various primary alkyl bromides providing a path for benzene-fused cyclic compounds, such as indanes, tetrahydroisoquinolines, indolines and isochromanes, which are characteristic motifs in numerous biologically active compounds[6] (Scheme 1B).

Results and discussion

For the optimization of reaction conditions, we used bromobenzene (**1a**) tethering a terminal olefinic unit and 4-bromobutyl acetate (**2a**) as the standard substrate (Table 1). Systematic screening of the reaction parameters provided the optimum conditions using $NiBr_2$ as a catalyst, **L1** as a ligand, DMA as a solvent and Zn as a reducing agent at 55 °C (entry 1). Generally, all the reactions delivered a dimer compound **3a-1** in a 1 : 1 diastereomeric ratio as the major by-product and its yields are also shown in the table (entries 2–23). Furthermore, the formation of a low amount of reductive Heck product **3a-2**, debromination product **3a-3** and cross-coupling product **3a-4** was also observed. In comparison, replacing either or both of these bromide precursors with their iodo-analogues gave rise to increasing amounts of the reductive Heck product **3a-2** in the product mixtures (entries 2–4). The use of other pyridine-based ligands **L2–L6** resulted in lower reaction efficiency (entries 5–9).



Scheme 1 Redox-neutral (A) and reductive (B) arylalkylation of tethered alkenes for the synthesis of benzene-fused cyclic compounds.

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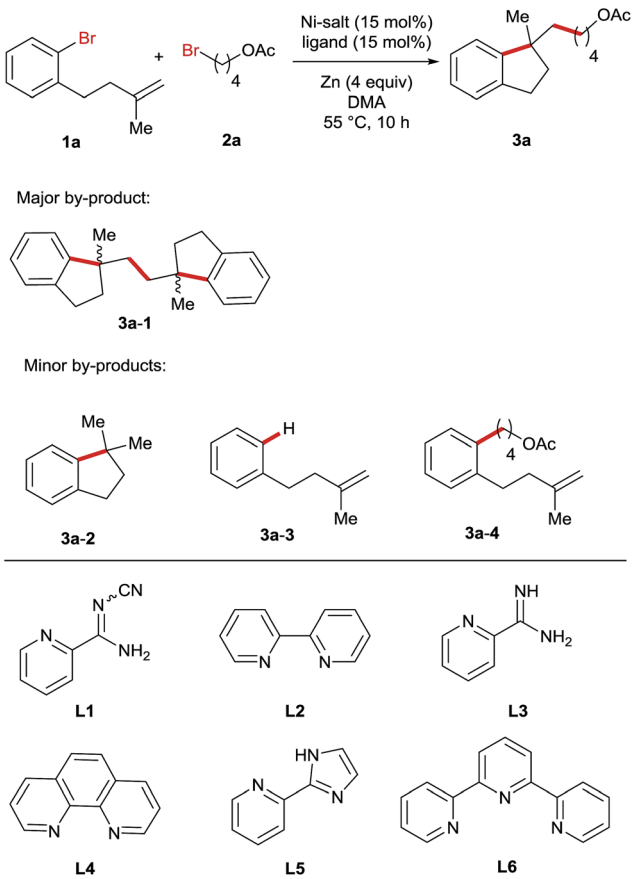
Table 1 Variation of the reaction parameters for the Ni-catalysed reductive arylalkylation reaction[a]



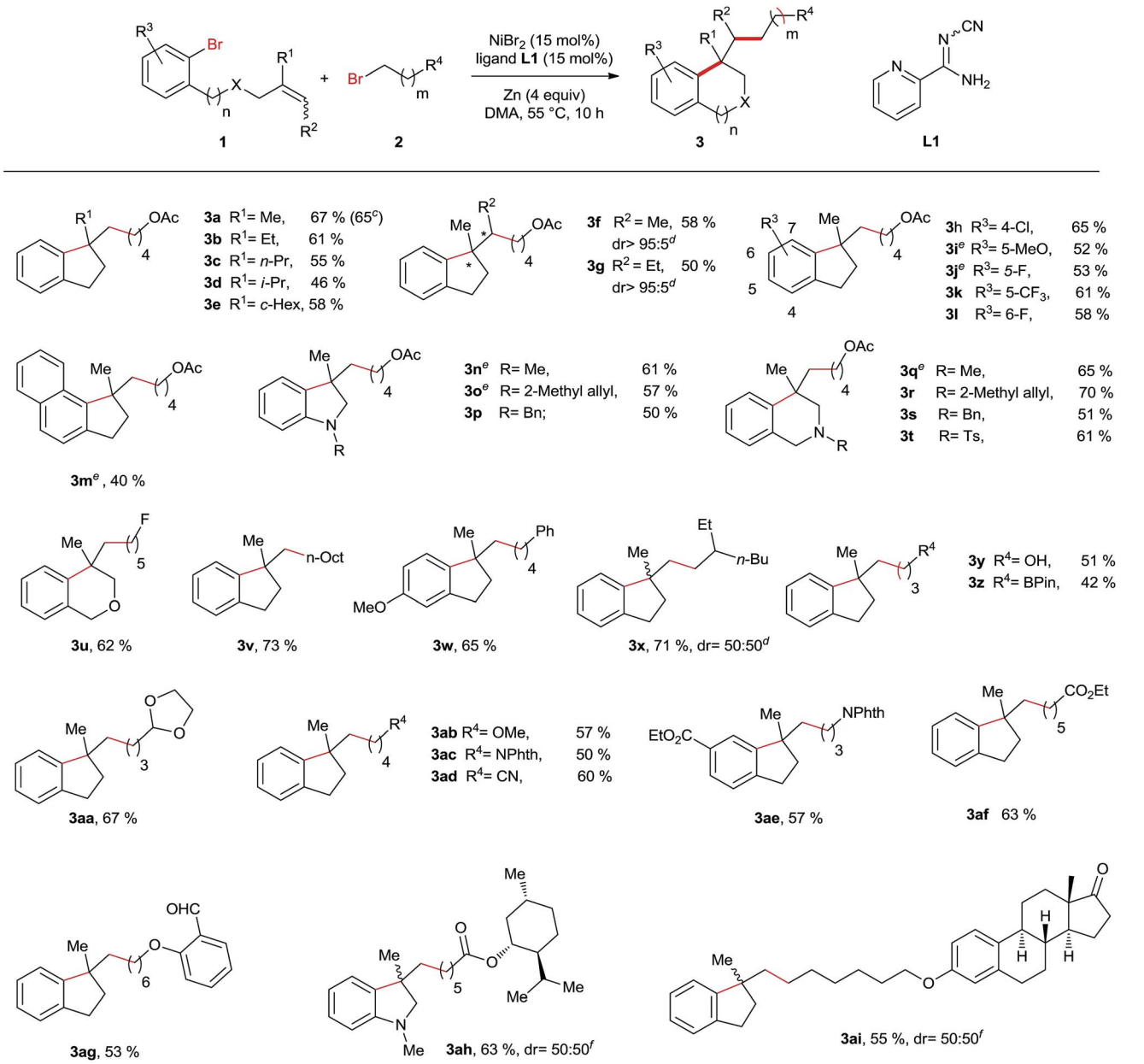
Entry	Variation from the optimum conditions	Yield **3a**[b] (%)	Yield: **3a-1**[b] (%)
1	None	69 (67[c])	9
2	Iodo-analogue of **1a** used	32	19 (8[d])
3	Iodo-analogue of **2a** used	10	18 (31[d])
4	Both iodo-analogues of **1a** and **2a** used	17	10 (30[d])
5	**L2** instead of **L1**	30	49
6	**L3** instead of **L1**	45	2
7	**L4** instead of **L1**	54	13
8	**L5** instead of **L1**	32	50
9	**L6** instead of **L1**	0	0
10	NiI_2 instead of $NiBr_2$	61	8
11	$Ni(OTf)_2$ instead of $NiBr_2$	32	4
12	$NiBr_2$·glyme instead of $NiBr_2$	63	8
13	$Ni(COD)_2$ instead of $NiBr_2$	63	7
14	DMF instead of DMA	43	3
15	NMP	68	8
16	THF instead of DMA	0	0
17	MeCN instead of DMA	0	0
18	Mn instead of Zn	51	17
19	75 °C instead of 55 °C	62	8
20	35 °C instead of 55 °C	27	2
21	1.2 equiv. **2a** used	50	13
22	10 mol% $NiBr_2$ used	63	13
23	2 equiv. Zn used	50	7

[a] Unless otherwise specified, reactions were performed on a 0.2 mmol scale of aryl bromide **1a** with 2 equiv. bromobutyl acetate (**2a**), 15 mol% $NiBr_2$, 15 mol% ligand **L1** and 4 equiv. Zn as the reductant in 0.5 mL DMA at 55 °C for 10 h. [b] GC-yields using *n*-dodecane as an internal standard. [c] Yield of the isolated product. [d] Yield of **3a-2**.

Ni-salt screening indicated that the studied reactions could be promoted by both Ni(II)- and Ni(0)-catalysts (entries 10–13). Performing the reaction in other polar solvents including DMF and NMP led to decreased yields (entries 14 and 15), whereas the reaction was completely shut down when using THF or MeCN as the solvent (entries 16 and 17). The reaction employing Mn instead of Zn as a reducing agent yielded the product in a reduced yield (entry 18). In addition, the temperature impact on this reaction was also investigated and both raising and lowering the reaction temperature had a detrimental effect on the reaction efficiency (entries 19 and 20). Moreover, reducing the amount of alkyl bromide **4**, $NiBr_2$ or Zn-powder all resulted in lower yields (entries 21–23).

After establishing the best reaction conditions, we started to evaluate the substrate spectrum of this Ni-catalyzed reductive arylalkylation reaction by varying the structure of both pendant alkenes **1** and alkyl bromides **2** (Table 2). First, we studied the influence of the alkene substitution pattern on the outcome of this reaction. In the case of disubstituted terminal olefins all the reactions provided the products **3a–e** in moderately good yields.

Table 2 Evaluation of the substrate scope of the Ni-catalysed reductive arylalkylation reaction[a,b]

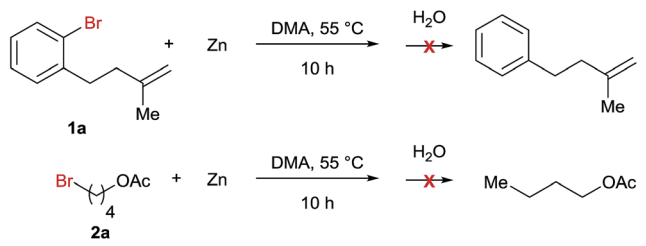


[a] Unless otherwise specified, reactions were performed on a 0.4 mmol scale of aryl bromides **1** with 2 equiv. alkyl bromides **2**, 15 mol% $NiBr_2$, 15 mol% ligand **L1** and 4 equiv. Zn as the reductant in 1.0 mL DMA at 55 °C for 10 h. [b] Yields of the isolated products. [c] Reaction was performed on a 1 g scale using 5 mol% $NiBr_2$ and 5 mol% ligand **L1** at 65 °C for 12 h. [d] Determined by ^{13}C-NMR-spectroscopy. [e] Reactions were performed at 70 °C. [f] Determined by HPLC-analysis.

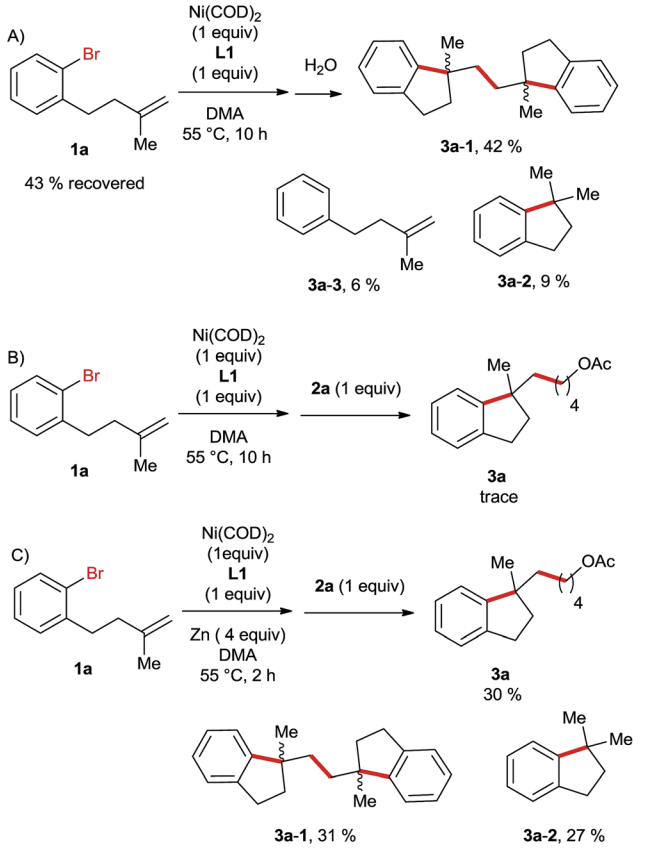
Remarkably, the reactions employing 1,1,2-trisubstituted alkenes also proceeded smoothly under the optimum reaction conditions yielding the products **3f** and **3g** in excellent diastereoselectivities, although the *E*/*Z* ratios of the alkene precursors are nearly 1 : 1. The high diastereocontrol indicates that this Ni-catalyzed reaction is probably not initiated by the radical addition of the alkyl group to the C–C double bond. When 1,2-disubstituted and monosubstituted alkenes were used as substrates, no desired products were obtained due to the high tendency to undergo the Heck reaction. Next, the examination of the substituent effect on the phenyl ring was undertaken. To our delight, all the substrates bearing electron-withdrawing or donating groups turned out to be suitable substrates providing the corresponding products **3h–m**, **3w** and **3ae** in moderate to good yields. Furthermore, our method is not limited to the synthesis of indane derivatives. A series of indolines **3n–p** and **3ah** and tetrahydroisoquinolines **3q–t** and an isochromane **3u** were also successfully prepared through this Ni-catalysed reaction. Subsequently, diverse primary alkyl bromides were reacted with various pendant olefins. Of note is that this Ni-catalysed reaction demonstrates the high compatibility of a wide range of functional moieties including alcohol (**3y**), boronate (**3z**), acetal (**3aa**), imide (**3ac** and **3ae**), nitrile (**3ad**), ester (**3af** and **3ah**), aldehyde (**3ag**) and ketone (**3ai**). Moreover, the reaction using **1a** and **2a** was performed on a one-gram scale still furnishing the product **3a** in a 65% yield with 5 mol% catalyst loading. A limitation of this method was observed in the case of secondary and tertiary bromides, which failed to yield the arylalkylation products.

A series of control experiments were carried out to explore the mechanism of this Ni-catalyzed ring opening reaction. First, we reacted Zn-powder with both bromide precursors under the standard reaction conditions and the results indicated that no organozincs were formed in the reaction mixture (Scheme 2). Consequently, the Negishi coupling reaction pathway is less likely for the studied reaction.

Next, we carried out a stoichiometric reaction between $Ni(COD)_2$ and the aryl bromide **1a**. After 10 h the reaction was quenched with water and it turned out that nearly half of the starting material was recovered and the major product was the dimer **3a-1** (Scheme 3A). If the alkyl bromide **2a** was added to the reaction mixture instead of water, only traces of the desired product **3a** were formed in this case (Scheme 3B). In contrast, the sequential stoichiometric reactions of $Ni(COD)_2$ with **1a** and **2a** in the presence of Zn furnished the product **3a** in a 30% yield



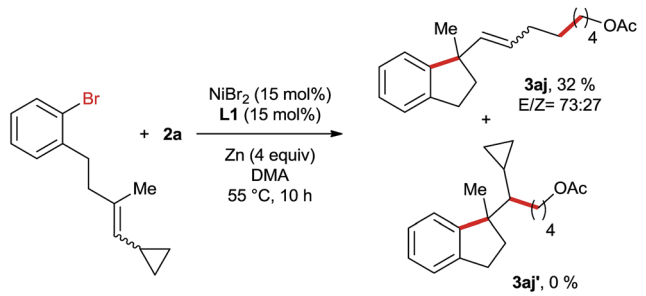
Scheme 2 Stoichiometric reactions of bromides **1a** and **2a** with Zn-powder.



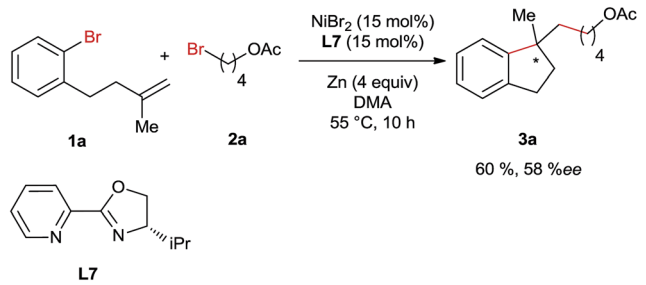
Scheme 3 Stoichiometric control experiments for the Ni-catalyzed reductive arylalkylation.

(Scheme 3C). These results suggest that Zn is required in a step of an intermediate reduction instead of serving as a terminal reductant in this Ni-catalysed reaction, which is likely initiated by the oxidative addition of aryl bromide to a Ni(0)-species followed by an intramolecular migratory insertion. A similar process was reported very recently by Kong *et al.* in Ni-catalysed reductive diarylation of activated olefins.[5]

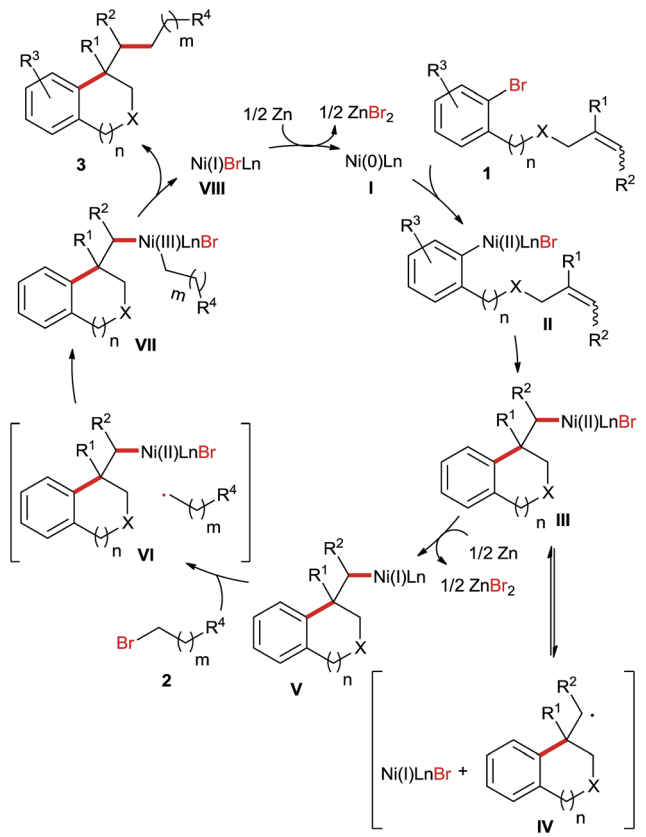
Subsequently, we conducted the reaction using TEMPO as a radical scavenger and in this case the reaction was completely shut down revealing that a radical species might be involved in the key step of this reaction. This is not surprising since alkyl bromide can easily form radicals in Ni-catalyzed reductive coupling reactions according to numerous reports in the literature.[7,8] However, it is unknown whether the migratory insertion of Ni–Ar into the C–C double bond proceeds through a radical pathway or not under reductive conditions. In order to gain more insights into the mechanism of this reaction, a radical clock experiment employing a cyclopropyl-substituted alkene as a substrate was conducted (Scheme 4). In this case a ring opening product **3aj** was obtained in 32% yield, whereas the formation of unrearranged product **3aj′** was not observed. This result could be rationalized by cyclisation involving an aryl radical, which is generated through the interaction of aryl bromide with the Ni-catalyst. Alternatively, the initial migratory insertion could be non-radical, but the resultant Ni-alkyl species after cyclisation might undergo homolytic Ni–alkyl bond



Scheme 4 Radical clock experiment for the Ni-catalyzed reductive arylalkylation.



Scheme 5 Ni-catalysed arylalkylation employing a chiral oxazoline ligand.



Scheme 6 Proposed mechanism of the Ni-catalyzed reductive arylalkylation.

cleavage, affording the same C-centered radical as the one generated in the aryl-radical-mediated ring closure. Moreover, the high diastereoselectivities of **3f** and **3g** also support the formation of this alkyl radical; otherwise similar diastereomeric ratios would be obtained to their trisubstituted alkene-precursors. To differentiate the two possible pathways mentioned above we conducted Ni-catalysed reductive arylalkylation employing a chiral oxazoline ligand (Scheme 5). In this case the product **3a** was obtained with a moderate enantioselectivity. This report clearly excludes the possibility of radical-mediated cyclisation, which is supposed to provide the product as a racemic mixture.

Based on the aforementioned experimental results we proposed the following plausible mechanism for this Ni-catalyzed reaction (Scheme 6). Initially, under the reductive reaction conditions a Ni(0)-species **I** is generated, which undergoes oxidative addition with aryl bromides **1** to afford a Ni(II) complex **II**. Next, the ring closure is accomplished *via* an intramolecular non-radical migratory insertion. The generated Ni(II) species **III** stays in equilibrium with an alkyl radical **IV** and Ni(I)LnBr before Zn-mediated reduction to the Ni(I) species **V**. The subsequent oxidative addition of alkyl bromides **2** involves the formation of a cage **VI** and the following recombination provides a Ni(III) intermediate **VII**. Finally, the reductive elimination of the Ni(III) complex **VII** furnishes the products **3** and the Ni(I) species **VIII**, which is subsequently reduced to the Ni(0)-species **I** for the next catalytic cycle.

Conclusions

In conclusion, we have developed Ni-catalysed reductive arylalkylation of unactivated alkenes tethered to aryl bromides with an array of primary alkyl bromides, providing a new path to synthesize benzene-fused cyclic compounds such as indanes, tetrahydroisoquinolines, indolines and isochromanes with an all-carbon-stereogenic center. This new method is distinguished by avoidance of the use of pregenerated organometallics, high tolerance of a broad range of functional moieties and base-free reaction conditions. The preliminary mechanistic studies indicate that this Ni-catalysed reaction proceeds in a reaction pathway with an intermediate reduction. Further investigations into the asymmetric version of this reaction are in progress and will be published in due course.

Conflicts of interest

There is no conflict to declare.

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