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Ni-catalyzed regioselective and site-divergent reductive arylalkylations of allylic amines†

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Catalytic methods by switching the least parameters for regioselective and site-divergent transformations to construct different architectures from identical and readily available starting materials are among the most ideal catalytic protocols. However, the associated challenge to precisely control both regioselectivity and site diversity renders this strategy appealing yet challenging. Herein, Ni-catalyzed cross-electrophile regioselective and site-divergent 1,2- and 1,3-arylalkylations of *N*-acyl allylic amines have been developed. This Ni-catalyzed reductive three-component protocol enables 1,2-arylalkylation and 1,3-arylalkylation of allylic amines with aryl halides and alkyl halides with excellent chemo-, regio- and site-selectivity, representing the first example of controlled migratory difunctionalization of alkenes under reductive conditions. A wide range of terminal and internal unactivated allylic amines, aryl halides and alkyl precursors were tolerated, providing straightforward and efficient access to diverse C(sp^3)-rich branched aliphatic amines from identical starting materials.

Introduction

Transition-metal-catalyzed cross-coupling reactions are powerful tools for the construction of saturated carbon centres and are widely used in the construction of drugs, natural products, agricultural chemicals, and organic materials.[1] Among which, transition-metal-catalyzed reductive coupling reactions have attracted considerable attention due to the sole use of organo-electrophiles, circumventing the stepwise pre-synthesis of organometallic reagents.[2] More importantly, reductive cross-coupling reactions are better suited for the construction of saturated carbon centres partially attributed to the low-valent state of metal centres under reducing conditions, which suppresses the unwanted β-hydrogen elimination process thus facilitating the formation of saturated C–C bonds.[3] To this end, reductive cross-coupling between two electrophiles (such as aryl halides and alkyl halides) to build saturated C–C bonds has been extensively explored (Fig. 1a).[3c,4] However, the construction of C(sp^3)-rich scaffolds through multi-component reductive coupling reactions remains challenging due to the difficulties in distinguishing different electrophile coupling partners as well as the associated regio- and site-selectivity issues.[5]

On the other hand, alkenes have been recognized as a privileged platform for the construction of molecular complexity.[6] A

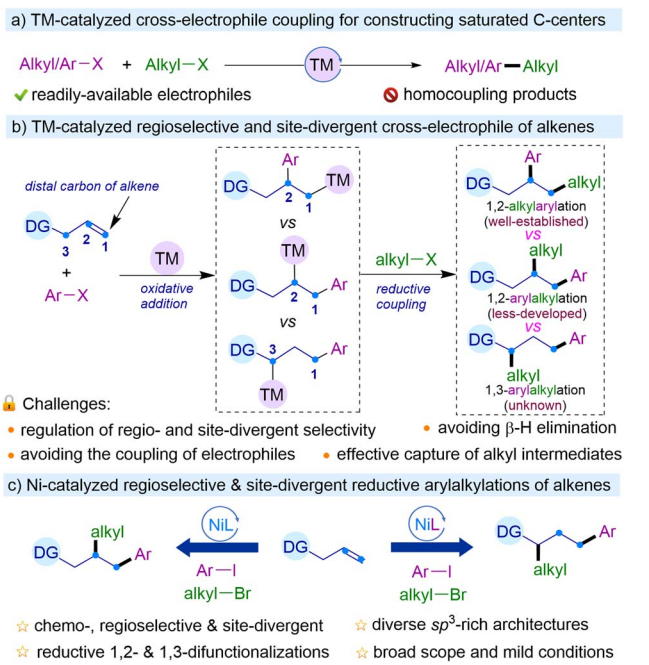

Fig. 1 Reductive cross-coupling enables regioselective and site-divergent arylalkylations of unactivated alkenes.

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notable advantage of alkenes is that they have two potential functionalization sites, offering profound chemical space for rapid buildup of diverse C(sp^3)-rich structures.[7] Recently, the regioselective incorporation of carbon-based motifs through nickel-catalyzed reductive 1,2-dicarbofunctionalization of conjugated alkenes (such as arylalkene,[8] vinyl esters[9] and vinyl amides[10]) has been developed to provide saturated hydrocarbon frameworks.[11] Notably, the regioselectivity is controlled by the π-system of the conjugated alkenes to form a thermodynamic stabilized alkyl intermediate.

However, it remains challenging to achieve the formation of double bonds to provide saturated hydrocarbon frameworks. Notably, the regioselectivity is controlled by the late regioselectivity of non-conjugated alkenes for such events.[12] Recently, Ni-catalyzed reductive 1,2-alkylarylation and 1,2-diarylation of unactivated alkenes facilitated by using strong coordinating groups (such as 8-aminoquinoline and oxygen atom) have been reported.[13] Notably, aryl groups are attached to the proximal carbon of the alkenes to directing groups. Instead, Ni-catalyzed reductive 1,2-arylalkylation of unactivated alkenes with the opposite regioselectivity, installing aryl groups to the distal carbon of the alkenes, remains less developed.[5a,14] During the preparation of this paper, MacMillan reported a visible-light-mediated Ni-catalyzed 1,2-arylalkylation of unactivated alkenes with aryl bromides and redox-active ester of aliphatic carboxylic acids.[5a] The regioselectivity of this method was achieved by bimolecular homolytic substitution (S_H2) and only applicable to primary alkyl radical precursors.[5a,b] However, Ni-catalyzed site-divergent arylalkylation of alkenes remains a formidable challenge due to the difficulties in precise regulation of alkyl–alkyl cross-coupling *versus* the β-hydrogen elimination process of alkylnickel intermediates (Fig. 1b).[15] Herein, we report Ni-catalyzed regioselective and site-divergent arylalkylations of allylic amines under reductive conditions (Fig. 1c). This cross-electrophile coupling protocol enables chemo- and regioselectivity along with site-divergent selectivity of three-component arylalkylation of unactivated alkenes with aryl electrophiles installed on the distal carbon of alkenes. The catalytic conditions regulate 1,2- and 1,3-arylalkylations of allylic amines allowing for rapid access to diverse sp^3-rich branched aliphatic amine derivatives from readily available and identical starting materials.

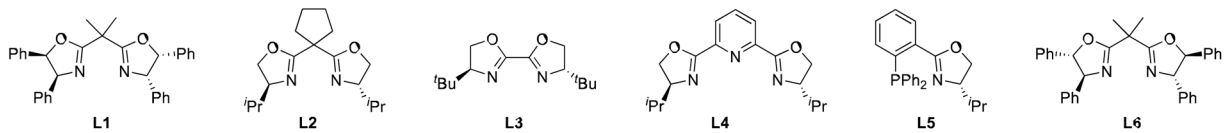
Results and discussion

We started to investigate the feasibility of these regioselective and site-divergent arylalkylations of allylic amines by using *N*-benzoyl allylic amine **1a**, 4-iodoanisole **2a**, and 3-phenyl-1-bromopropane **3a** as model substrates to evaluate the reaction parameters (Table 1). After extensive preliminary optimization (Tables S1–S5†),[16] 1,2-arylalkylation product **4aa** was formed in 85% yield with rr > 20 : 1 in DMA (0.1 M) at room temperature using $NiBr_2 \cdot$dme (10 mol%) as precatalyst, bisoxazoline ligand **L1** (12 mol%) as ligand, and NaI (2.5 equiv.) as additive in the presence of manganese (Mn, 3.5 equiv.) as sacrificial reductant (conditions A, Table 1, entry 1). The use of NMP as solvent decreased the efficiency of reductive 1,2-arylalkylation, delivering **4aa** in 61% with rr > 20 : 1 (Table 1, entry 2). Conducting the reaction in protic solvent IPA further decreased the yield of **4aa** to 52% with rr > 20 : 1 (Table 1, entry 3). Next, we further evaluated the ligand effect on this reductive 1,2-arylalkylation reaction (Table 1, entries 4–9). Altering the ligand from **L1** to **L2**–**L4** reduced the yields of **4aa** to 16–61%, albeit with excellent regioselectivity (rr > 20 : 1) (Table 1, entries 4–6). Phosphine-oxazoline ligand **L5** mediated the reaction smoothly, delivering **4aa** in 34% yield (Table 1, entry 7). Interestingly, the use of bisoxazoline (**L6**) as ligand decreased the yield of **4aa** to 43% along with the formation of migratory 1,3-arylalkylation product **5aa** in 19% yield (Table 1, entry 8). Monophosphine ligand PCy_3 delivered 1,2-arylalkylation product **4aa** in 34% yield (Table 1, entry 9). The reaction proceeded smoothly in the absence of sodium iodide or ligand, affording 1,2-arylalkylation product **4aa** in diminished yields and regioselectivities (Table 1, entries 10 and 11). Inspired by the results of using **L6** as ligand, we turned to explore the potential of **1a** to undergo migratory 1,3-arylalkylation reaction to give α-branched aliphatic amine **5aa**. It was found that reaction temperature was important for the efficient formation of **5aa**. When the reaction was conducted at 50 °C, the yield of **5aa** was increased to 39% (Table 1, entry 12). Altering the nickel salt from $NiBr_2 \cdot$dme to $Ni(BF_4)_2 \cdot 6H_2O$ in IPA (0.1 M) further improved the yield of **5aa** to 49% with rr > 20 : 1, and substantially suppressed the formation of 1,2-arylalkylation product **4aa** (Table 1, entry 13). Solvent effect evaluation indicated the use of methanol reduced the formation of **5aa** to 28% yield (Table 1, entry 14). To our delight, conducting the reaction in a mixture of alcohols (IPA : MeOH = 5 : 1) significantly improved the yield of the 1,3-arylalkylation reaction, affording **5aa** in 76% yield with 16 : 1 rr (conditions B, Table 1, entry 15). A mixed solvent of IPA : DMA furnished **5aa** in only 38% yield (Table 1, entry 16). Other ligands, such as PCy_3 and **L4**, failed to promote this three-component 1,3- and 1,2-arylalkylation reaction under otherwise identical conditions (Table 1, entries 17 and 18). In addition, sodium iodide proved to be essential for the reaction, only 26% of **5aa** being formed in the absence of sodium iodide (Table 1, entry 19). A control experiment revealed that ligand was also essential for 1,3-arylalkylation of allylic amines. No desired product **5aa** was detected without ligand (Table 1, entry 20).

With two sets of optimized reaction conditions in hand, the substrate scope of 1,2- and 1,3-arylalkylation of allylic amines was examined, with the results summarized in Fig. 2. We first investigated the scope of allylic amines. *N*-Benzoyl allylic amines with electron-withdrawing or electron-donating groups are all good substrates for this reaction, affording corresponding 1,2-arylalkylation products (**4aa**–**4ad**) and 1,3-arylalkylation products (**5aa**–**5ad**) in good to excellent yields (66–91%) with rr of 11 : 1 to >20 : 1. 3,5-Dimethyl-substituted *N*-benzoyl allylic amine yielded products **4ae** and **5ae** in 73% and 81% yields, with regioselectivity >20 : 1. The *ortho*-substituted *N*-benzoyl allylic amine provided **4af** and **5af** in 65% and 72% yields with 9 : 1 and 4 : 1 rr. *N*-Heteroarylacyl-derived allylic amines, such as furans (**4ag** and **5ag**) and thiophenes (**4ah** and **5ah**), were successfully converted to corresponding target products in moderate to good yields (54–73%) and good regioselectivity (rr of 5 : 1 to >20 : 1).

Table 1 Condition evaluation of Ni-catalyzed regioselective 1,2- and 1,3-arylalkylations of *N*-acyl allylic amines[a]

Entry	Solvent	T (°C)	[Ni]	Ligand	Yield of **4aa**[b]	Yield of **5aa**[b]
1	**DMA**	**rt**	**$NiBr_2$·dme**	**L1**	**85% (82%)**	**Trace**
2	NMP	rt	$NiBr_2$·dme	**L1**	61%	2%
3	IPA	rt	$NiBr_2$·dme	**L1**	52%	2%
4	DMA	rt	$NiBr_2$·dme	**L2**	61%	2%
5	DMA	rt	$NiBr_2$·dme	**L3**	16%	ND
6	DMA	rt	$NiBr_2$·dme	**L4**	39%	ND
7	DMA	rt	$NiBr_2$·dme	**L5**	34%	ND
8	DMA	rt	$NiBr_2$·dme	**L6**	43%	19%
9	DMA	rt	$NiBr_2$·dme	PCy_3	34%	ND
10[c]	DMA	rt	$NiBr_2$·dme	**L1**	67%	14%
11[d]	DMA	rt	$NiBr_2$·dme	—	32%	6%
12	DMA	50	$NiBr_2$·dme	**L6**	28%	39%
13[e]	IPA	50	$Ni(BF_4)_2·6H_2O$	**L6**	0%	49%
14[e]	MeOH	50	$Ni(BF_4)_2·6H_2O$	**L6**	0%	28%
15[e]	**IPA/MeOH**	**50**	**$Ni(BF_4)_2·6H_2O$**	**L6**	**5%**	**76% (72%)**
16[e]	IPA/DMA	50	$Ni(BF_4)_2·6H_2O$	**L6**	12%	38%
17[e]	IPA/MeOH	50	$Ni(BF_4)_2·6H_2O$	PCy_3	ND	ND
18[e]	IPA/MeOH	50	$Ni(BF_4)_2·6H_2O$	**L4**	ND	ND
19[c,e]	IPA/MeOH	50	$Ni(BF_4)_2·6H_2O$	**L6**	3%	26%
20[d,e]	IPA/MeOH	50	$Ni(BF_4)_2·6H_2O$	—	ND	ND



[a] Reactions were conducted using **1a** (0.10 mmol), **2a** (0.20 mmol), **3a** (0.20 mmol), Mn (0.35 mmol), NaI (0.25 mmol), [Ni] (10 mol%), ligand (12 mol%) in indicated solvent (0.1 M) at room temperature for 18 h. ND = not determined. [b] Yield was determined by GC analysis using *n*-dodecane as internal standard. Isolated yield is shown in parentheses. [c] No NaI was used. [d] No ligand was used. [e] Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), **3a** (0.15 mmol), Mn (0.30 mmol), NaI (0.05 mmol), $Ni(BF_4)_2·6H_2O$ (10 mol%), ligand (12 mol%) in solvent (0.1 M) for 18 h.

Acyclic and cyclic aliphatic acyl-derived allylic amines were also compatible under corresponding standard conditions (1,2-arylalkylation: **4ai–4ak** (62–88% yields); 1,3-arylalkylation: **5ai–5ak** (69–85% yields)). Tertiary allylic amines without free *N*–H produced desired products in 68% (**4al**) and 43% (**5al**) yields with rr > 20 : 1. Notably, internal allylic amines are compatible in the reaction, affording corresponding 1,2-arylalkylation (**4am–4ao**) and 1,3-arylalkylation (**5am–5ao**) in moderate yields with good to excellent regioselectivities (rr of 4 : 1 to >20 : 1) as well as excellent levels of diastereoselectivity (dr > 20 : 1). In addition, drug molecule-based *N*-acyl allylic amines, such as probenecid and isoxepac, were well tolerated, furnishing the desired products in 73–79% yields with rr of 10 : 1 to >20 : 1 (1,2-arylalkylation: **4ap** and **4aq**; 1,3-arylalkylation: **5ap** and **5aq**). Next, the scope of aryl iodides was examined. Aryl iodides with diverse substitution patterns, such as *ortho*-, *meta*-, and *para*-substituents with electron-donating or electron-withdrawing groups, reacted smoothly to deliver 1,2- and 1,3-arylalyations of *N*-acyl allylic amines in 49–86% yields with rr of 7 : 1 to >20 : 1 (1,2-arylalkylation: **4ba–4bj** (49–78% yields); 1,3-arylalkylation: **5ba–5bj** (51–86% yields)). 3-Iodo-*N*-phenylcarbazole **2l** gave the target products (**4bk** and **5bk**) in moderate yields (69% and 74%) with excellent regioselectivity (rr > 20 : 1).

Finally, we tested the scope of alkyl halides. Linear and branched unactivated alkyl bromides afforded the corresponding selective products of 1,2- and 1,3-arylalkylation of *N*-acyl allylic amines in 52–71% yields with rr of 4 : 1 to >20 : 1 (1,2-arylalkylation: **4ca–4cc**; 1,3-arylalkylation: **5ca–5cc**). Alkyl chloride was well tolerated in the reaction, furnishing 1,2-arylalkylation (**4cd**) and 1,3-arylalkylation (**5cd**) products with the chloride unattached. Moreover, amide and ester substituents on alkyl bromides were smoothly involved in the two sets of reaction conditions, providing the desired products (**4ce** and **5ce**, **4cf** and **5cf**) in 42–70% yields with rr of 7 : 1 to >20 : 1. 2-Phenylethyl bromide can also undergo 1,2- and 1,3-arylalkylation of *N*-acyl allylic amines to furnish corresponding products

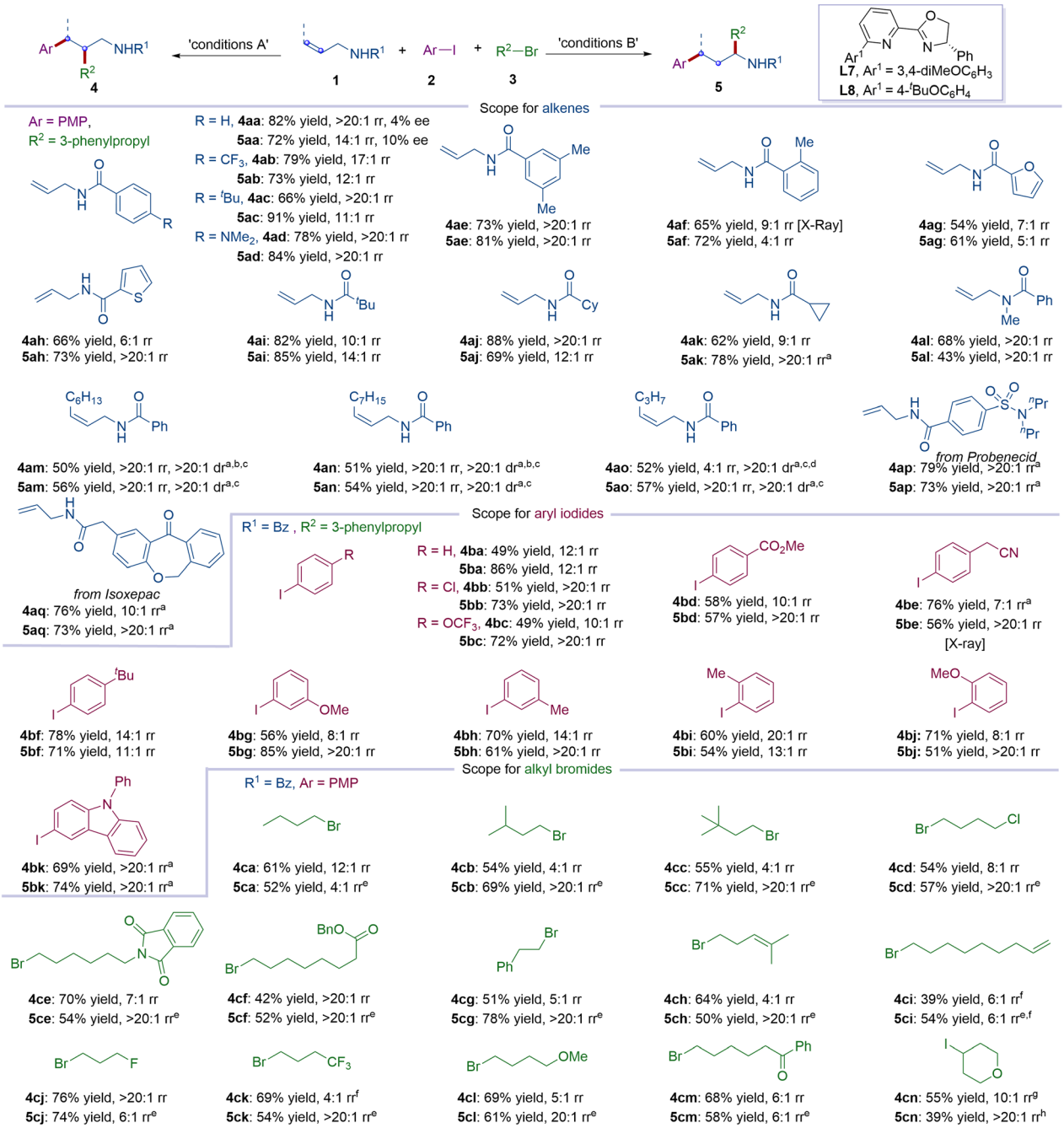


Fig. 2 Scope for regioselective and site-divergent arylalkylations of *N*-acyl allylic amines. Unless otherwise noted, reaction was conducted under conditions A (**1a** (0.20 mmol), **2a** (0.40 mmol), **3a** (0.40 mmol)) and conditions B (**1a** (0.20 mmol), **2a** (0.30 mmol), **3a** (0.30 mmol)). Regioselectivity ratio was determined by GC analysis. Yield refers to the isolated yield of single isomer. 'rr' was determined by GC using crude mixture of the reaction. [a] Reaction was conducted on 0.10 mmol scale. [b] **L7** was used instead of **L1**. [c] 4-Iodotoluene (2.0 equiv.) was used instead of **2a**. [d] **L8** was used instead of **L1**. [e] Mn (2.0 equiv.) was used instead of Mn (3.0 equiv.). [f] The reaction was conducted for 72 h. [g] 1-Iodo-4-*tert*-butylbenzene was used instead of **2a**. [h] *p*-Trifluoromethyliodobenzene was used instead of **2a**. NaBr (4.0 equiv.) was used instead of NaI.

(**4cg** and **5cg**) in 51% and 78% yields with rr of 5 : 1 and >20 : 1. It deserves mentioning that alkene-containing alkyl bromides were well tolerated in the reaction, leaving the alkene intact during the reaction course (1,2-arylalkylation: **4ch** and **4ci**; 1,3-arylalkylation: **5ch** and **5ci**). Alkyl bromides with other substituents, such as –F (**4cj** and **5cj**), –CF_3 (**4ck** and **5ck**), ethers (**4cl** and **5cl**) and ketones (**4cm** and **5cm**), were all compatible in the reaction, affording 1,2-arylalkylation and 1,3-arylalkylation products of *N*-acyl allylic amines in 54–76% yields with rr of 4 : 1 to >20 : 1. Impressively, a secondary alkyl iodide was successfully involved in the reaction, affording desired 1,2- and 1,3-arylalkylation products **4cn** and **5cn** in 55% and 39% yields with

rr of 10 : 1 and >20 : 1, respectively. Unfortunately, tertiary alkyl iodides/bromides failed to deliver target products under the reaction conditions.

To further explore the synthetic application of this strategy, gram-scale experiments of 1,2- and 1,3-arylalkylations were conducted. This regioselective and site-divergent, three-component arylalkylation protocol could be easily scaled up to 2.0 mmol scale under the two sets of standard conditions, affording 1,2-arylalkylation product **4aa** in 84% yield with rr of 9 : 1 and 1,3-arylalkylation product **5aa** in 78% yield with rr of 10 : 1 (Fig. 3a).

To shed some light on the origin of regio- and site-selectivity of the nickel-catalyzed regiodivergent arylalkylations of allylic amines, a series of mechanistic experiments were conducted (Fig. 3b–f). First, a cross-over reaction was conducted using allylic amine **1a** with **2a** and **3a** under standard conditions for migratory 1,3-arylalkylation reaction in the presence of *N*-acylpropenylamine **1k′** (Fig. 3b). The reaction proceeded smoothly to afford 1,3-arylalkylation product **5aa** from **1a** in 38% yield. No cross-over cross-coupling product from **1k′** was detected. These results indicate that nickel migration over the alkyl chain *via* β-H elimination and

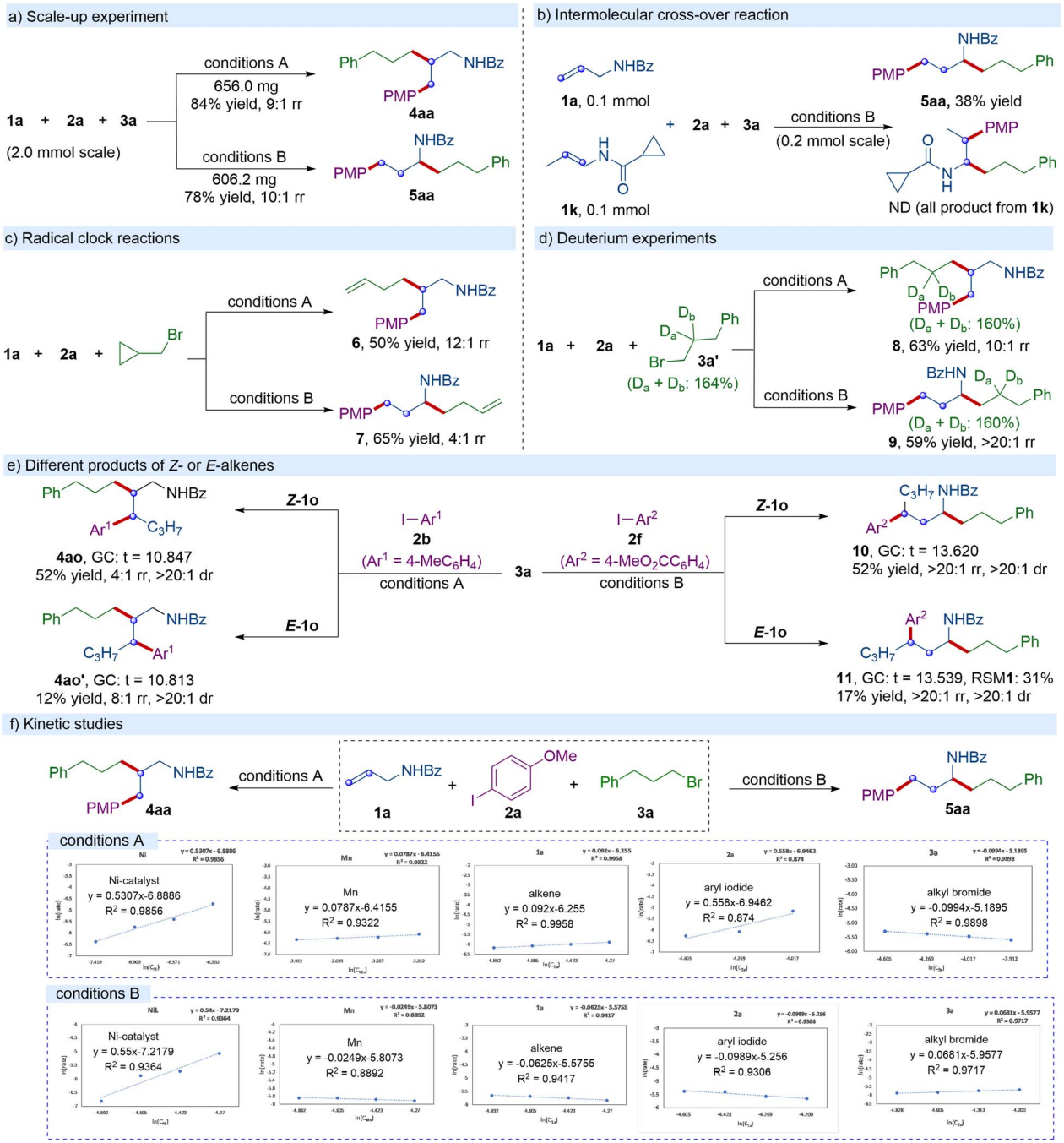


Fig. 3 Scale-up experiments and mechanistic investigations.

insertion to form a nitrogen-stabilized alkyl-Ni intermediate for 1,3-arylalkylation is an intramolecular process. Subsequently, a radical clock experiment of the reaction was conducted using **1a** and **2a** with cyclopropylmethyl bromide. The ring-opening of cyclopropane occurred under both standard conditions for 1,2-arylalkylation (conditions A) and 1,3-arylalkylation (conditions B), delivering corresponding coupling products **6** and **7** in 50% and 65% yields, respectively (Fig. 3c). These results suggest that oxidative addition of alkyl halides may occur *via* a single-electron oxidative addition process. When 1,1-deuterated 3-phenyl-1-bromopropane **3a**′ was used as alkyl electrophile for both 1,2- and 1,3-arylalkylation reactions, desired cross-coupling products (**8** and **9**) were obtained in 63% and 59% yields (Fig. 3d). No deuterium scrambling was observed for the reaction. These results exclude the possibility of reversible β-H elimination and insertion of alkyl-Ni intermediate resulting from alkyl electrophiles. Next, the reaction of internal alkenes with different configurations was investigated (Fig. 3e). Under standard conditions for 1,2-arylalkylation (conditions A), 3-phenyl-1-bromopropane (**3a**) and 4-methyliodobenzene (**2b**) reacted with *Z*-configuration of **1o** (*Z*-**1o**) to deliver **4ao** in 57% yield with 6 : 1 rr and >20 : 1 dr. In contrast, the reaction of **2b** and **3a** with *E*-configuration **1o** (*E*-**1o**) yielded the other diastereomer **4ao**′, with diminished yield (12%) with 8 : 1 rr and >20 : 1 dr. Under standard conditions for 1,3-arylalkylation (conditions B), two different diastereomers (**10** and **11**) were obtained in 52% (**10**) and 17% (**11**) yields with rr and >20 : 1 dr from *Z*-configuration of **1o** (*Z*-**1o**) and *E*-configuration of **1o** (*E*-**1o**), respectively. The results revealed that the carbometallation of alkenes is a stereospecific process. Furthermore, kinetic studies for each reaction component were conducted to gain insight into the turnover-limiting step of this regioselective and site-divergent process (Fig. 3f). Under standard conditions for 1,2-arylalkylation (conditions A), the reaction was determined as first-order-dependent on Ni catalyst and aryl iodide **2a**, and zero-order-dependent on reductant (Mn), allylic amine **1a** and alkyl bromide **3a**. The results indicate that Ni catalyst and aryl iodides may be involved in the turnover-limiting step, suggesting the oxidative addition of Ni catalyst to aryl iodides may be the rate-determining step for 1,2-arylalkylation. Under standard conditions for 1,3-arylalkylation (conditions B), the reaction was determined as first-order-dependent on Ni catalyst, while zero-order-dependent on reductant (Mn), allylic amine **1a**, aryl iodide **2a** and alkyl bromide **3a**. The results indicate that only the Ni catalyst may be involved in the turnover-limiting step and regeneration of Ni(0) could be the rate-determining step.

Based on the experimental results and previous literature,[12b,14,17] possible mechanisms for 1,2- and 1,3-arylalkylations of allylic amines with aryl and alkyl electrophiles are proposed (Fig. 4). First, Ni^0**L** species could be *in situ* formed from Ni^{II} precursors in the presence of **L1** and manganese (Mn), which could undergo oxidative addition with aryl electrophiles to give Ar-Ni^{II}**L** intermediate **A**. Subsequently, **A** undergoes regioselective carbometallation into the alkene to provide Ni^{II} intermediate **B**. The presence of *N*-acyl in the allylic amines enhances the stability of intermediate **B** by forming a six-membered ring. Intermediate **B** (Ni^{II}**L1**) could be reduced to

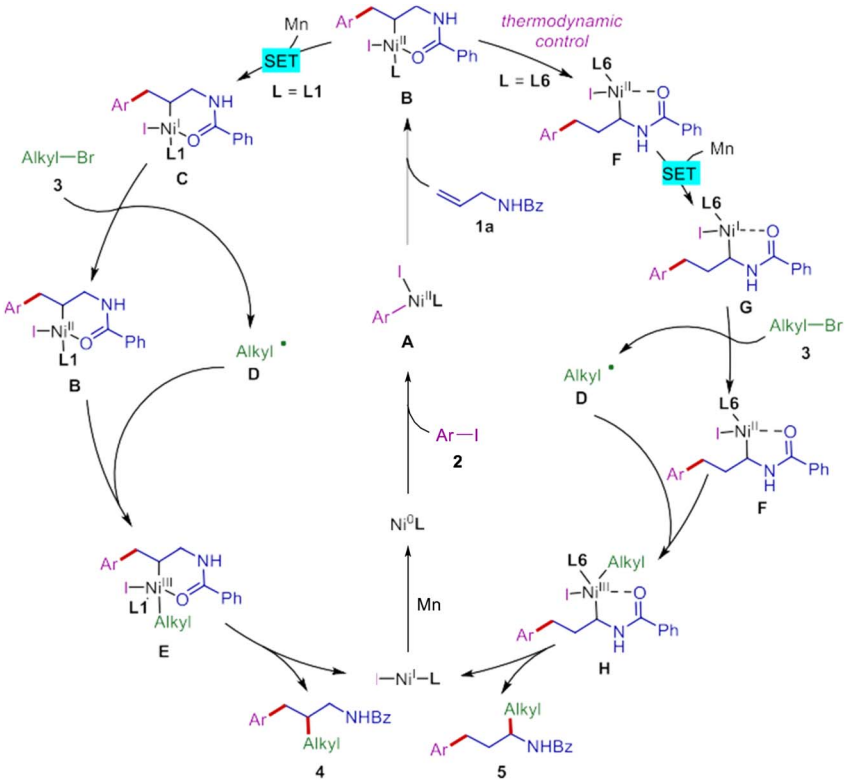


Fig. 4 Proposed mechanism for the reaction.

Ni^{I}**L1** intermediate **C** by single-electron transfer in the presence of Mn. Subsequently, alkyl bromides **3** are activated by Ni^{I}**L1** species (**C**) to give alkyl radicals **D** and Ni^{II}**L1** species **B**. Trapping of the alkyl radicals **D** with Ni^{II}**L1** (**B**) leads to the formation of Ni^{III}**L1** species **E**. **E** would undergo reductive elimination to give 1,2-arylalkylation products **4** along with Ni^{I} species, which could be reduced by Mn to regenerate Ni^{0}**L1** to close the catalytic cycle. Using **L6** as ligand, the ligated six-membered ring intermediate **B** undergoes β-H-elimination and insertion to form the five-membered intermediate **F**.[18] Similarly, Mn reduces **F** (Ni^{II}**L6**) to **G** (Ni^{I}**L6**), which interacts with alkyl bromides **3** to furnish alkyl radicals **D** and Ni^{II}**L6** species **F**. Recombination of **F** with alkyl radicals **D** generates Ni^{III}**L6** species **H**, which undergoes reductive elimination to deliver 1,3-arylalkylation products **5** and Ni^{I}**L6** species. Further reduction of Ni^{I}**L6** to Ni^{0}**L6** finishes the catalytic cycle.

Conclusions

In summary, a controllable Ni-catalyzed regioselective and site-divergent reductive arylalkylation of allylic amines has been developed for the first time. This work has established a protocol for simultaneous construction of C_{sp^3}–C_{sp^3} and C_{sp^3}–C_{sp^2} bonds over 1,2- and 1,3-positions of unactivated alkenes. In particular, the aryl group is selectively installed on the distal carbon of the olefin. This reaction proceeds under mild conditions and tolerates a broad range of functional groups as well as terminal and internal alkenes. The catalytically controlled 1,2- and 1,3-arylalkylations of allylic amines provide an ideal way to build diverse C(sp^3)-rich α- and β-branched aliphatic amines from identical starting materials.

Data availability

The data supporting this article have been included as part of the ESI.† Crystallographic data for **4af** (CCDC 2361506) and **5be** (CCDC 2361509) have been deposited at the Cambridge Crystallographic Data Centre.

Author contributions

W. S. conceived and directed the project. H. M. and P. F. Y. discovered and developed the reaction. H. M., Q. Y. and J. S. J. performed the experiments and collected the data. Q. Y. and Y. L. L. co-supervised the project. All authors discussed and analyzed the data. W. S., J. S. J. and H. M. wrote the manuscript with contribution from other authors.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

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