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RESEARCH ARTICLE

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Radical 1,4-Aryl Migration Enabled Remote Cross-Electrophile Coupling of α-Amino-β-Bromo Acid Esters with Aryl Bromides

Shi Tang,*[a] Zhen-Hua Xu,[a] Ting Liu,[a] Shuo-Wen Wang,[a] Jian Yu,[a] Jian Liu,[a] Yu Hong,[a] Shi-Lu Chen,[b] Jin He,[a] and Jin-Heng Li*[c]

Dedication ((optional))

[a] Prof. Dr. S. Tang, Z.-H. Xu, T. Liu, S.-W. Wang, J. Liu, Y. Hong, J. He
College of Chemistry and Chemical Engineering
Jishou University
Jishou 416000, China.
E-mail: stang@jsu.edu.cn
[b] Prof. Dr. S.-L. Chen
Key Laboratory of Cluster Science of Ministry of Education
Beijing Institute of Technology
Beijing 100081, China.
[c] Prof. Dr. J.-H. Li
Key Laboratory of Jiangxi Province for Persistent Pollutants Control and Resources Recycle
Nanchang Hangkong University
Nanchang 330063, China
State Key Laboratory of Chemo/Biosensing and Chemometrics
Hunan University
Changsha 410082, China.
E-mail: jhli@hnu.edu.cn

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Abstract: Herein, we report an unprecedented, efficient nickel-catalysed radical relay for the remote cross-electrophile coupling of β-bromo-α-benzylamino acid esters with aryl bromides *via* 1,4-aryl migration/arylation cascades. β-Bromo-α-benzylamino acid esters are considered as unique molecular scaffolds allowing for the aryl migration reactions, which are conceptually novel variants for the radical Truce–Smiles rearrangement. This reaction enables the formation of two new C(sp^3)-C(sp^2) bonds using a bench-stable Ni/bipyridine/Zn system featuring a broad substrate scope and excellent diastereoselectivity, which provides an effective platform for the remote aryl group migration and arylation of amino acid esters *via* redox-neutral C(sp^3)-C(sp^2) bond cleavage. Mechanistically, this cascade reaction is accomplished by combining two powerful catalytic cycles consisting of a cross-electrophile coupling and radical 1,4-aryl migration through the generation of C(sp^3)-centred radical intermediates from the homolysis of C(sp^3)-Br bonds and the switching of the transient alkyl radical into a robust α-aminoalkyl radical.

Introduction

Over the past few decades, cross-coupling chemistry has emerged as a powerful technology for the efficient construction of carbon–carbon bonds.[1] As an alternative to classic cross-coupling reactions, reductive cross-coupling represents a valuable strategy, wherein two bench-stable and easily accessible electrophiles (often alkyl or aryl halides) can be coupled in the presence of an external reductant (such as Zn and Mn). This strategy circumvents the preparation and handling of organometallic reagents that have limited stability and commercial availability, thus making the strategy considerably important for synthetic chemists.[2] Consequently, the construction of C(sp^2)–C(sp^3) bonds via the cross-coupling of two (pseudo)halide partners has recently received considerable research attention,[3] and progress in this research field has been achieved through the use of the earth-abundant nickel catalyst.[4]

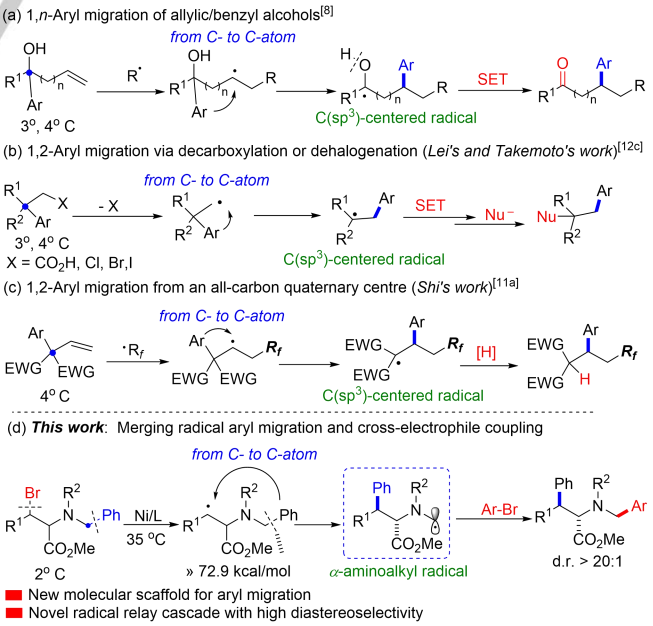


Figure 1. Radical 1,*n*-aryl migration from carbon atom to carbon atom via the C(sp^3)-centred radical intermediate.

reactions commonly occurs at a specific reactive functional group (such as Cl, Br, I and OTf) preinstalled on the two coupling partners. Accordingly, a complementary technique that facilitates the formation of a new C−C bond at a remote, unfunctionalised site in the starting materials is still in high demand in chemistry, which will allow straightforward access to some novel motifs that would otherwise be difficult to prepare (such as "chain-walking" cross-coupling).[5]

The radical Smiles-type rearrangement is an aryl migration strategy that usually involves the homolysis of C-X (X = S, N, O, etc.) bonds to form robust C- and X-centred radicals;[6] this is an effective strategy for the synthesis of substituted aromatic structural motifs with difficult-to-construct connectivity otherwise.[7] This rearrangement is widely utilised for the reorganisation of the carbon skeleton of various molecular scaffolds such as allylic/benzyl alcohols[8], sulfonylamides[9], vinylboronate complexes[10] as well as less common, but still established, functionalised aliphatic/aryl amines[6b,11] and others[12]. By analysing the mechanism of these reactions,[8-12] it was found that the C(sp^3)-centred radical intermediate is frequently formed in an array of radical aryl migration reactions. Inspired by the well-established cross-electrophile coupling reactions,[2,3] we propose that the readily formed C(sp^3)-centred radical arising from the aryl migration process could be directly funnelled into a subsequent catalytic cycle (i.e. nickel-catalysed cross-coupling with aryl halides), thereby offering the possibility of a remote cross-coupling leading to the formation of a new C(sp^3)–C(sp^2) bond. However, a strategy that combines radical aryl migration and cross-coupling reactions in a radical cascade poses a significant challenge and remains unexplored to date. In general, the as-formed C(sp^3)-centred radical in these previously reported 1,*n*-aryl migration reactions (e.g. from C to C atom) are terminated by a common process, such as single-electron transfer (SET) oxidation (Figure 1a),[8] SET oxidation followed by nucleophilic substitution (Figure 1b),[8l,12c], and hydrogen atom transfer (HAT) (Figure 1c).[11a] Herein, we disclose the first cascade Smiles rearrangement and cross-electrophile coupling using a Ni-catalysed radical relay strategy, which leads to the distal trans-arylation of *N*-benzyl amino acid esters via redox-neutral C-C bond cleavage at the 2°-C atom site (Figure 1d).

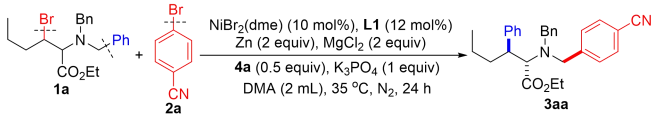
Amino acids are important building blocks for bioactive molecules and are extensively employed in many fields, such as medicinal chemistry, process chemistry, and materials science.[13] In this context, cross-coupling technology is a valuable approach to the site-selective functionalisation of amino acid scaffolds, and substantial progress has been achieved by employing conventional Negishi[14] and Suzuki–Miyaura[15] coupling reactions, reductive cross-coupling reactions[16], and C-H functionalisation[17]. Despite the aforementioned success, continued expansion of the cross-coupling technology in this regard will provide a new platform for the late-stage modification of amino acids and their derivatives. Considering this background in mind, we sought to explore the chemistry of radical aryl migration and cross-electrophile coupling in a radical cascade using readily accessible *β*-bromo-substituted amino acid esters as precursors. In the presence of bench-stable $NiCl_2$(dme)/4,4'-dimethoxy-2,2'-bipyridine/Zn, the nascent α-aminoalkyl radical formed via C→C aryl migration with concomitant C(sp^2)–C(sp^3) bond cleavage via intramolecular radical *ipso*-substitution, which is a frequently encountered and robust radical cross-coupling partner,[18] smoothly undergoes further radical–metal crossover reactions with Ar-Ni^{II}L-Br complexes to form a new C(sp^2)–C(sp^3) bond. Remarkably, this process might represent a new mode of aryl radical Smiles-type rearrangement, and *N*-benzyl amino acid esters were unprecedentedly disclosed as a molecular skeleton for radical rearrangement chemistry.[19] In addition, this cascade reaction has the advantages of involving redox-neutral conditions, mild reaction conditions (35 °C) and having broad substrate scope and good diastereoselectivity (dr > 20:1). Compared to the typical stepwise synthesis of phenylalanine derivatives via *N*-benzylation followed by Ni-catalysed direct arylation of the C(sp^3)–Br bond,[13-15] our method undoubtedly has numerous positive characteristics such as the formation of two new C–C bonds in one reaction step, mild reaction conditions, excellent regioselectivity (dr), and rapid entry to interesting motifs with asymmetric tertiary amine moieties.[20,21]

Results and Discussion

We investigated the optimal conditions for the cascade Smiles rearrangement/cross-coupling reaction of ethyl 3-bromo-2-(dibenzylamino) hexanoate **1a** and 4-bromobenzonitrile **2a** as model substrates (Table 1). After extensive investigation of the reaction parameters (see SI for details), we found that the remote coupling product (**3aa**) was obtained in 71% yield when $NiBr_2$(dme) (10 mol%), 4,4'-dimethoxy-2,2'-bipyridine **L1** (12 mol%), and zinc powder (2 equiv.) were used as the catalyst, ligand, and reductant, respectively, in the presence of $MgCl_2$ (2 equiv.) and melamine (0.5 equiv.). In contrast, almost no regioselective isomer (**3aa'**) formed via the direct coupling of the two pre-halogenated sites was detected through GC–MS. The exact configuration of the as-obtained product (**3aa**) was unambiguously confirmed by X-ray crystallography (see SI for details).[22] The addition of $MgCl_2$ appears to be important for this cascade reaction, wherein the yield decreased noticeably in the absence of this reagent (entry 2), which is consistent with the fact that $MgCl_2$ accelerates the reduction of Ni^{II} complexes by Zn.[23] When investigating the efficiency of other *N* ligands, such as bidentate ligands **L2**–**L8**, **L12-15**, tridentate ligands **L9**–**L10**, and carbene ligand **L11**, 4,4'-dimethoxy-2,2'-bipyridine **L1** exhibited the optimal performance (entries 4-17; Table S1; Supporting Information). In addition, other readily accessible nickel(II) sources, including $NiCl_2$(dme), NiI_2, and $Ni(acac)_2$, failed to afford better yields (entries 3–5). Pyridine-derived additives seem to be important for the Smiles rearrangement/cross-coupling sequence, and melamine **4a** bearing a 1,3,5-triamino-substituted motif showed the highest efficiency compared to the additives studied, such as 3-fluoropyridine and 3-aminopyridine (entries 6–8). In the control experiments, the migratory coupling reactions were observed to be significantly suppressed with the removal of **L1** or **4a** (entries 9 and 10), whereas **4a** could prefer to function as a labile ligand,[24] according to its catalytic efficiency.

With the optimized conditions in hand, the scope of the aryl bromides used in this radical cascade reaction was examined (Table 2). To our delight, the coupling reactions of **1a** with an array of activated aryl bromides, including 4-bromobenzonitrile,1-(4-bromophenyl)ethenone and ethyl 4-bromobenzoate, proceeded smoothly, leading to the formation of the corresponding remote coupling products in moderate to good yields and at dr of >20:1. This set of reactions also exhibited excellent regioselectivity toward the remote coupling

Table 1. Screening of optimal reaction conditions[a]



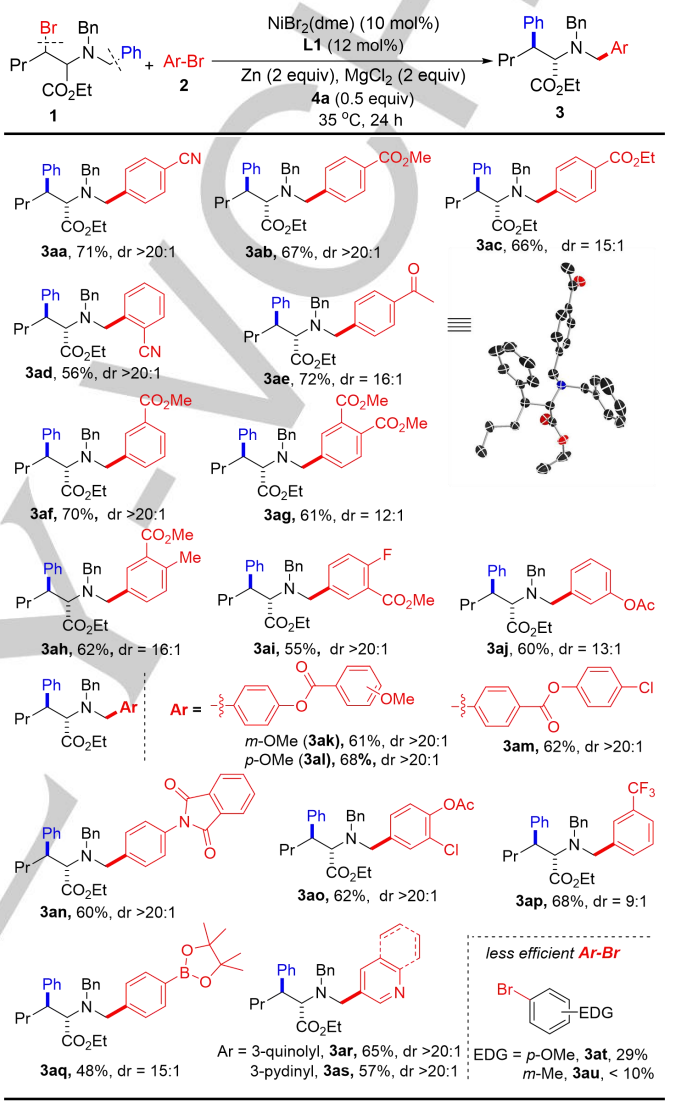
Entry	Variation from the Standard Conditions	Yield [%][b]
1	none	76 (71; >20:1 dr)[c]
2	without $MgCl_2$	32
3	$NiCl_2$(dme) instead of $NiBr_2$(dme)	62
4	NiI_2 instead of $NiBr_2$(dme)	47
5	$Ni(acac)_2$ instead of $NiBr_2$(dme)	33
6	Py instead of **4a**	52
7	**4b** instead of **4a**	57
8	**4e** instead of **4a**	25
9	without **L1**	<10
10	without **4a**	49

[a] Standard conditions: 4-Bromobenzonitrile **2a** (0.2 mmol), **1a** (1.5 equiv.), $NiBr_2$(dme) (10 mol%), **L1** (12 mol%), Zn (2 equiv.), $MgCl_2$ (2 equiv.), melamine **4a** (0.5 equiv.), K_3PO_4 (1 equiv.), and DMA (2 mL) at 35 °C under N_2 atmosphere for 24 h. [b] Yields were determined by GC using an internal standard and the isolated yield reported in the parentheses. DMA = dimethyl acetamide; Py = pyridine. [c] The diastereomeric ratio (dr) was determined by ^{1}H NMR analysis.

products (**3aa**–**3ai**). Sterically hindered 2-bromobenzonitrile was also shown to be a viable coupling partner in this cascade reaction, albeit with a slightly lower yield (**3ad**). Moreover, the configuration of **3ae** was unambiguously confirmed through X-ray crystallography.[22] In addition, unactivated aryl bromides such as phenolic ester and aniline derivatives were well tolerated in this cascade reaction (**3ak**–**3an**), while halogen functional groups (e.g., Cl, F, and CF_3) remained intact during the cascade reaction (**3am**, **3ao**, and **3ap**). The synthetically interesting Bpin substituent was also compatible with the optimal reaction conditions, thereby allowing the introduction of some functional groups via a further cross-coupling reaction (**3aq**). The cascade process also provides successful results for *N*-heterocyclic motifs, such as quinoline and pyridine, which are in high demand in medicinal chemistry (**3ar** and **3as**). Additionally, this migratory coupling reactions were observed to be less efficient for some electron-rich aryl bromides such as *p*-BrC_6H_4OMe and *m*-BrC_6H_4Me, possibly owing to the drawback that it is sluggish for Ni complex to add onto the inert C(sp^2)-Br bond (**3at** and **3au**). Overall, **1a** was found to be a robust starting material for the sequential Smiles rearrangement and cross-electrophile coupling reaction, affording good yields with excellent diastereoselectivity (usually dr > 20:1).

Subsequently, we investigated the compatibility of structurally diverse *N*-benzyl amino acid esters under the optimal reaction conditions (Table 3). A series of R^1 substituents on this coupling partner (**1**), such as *n*-Pr, Et, *i*-Pr, $PhCH_2CH_2$, cyclohexyl, and H, were well tolerated under the optimal reaction conditions and afforded their corresponding remote coupling products (**3av**–**3bc**) with excellent diastereoselectivity (dr > 20:1). Notably, serine primary bromides (R^1 = H) also appeared to be compatible with the optimal reaction conditions leading to the phenylalanine derivative (**3bd**) *via* the tandem radical rearrangement/cross-coupling reaction.[3c] Changing the ester moiety from ethyl to methyl did not affect the reaction outcome (**3be**–**3bg**). The exact configuration of **3bg** was unambiguously confirmed through X-ray crystallography.[22] Subsequently, we examined the compatibility of other *N*-benzyl groups in this remote cross-coupling reaction and a variety of amino acid esters bearing symmetric benzyl groups on the *N*-atom, including *p*-(*t*-Bu)$C_6H_4CH_2$, *p*-$CH_3C_6H_4CH_2$, and *p*/*m*-$ClC_6H_4CH_2$, were observed to undergo the migration process, thereby leading to the formation of **3bh**–**3bo** in good yield. Subsequently, we investigated the aryl migratory ability of different benzyl groups tethered to the *N atom* (Scheme 2). Minimally differentiated benzyl and 4-methylbenzyl groups on the *N* atom were initially examined, and both phenyl and 4-methylphenyl served as migrating groups, but the relatively more electron-rich 4-methylphenyl group was preferred, resulting in a regioselective

Table 2. Variation of aryl bromides (**2**)[a]



[a] Reaction conditions: **1a** (1.5 equiv.), **2a** (0.3 mmol), $NiBr_2$(dme) (10 mol%), **L1** (12 mol%), Zn (2 equiv.), $MgCl_2$ (2 equiv.), **4a** (0.5 equiv.), K_3PO_4 (1 equiv.), and DMA (2 mL) at 30 °C under N_2 atmosphere for 24 h; isolated yield. The diastereomeric ratio (dr) was determined by ^{1}H NMR and/or ^{19}F NMR analysis.

ratio (rr) of 2:1 (**3bp**). Another pair comprising 4-*tert*-butylbenzyl with benzyl groups showed similar selectivity to yield the diarylation product (**3bq**) with 66% yield and rr = 4:1. Moreover, electronically biased arenes, such as pairs of Ph/*p*-FC_6H_5 or *t*-BuC_6H_4/*p*-FC_6H_5, demonstrate specific migratory abilities to afford the trans-arylation of the electron-rich aromatic ring (**3br–3bu**). Notably, the amino acid ester bromides with an alkyl or hydrogen on the *N* atom seem to be unstable and difficult to prepare efficiently; therefore, we used the corresponding mesylate instead of bromide to investigate the effect of the *N* substituent on the amino acid ester in the radical rearrangement. Unfortunately, the results demonstrate that amino acid esters with H or Me on the *N* atom are inefficient substrates in this radical cascade reaction. Thus, substrates bearing a dibenzyl-substituted *N*-atom moiety are critical for sequential migration and cross-coupling processes.

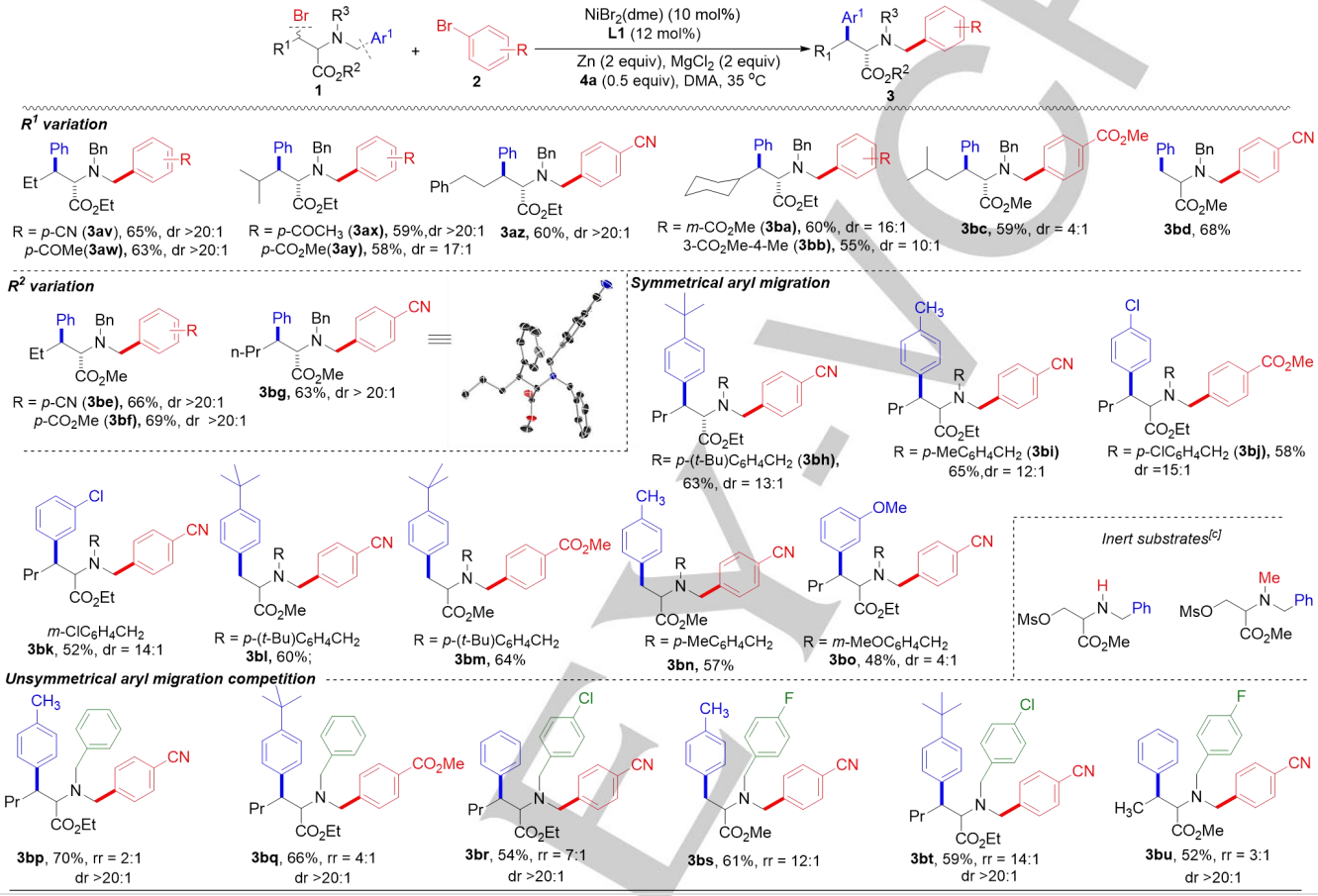
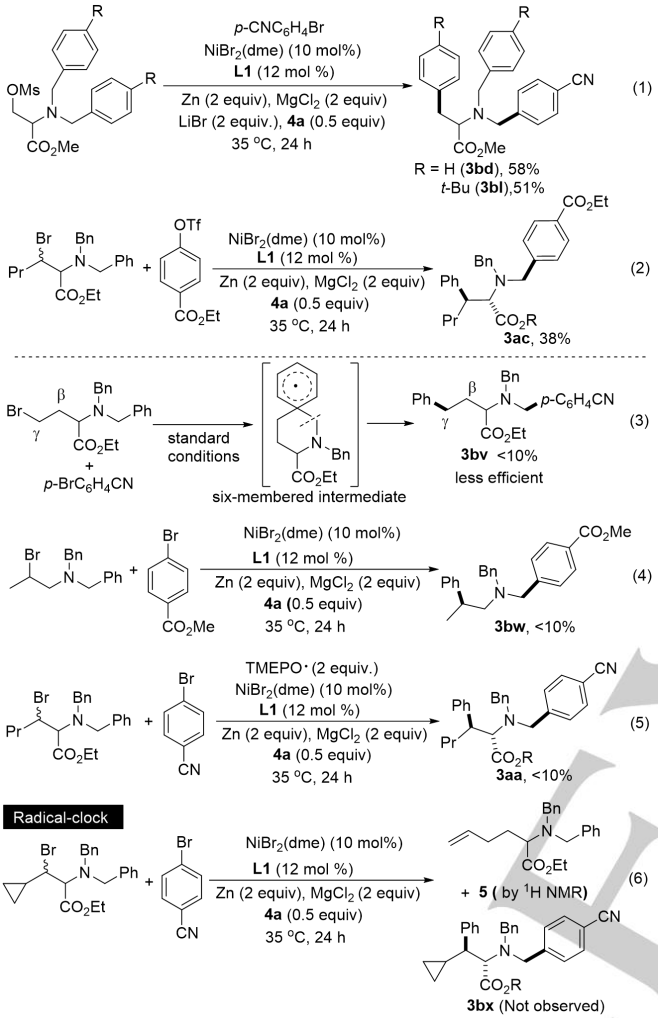


Table 3. Scope of the *α*-amino-*β*-bromo acid esters.[a,b] [a] Reaction conditions: **2a** (0.3 mmol), **1a** (1.5 equiv.), $NiBr_2$(dme) (10 mol%), **L1** (12 mol%), Zn (2 equiv.), $MgCl_2$ (2 equiv.), **4a** (0.5 equiv.), K_3PO_4 (1 equiv.), and DMA (2 mL) at 35 °C under N_2 atmosphere for 24 h; isolated yield. [b] The diastereoselective ratio (dr) and regioselective ratio (rr) were determined by ^{1}H NMR and/or ^{19}F NMR analysis. [c] In these reactions, 2.0 equiv. of LiBr was added.

Considering their ready availability from inexpensive serine derivatives, we next investigated the compatibility of serine mesylates instead of serine bromides under the reaction conditions. After brief screening, we found that serine mesylate with 4-bromobenzonitrile in the presence of LiBr (2 equiv.) underwent sequential radical rearrangement and cross-coupling to yield the desired products in moderate yields [Eq. (1), Scheme 1]. In addition, aryl trifluoromethanesulfonate (*p*-$EtO_2CC_6H_4OTf$) was also a viable coupling partner, albeit with a lower product yield [Eq. (2)]. Based on our investigation about the cascade migration/cross-coupling of amino acid esters, we found that 1,4-FGM (FGM = functional group migration) was beneficial in the kinetically favoured five-membered cyclic transition state, whereas 1,5-FGM using a *γ*-bromo amino acid ester *via* a six-membered cyclic transition state appeared to be less effective [Eq. (3)]. In addition, a *β*-bromo alkyl amine upon the removal of the α-ester group, independent of the amino acid ester bromide, underwent a radical cascade reaction with low efficiency, which can be attributed to the increasing torsional strain triggered by the adjacent ester substituent in the five-membered cyclic transition state and was beneficial for breaking the cyclic transition state to initiate migration [Eq. (4)]. We investigated the use of a radical scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO). As expected, the migratory coupling process was significantly suppressed, suggesting the involvement of a radical-mediated process in the reaction [Eq. (5)]. In addition, a standard radical clock cyclopropane substrate was subjected to the optimal reaction conditions, and no expected *β*-arylation amino acid ester (**3bv**) was observed. However, the formation of **5** was observed through ^{1}H NMR analysis via a radical cyclopropane ring-opening reaction [Eq. (6)], which clearly indicates that the alkyl radical formed via dehalogenation by Ni likely triggered the sequential migration/cross-coupling reaction.[25]

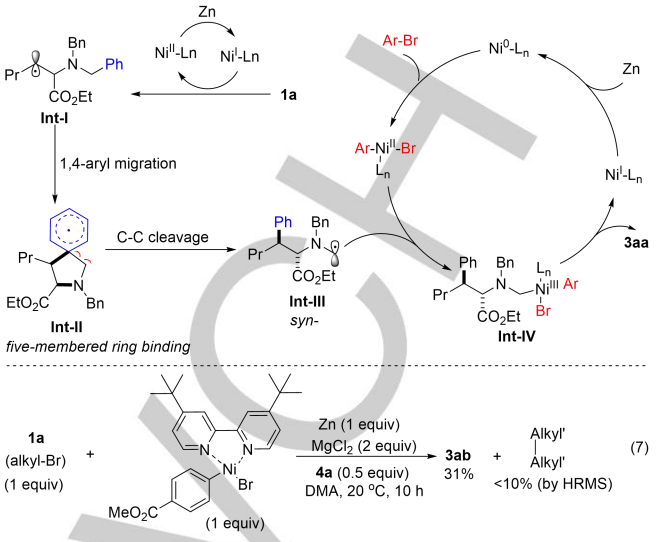
Based on the aforementioned experimental results and previously reported mechanisms[2-17], a possible mechanism for the cascade reaction was proposed, as shown in Scheme 2. $Ni^{II}X_2$(dme) is reduced to a Ni^{I}-Ln species *via* a single-electron

reduction process with Zn powder in the presence of the *N* ligand, which is then oxidatively treated with amino acid ester bromide (**1a**) to yield the alkyl radical (**Int-I**) and a Ni^{II}-Ln complex *via* a single-electron transfer process. A C→C atom aryl migration with concomitant $C(sp^2)$-$C(sp^3)$ bond homolytic cleavage (with a bond dissociation energy of 72.9 kcal/mol) via a



Scheme 1. Application investigation and control experiments used to determine the reaction mechanism.

spiro radical σ-complex (**Int-II**) then occurs,[11] generating an α-aminoalkyl radical (**Int-III**), which is stabilised by the p-p conjugation effect with its adjacent electron-rich *N* atom. Because of the binding effect of the inflexible five-membered ring, the syn-configuration of the α-aminoalkyl radical is favoured, which is consistent with the fact that this coupling reaction typically exhibits high diastereoselectivity (*syn/trans* > 20:1). In the cross-coupling catalytic cycle, $Ni^{II}Br_2$(dme) is first reduced to a Ni^0 species via a two-electron reduction with Zn, which then undergoes oxidative addition to the aryl bromide to produce an $ArNi^{II}Br$ complex. Subsequently, the α-aminoalkyl radical (**Int-III**) generated via 1,4-aryl migration adds to $ArNi^{II}Br$ to form a Ni^{III} complex (**Int-IV**). Finally, the Ni^{III} complex undergoes reductive elimination to give the desired product (**3aa**) and the Ni^{I}-Ln complex, which is then directly involved in the next catalytic cycle or reduced to Ni^0-Ln species by Zn powder.



Scheme 2. Possible mechanism for the Smiles rearrangement and cross-coupling reaction.

The exposure of the Ar-Ni^{II}(Ln)Br complex to **1a** gave the corresponding coupling product (**3ab**) in 31% yield (Eq. 7). This result provides evidence for the oxidative capture of the α-aminoalkyl radical (**Int-III**) by a Ni complex, Ar-Ni^{II}-X.[26] In addition, the formation of the alkyl-alkyl dimerisation products, as an isomeric mixture of the homo/cross-dimerisation of radicals **Int-III** and **Int-1** possibly, was observed to form by HRMS, which gives substantial proof for the proposed mechanism wherein the radical 1,4-aryl migration process was possibly involved.

Next, unrestricted density functional theory (DFT) calculations with the hybrid functional B3LYP implemented in the Gaussian 09 package were conducted to further understand the key 1,4-aryl migration process from **Int-I** to **Int-III** (Figure 2; see SI for details).[27] Our computational studies revealed that the radical moiety in the **Int-I** intermediate was localised on the alkyl C atom. From **Int-I**, a transition state (TS1, Figure 2a) for its intramolecular *ipso* attack on the distal phenyl ring to form the key intermediate σ-complex (**Int-II**) via dearomatisation was found and confirmed through frequency analysis to be a first-order saddle point with an imaginary frequency of 458.4 cm^{-1}. In TS1, the key C_a-C_b distance was 2.11 Å. This step leads to the formation of a spiro five-membered *N*-heterocycle connected to a benzene radical (**Int-II**). The free energy barrier was calculated to be 14.7 kcal/mol with a low endothermicity of 4.2 kcal/mol. The spiro *N*-heterocycle complex (**Int-II**) readily breaks *via* a transition state involving sequential C–C bond homolytic dissociation and rearomatisation (TS2, Figure 2b), yielding the α-aminoalkyl radical (**Int-III**). The barrier of this step is 17.1 kcal/mol relative to **Int-I**. The free energy of resultant **Int-III** lies 3.5 kcal/mol higher than that of **Int- I**, and **Int-III** is proposed to react with the $ArNi^{II}Br$ complex to generate the final cross-coupling product. These results indicate that the mechanism shown in Scheme 2 is reasonable.

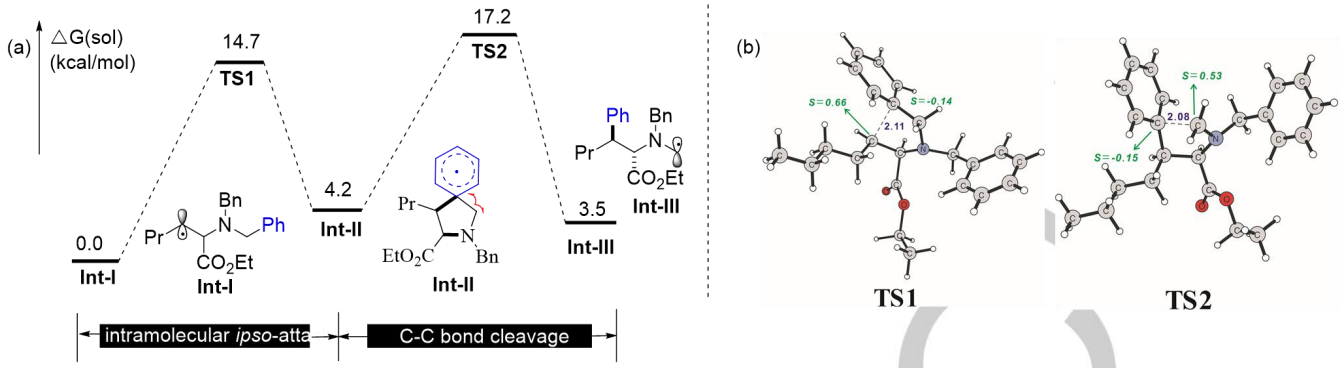


Figure 2. (a) Free energy profile for the mechanism from **Int-1** to **Int-III**; (b) Transition states optimised using density functional calculations. The distances are reported in angstrom (Å). The unpaired spin populations are also shown, indicated by "S".

Conclusions

In summary, we have discovered a new molecular scaffold (i.e., *N*-benzyl amino acid ester) that enables sequential aryl migration and cross-coupling reactions through a Ni-catalysed radical relay for the first time. Mechanistically, the radical cascade reaction was achieved by combining two powerful catalytic cycles consisting of an aryl radical rearrangement and cross-electrophile coupling reaction via a C(sp^3)-centred radical intermediate, wherein an umpolung strategy for switching the transient alkyl radical into a robust α-aminoalkyl radical via 1,4-aryl migration from C to C atom was demonstrated, which serves as a mild, efficient strategy for the synthesis of unnatural or natural phenylalanine and their derivatives as well as versatile tertiary aliphatic amines. Likewise, this synthetic strategy affords an elusive entry to the late-stage functionalisation of amino acid esters via redox-neutral C(sp^3)–C(sp^2) bond cleavage through Ni catalysis, representing an interesting complement to both the radical rearrangement and cross-electrophile coupling reactions in the synthetic community.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: radical aryl migration, cross-electrophile coupling, nickel radical relay, amino acid esters

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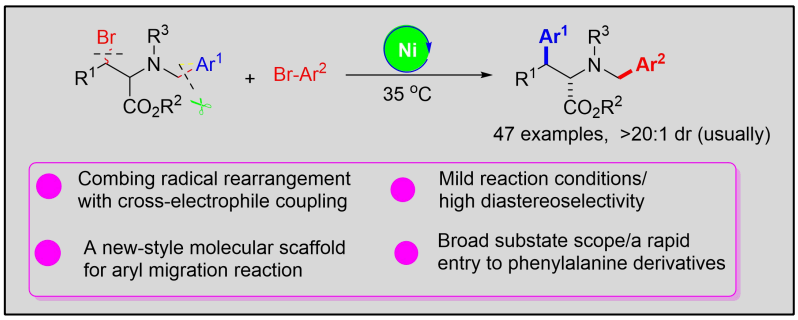

A nickel-catalysed radical relay strategy has been developed to combine radical rearrangement and cross-coupling reaction via a C($_{sp3}$)-centred radical, wherein an *N*-benzyl amino acid ester was also discovered as a new molecular scaffold for the aryl migration reaction. This synthetic method is advantageous because of mild reaction conditions, high diastereoselectivity, and broad substrate scope; therefore, it represents a rapid approach to valuable phenylalanine derivatives that would otherwise be difficult to prepare.