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Rapid access to *t*-butylalkylated olefins enabled by Ni-catalyzed intermolecular regio- and *trans*-selective cross-electrophile *t*-butylalkylation of alkynes†

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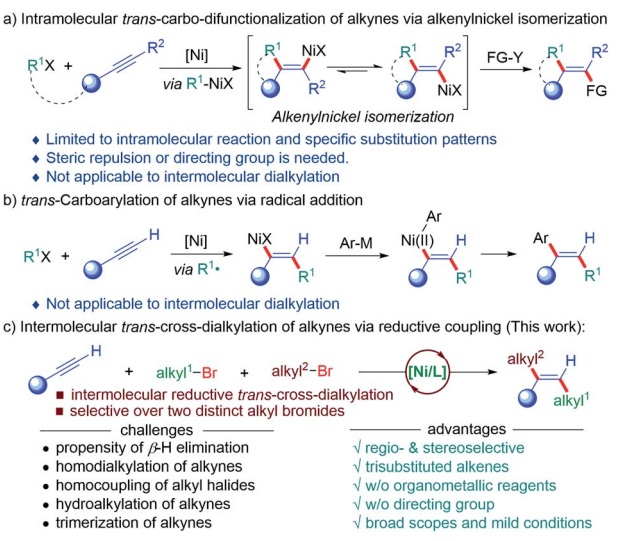
Among the carbo-difunctionalization of alkynes, the stereoselective dialkylation of alkynes is the most challenging transformation due to associated competitive side reactions and thus remains underdeveloped. Herein, we report the first Ni-catalyzed regio- and *trans*-selective cross-dialkylation of alkynes with two distinct alkyl bromides to afford olefins with two aliphatic substituents. The reductive conditions circumvent the use of organometallic reagents, enabling the cross-dialkylation process to occur at room temperature from two different alkyl bromides. This operationally simple protocol provides a straightforward and practical access to a wide range of stereodefined dialkylated olefins with broad functional group tolerance from easily available starting materials.

Introduction

Multi-alkyl substituted olefins with defined stereochemistry are ubiquitous subunits in natural products, bioactive molecules and conjugated organic materials,[1] and also serve as important precursors for other functional groups due to their orthogonal reactivity with respect to carbonyls and other polar functional groups.[2] Although numerous methods to construct olefins have been well-established, the stereoselective synthesis of multi-substituted olefins, particularly multialkyl-substituted ones, remains an unmet challenge.[3] Over the past decades, the carbo-difunctionalization of alkynes represents one of the most step-economic and efficient ways to construct multi-substituted olefins as they selectively forge two carbon–carbon bonds and build up molecular complexity from simple starting materials in one single step.[4] Among these, the Ni-catalyzed *cis*-selective carbo-difunctionalization of alkynes has been extensively explored using different strategies, such as the carbonickelation of alkynes,[5] migratory insertion of alkynes into the nickelacycle intermediates,[6] cyclonickelation of alkynes with unsaturated systems,[7] and olefin isomerization by photo-redox/nickel dual catalysis.[8] On the contrary, the Ni-catalyzed *trans*-selective carbo-difunctionalization of alkynes is still nontrivial.[4] One strategy for the trans-selective carbo-difunctionalization of alkynes relies on the *Z*/*E* isomerization of the key alkenylnickel intermediates from the carbo-metallation of alkynes to form thermodynamically more stable alkenylnickel species (Scheme 1a). Arai,[9] Martin and Montgomery[10] developed the Ni-catalyzed *trans*-selective difunctionalization of alkynes, in which the *E*/*Z* isomerization of alkenylnickel species was dominated by the steric hindrance of substrates. Moreover, Liu,[11] Lam,[12] Kong[13] and others[14] disclosed a *Z*/*E* isomerization driven by the formation of chelation in the *E*-alkenyl-nickel species facilitated by a tethered chelation in the substrate to deliver the *trans*-alkylarylation of alkynes. Unfortunately, this strategy could



Scheme 1 Ni-catalyzed *trans*-selective carbo-difunctionalization of alkynes.

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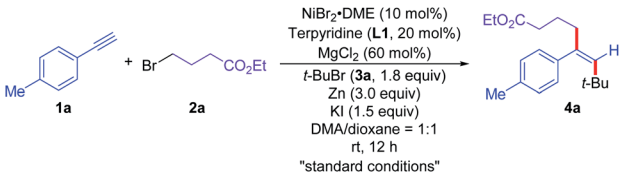
not be applied to intermolecular three-component reactions. The other strategy is the Ni-initiated *trans*-radical addition onto alkynes, followed by a Ni-catalyzed coupling with organometallic reagents (Scheme 1b). Kambe developed a Ni-catalyzed regioselective alkylarylation of alkynes using alkyl iodides and aryl metallic reagents (M = Mg, Zn).[15] Using a similar strategy, Nevado *et al.* disclosed an Ni-catalyzed intermolecular three-component coupling reaction of terminal alkynes with alkyl halides and arylboronic acids (M = B) for the *trans*-selective synthesis of 1,1-bisarylolefins.[16] This approach provides a valuable platform to install C(sp^3)-components onto alkynes with defined regio- and stereoselectivity. To date, the above-mentioned two strategies are still not able to access the *trans*-dialkylation of alkynes due to associated challenges, such as β-hydrogen elimination of alkylnickel intermediates, homocoupling of alkyl precursors, and hydroalkylation of alkynes (Scheme 1c).[17] Moreover, the regio- and stereoselectivity issues of intermolecular reactions impose an additional challenge for the dialkylation of alkynes. To this end, the use of two distinct alkyl electrophiles to sequentially couple across alkynes under reductive conditions renders an appealing alternative to access multialkylated olefins with defined stereochemistry.[18] As our continuous interest in earth-abundant metal-catalyzed reductive selective transformations,[19] we herein report the Ni-catalyzed radical addition of one alkyl bromide onto alkynes, followed by a Ni-catalyzed coupling with another alkyl halide to afford the dialkylation of alkynes with exquisite *trans*-selectivity under reductive conditions (Scheme 1d). This three-component reaction enables the sequential installation of two distinct alkyl bromides onto alkynes, allowing for the regio- and diastereoselective dialkylation of alkynes without the use of organometallic reagents at room temperature.

Results and discussion

To test the feasibility of this proposal, we commenced the dialkylation reaction of alkynes using alkyne (**1a**), ethyl 4-bromobutanate (**2a**), and *tert*-butyl bromide (**3a**) as the prototype substrates under reductive conditions. After the evaluation of a wide range of parameters, the use of $NiBr_2$·DME (10 mol%), terpyridine (**L1**, 20 mol%), $MgCl_2$ (60 mol%), zinc (3.0 equiv.), potassium iodide (1.5 equiv.) in the mixture of *N*,*N*-dimethylacetamide (DMA) and 1,4-dioxane (1 : 1) at room temperature was defined as standard conditions for the reaction, affording the cross-electrophile *trans*-cross-dialkylation product **4a** in 75% isolated yield (Table 1, entry 1). No desired product **4a** was detected in the absence of **L1**, while **4a** was formed in 53% yield with 10 mol% of **L1** (Table 1, entries 2 and 3). Other nickel-based precatalysts could also mediate the reaction to afford **4a**, albeit in lower efficiency (Table 1, entries 4–6). Replacing the reductant with manganese furnished comparable outcome, delivering **4a** in 74% yield (Table 1, entry 7). Both nickel catalyst and reductant are required for this reductive cross-dialkylation reaction. No desired reaction occurred in the absence of nickel catalyst or reductant (Table 1, entry 8). The use of potassium iodide significantly enhanced the reactivity of the cross-dialkylation reaction probably due to the slow halide exchange with the alkyl bromides (Table 1, entries 9 and 10). The reaction furnished **4a** in 71% yield without $MgCl_2$ (Table 1, entry 11).[20] The reaction delivered diminished yields in either DMA or 1,4-dioxane, affording the desired product **4a** in 68% and 25% yields, respectively (Table 1, entries 12 and 13).[21]

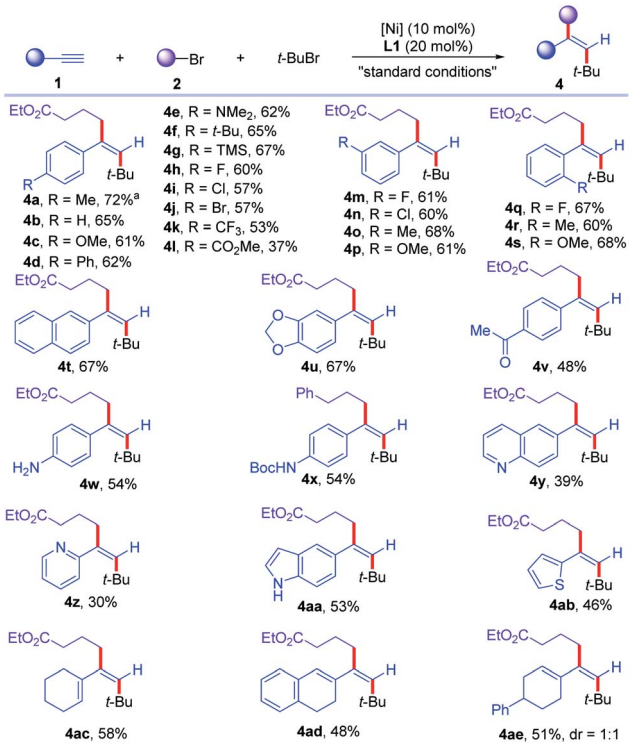
Table 1 Condition evaluation for the *trans*-cross-dialkylation of alkynes



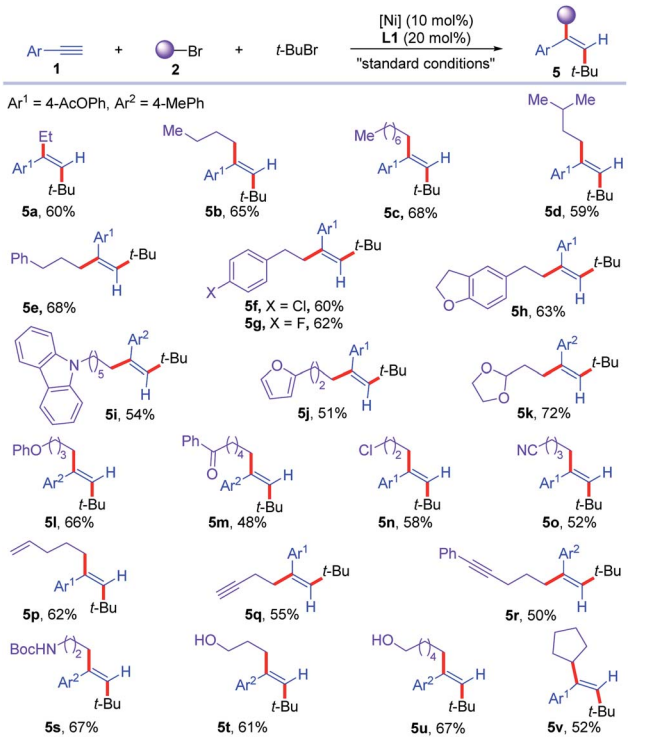
Entries	Variations from "standard conditions"	Yield of **4a**[a]
1	None	77% (75%)
2	w/o **L1**	N.R.
3	**L1** (10 mol%)	53%
4	$NiCl_2$·DME instead of $NiBr_2$·DME	73%
5	$NiBr_2$ instead of $NiBr_2$·DME	57%
6	NiI_2 instead of $NiBr_2$·DME	56%
7	Mn instead of Zn	74%
8	w/o "Ni" or Zn	N.R.
9	NaI instead of KI	49%
10	w/o KI	42%
11	w/o $MgCl_2$	71%
12	DMA as solvent	68%
13	1,4-Dioxane as solvent	25%

[a] The reaction was conducted using 0.2 mmol of **1a**, 0.6 mmol of **2a**, 0.36 mmol of **3a** in a mixture of DMA and 1,4-dioxane (1 : 1, 0.033 M) under indicated conditions for 24 h. N.R. = No reaction. **L1** = 2,2' : 6′,2″-terpyridine. Yield was determined by GC analysis using *n*-dodecane as internal standard. Isolated yield after flash chromatography is shown in the parentheses.

With the optimized conditions in hand, we turned to evaluate the scope of the reaction. First, the scope of alkynes (**1**) was examined (Scheme 2). Various aromatic alkynes with *para*-substituents were all good substrates for this transformation, affording the desired dialkylated olefins in moderate to good yields (**4b–4l**). Electron-donating groups, such as alkyl, dimethylamino, silyl groups (**4c–4g**) and electron-withdrawing (**4h–4l**) groups, such as halogens, trifluoromethyl, esters on aromatic rings were all well-tolerated. Aromatic alkynes with *meta*-substituents could be tolerated in the reaction, delivering the desired products (**4m–4p**) in 60–68% yields. In addition, more steric congested *ortho*-substituted aromatic alkynes could be transformed to corresponding olefins (**4q–4s**) in 60–68% yields. Multi-substituted aromatic alkynes were converted to trisubstituted olefins (**4t** and **4u**) in 67% yield. Moreover, this reaction conditions tolerated more sensitive functional groups. Acidic proton containing ketone was compatible in the reaction, affording corresponding ketone containing olefin (**4v**) in 48% yield. Free aniline and N–H containing amide were well-tolerated under the reaction conditions, furnishing corresponding olefins (**4w** and **4x**) in 54% yield. Heteroaromatic alkynes, such as quinoline, pyridine, indole, and thiophene,



Scheme 2 Scope for the cross-electrophile dialkylation of alkynes with respect to alkynes. For standard conditions, see Table 1. [a] The reaction was conducted on 2.0 mmol scale.



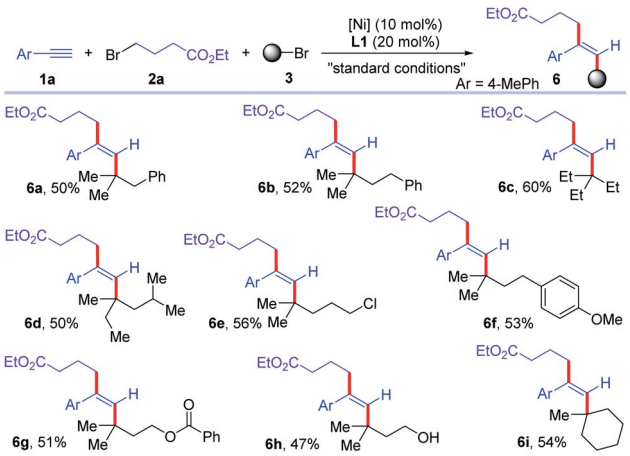
Scheme 3 Scope of alkyl bromides for the cross-electrophile dialkylation of alkynes with respect to first alkyl bromides. For standard conditions, see Table 1.

were all converted smoothly to corresponding heteroaryl dialkylated olefins (**4y–4ab**) in synthetic useful yields. Notably, various 1,3-enynes could be converted to deliver multi-substituted conjugated dienes (**4ac–4ae**) in 48–58% yields. Internal alkynes showed no reactivity to the desired reaction due to the increased steric hindrance for radical addition onto alkynes. Moreover, aliphatic alkynes proved unsuccessful for the reaction, partially due to the low stability and reactivity of resulting vinyl radical intermediates for Ni-catalyzed C_{sp^2}–C_{sp^3} cross-coupling reaction. Furthermore, the reaction could be scaled up to 2.0 mmol scale to deliver **4a** in 72% yield, without erasing the efficiency of this transformation.

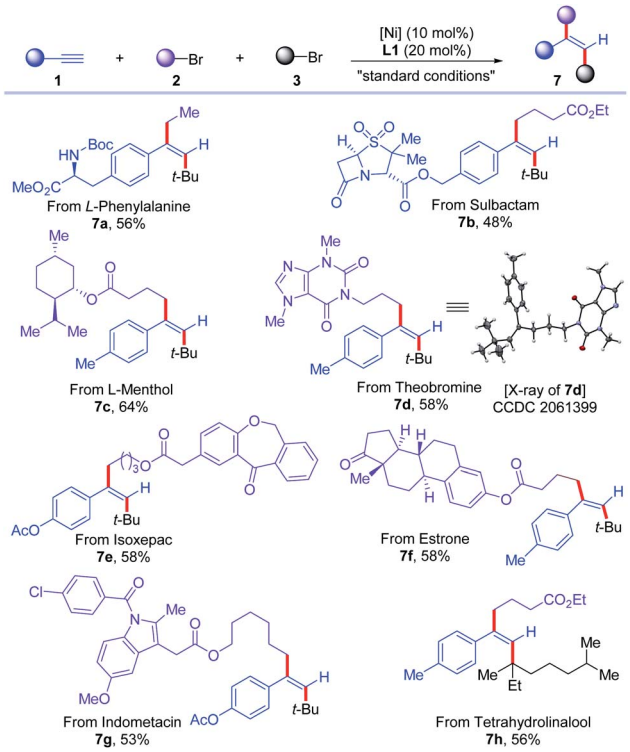
Next, the scope of the first component of alkyl bromides (**2**) was tested (Scheme 3). Unfunctionalized alkyl bromides with different alkyl chains were good substrates for the reaction, furnishing dialkylated olefins with different alkyl chains in 59–68% yields (**5a–5d**). Phenyl and diverse substituted aryl pendent alkyl bromides were transformed into corresponding olefins in 60–68% yields (**5e–5h**). Heteroaryl containing alkyl bromides were successfully converted to *trans*-dialkylated olefins (**5i** and **5j**) in 54% and 51% yields. Acetals, ethers, ketones, chlorides, and nitrile in alkyl bromides were tolerated in the reaction, affording corresponding olefins (**5k–5o**) in 48–72% yields. Moreover, unsaturated carbon–carbon bonds, such as terminal olefins, terminal and internal alkynes were all compatible in this reaction, undergoing chemoselective dialkylation reaction to furnish desired products (**5p–5r**) in 50–62% yields. Bromo-aliphatic amides and alcohols with free N–H and O–H were compatible under the reaction conditions, affording the desired amides or alcohols pendant dialkylated olefins (**5s–5u**) in 61–67% yields. In addition, secondary bromide was successfully involved in the reaction, delivering the corresponding *trans*-dialkylated olefin **5v** in 52% yield. Unfortunately, secondary and primary alkyl bromides failed to deliver the trisubstituted alkenes *via* a three-component cross-coupling reaction, partially due to the competitive cross coupling between two alkyl bromides.

Then, the scope of the other component of alkyl bromide was examined (Scheme 4). Various tertiary alkyl bromides were good substrates for this reductive *trans*-dialkylation reaction of alkynes. Tertiary alkyl bromides with different alkyl chain lengths were all good substrates for this cross-dialkylation reaction (**6a–6d**). Chloro, phenyl, ester, and alcohol were well-tolerated in the reaction, delivering corresponding functionalized *trans*-dialkylated olefins in moderate yields (**6e–6h**). Cyclic tertiary alkyl bromide was converted to corresponding olefin **6i** in 54% yield. Unfortunately, secondary alkyl bromides were unsuccessful to this reaction.

Next, the application of this protocol to the late-stage functionalization of complex molecules, including natural products and drug molecules, was demonstrated (Scheme 5). Alkynes based on *L*-phenylalanine and sulbactam were successfully converted to corresponding *trans*-dialkylated olefins (**7a** and **7b**) in 56% and 48% yields, respectively. Primary alkyl bromides from *L*-menthol, theobromine, isoxepac, estrone, and indometacin were all good substrates for this reaction, delivering



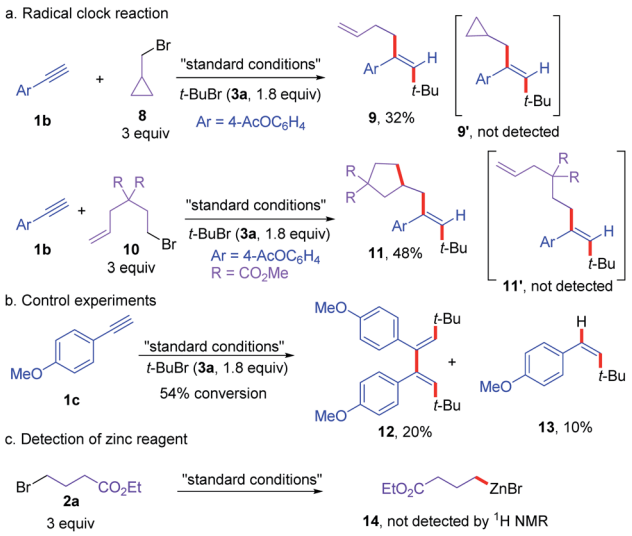
Scheme 4 Scope of alkyl bromides for the cross-electrophile dialkylation of alkynes with respect to tertiary alkyl bromides. For standard conditions, see Table 1.



Scheme 5 Application the cross-electrophile dialkylation of alkynes for complex molecules. For standard conditions, see Table 1.

corresponding *trans*-dialkylated olefins derived from various complex molecules (**7c**–**7g**) in 53–64% yields. Moreover, tetrahydrolinalool-derived tertiary alkyl bromide was successfully incorporated in the reaction to afford olefin **7h** in 56% yield. The configuration of the products was further confirmed unambiguously by the X-ray diffraction analysis of **7d**.

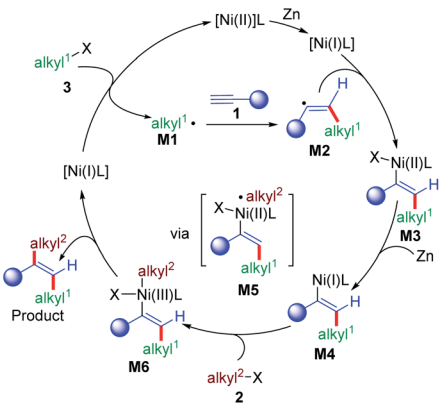
To gain some insights into the reaction mechanism, a series of control experiments were conducted (Scheme 6). First, the reaction of **1b** with **3a** and a radical clock substrate **8** under



Scheme 6 Mechanistic investigations and control experiments.

standard conditions did not deliver the regular coupling product **9′**, affording the ring opening three-component cross-coupling product **9** in 32% yield (Scheme 6a). Moreover, the reaction of olefin pendant alkyl bromide (**10**) with alkyne (**1b**) and *tert*-butyl bromide (**3a**) delivered the ring-closing three-component dialkylation product **11** in 48% yield, without the formation of **11′** (Scheme 6a). When the reaction of **1c** and **3a** was carried out without **2a**, the dimer (**12**) of vinyl radical from *tert*-butyl radical addition to alkyne along with the protonated product **13** were formed (Scheme 6b). In addition, the organozinc species was not detected under the standard conditions (Scheme 6c). These results indicated that the reaction proceeded *via* radical pathways and vinyl radical intermediates from the radical additional of *tert*-butyl radical to alkyne was involved.

Based on the mechanistic results and literature precedence,[16a,22] a plausible mechanism for this reaction is proposed in Scheme 7. First, Ni(II) was reduced to give Ni(I) in the presence of zinc, which could react with the first alkyl bromide (**3**) to give alkyl radical intermediate **M1** and Ni(II). **M1** was added to



Scheme 7 Proposed mechanism for the reaction.

an alkyne (**1**) to give a vinyl radical intermediate **M2** by the formation of a C_{sp^2}–C_{sp^3} bond, which could rebound with Ni(I) to generate the vinyl Ni(II) intermediate **M3.** The Ni(I)L approached **M2** to give **M3** in *trans*-selectivity due to the repulsion between alkyl[1] and the ligand on nickel.[16a] **M4** could be generated from **M3** by single electron reduction, which could undergo further oxidative addition with the second alkyl bromide (**2**) to give Ni(III) intermediate **M6** *via* **M5**. The final product was formed by the reductive elimination of **M6** to form the second C_{sp^2}–C_{sp^3} bond along with the regeneration of the Ni(I) intermediate.

Conclusions

In summary, a Ni-catalyzed fully intermolecular *trans*-cross-dialkylation of alkynes with two different alkyl bromides has been developed for the first time. Two distinct alkyl bromides could be selectively employed as alkylating agents to sequentially install across alkynes to afford *trans*-dialkylated olefins. The reaction undergoes with exclusive regio- and diastereoselectivity under reductive conditions, circumventing the preformation of organometallic reagents. The key to the success of this protocol includes the judicious selection of ligand and reaction conditions to suppress the competitive β-hydride elimination of alkyl nickel intermediates as well as the homo-dialkylation reaction.

Data availability

Experimental data has been provided as ESI.†

Author contributions

Y. Z. Z. discovered the reaction. W. S. conceived and directed the project. Y. Z. Z. and H. M. performed the experiments and analysed the data. W. S. and Y. Z. Z. wrote the manuscript. All authors discussed the experimental results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

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