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Letter

Pd-Catalyzed Regiodivergent Synthesis of Diverse Oxindoles Enabled by the Versatile Heck Reaction of Carbamoyl Chlorides

Xianqing Wu, Zaiquan Tang, Chengxi Zhang, Chenchen Wang, Licheng Wu, Jingping Qu,* and Yifeng Chen*

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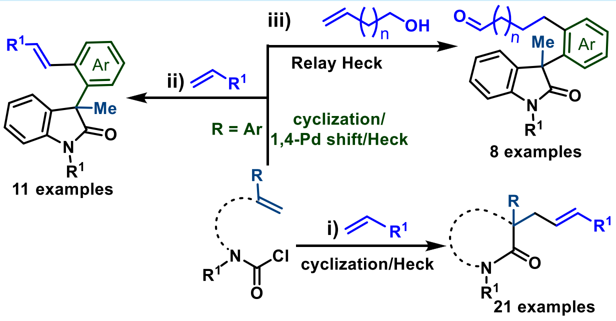
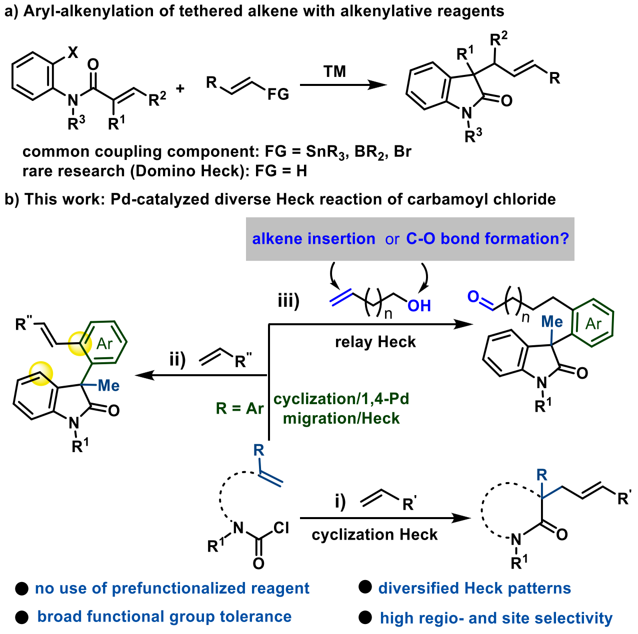
ABSTRACT: We report herein a miscellaneous oxindole synthesis bearing an all-carbon quaternary center, enabled by Pd-catalyzed intramolecular cyclization followed by multiple intermolecular Heck reactions of both easily accessible alkene-tethered carbamoyl chlorides and olefins. This protocol obviates the use of prefunctionalized olefinic reagents, exhibits excellent functional group tolerance, and features fascinating reactive versatility.



The oxindole skeleton, especially a 3,3-disubstituted one, as a representative nitrogen-containing heterocyclic compound prevails in cores of numerous complex molecules and exhibits a variety of great bioactivities found in natural products and pharmaceuticals.[1−4] Transition metal-catalyzed dicarbofunctionalization of *N*-arylacrylamides is a powerful synthetic tool for the rapid construction of oxindole skeletons.[5−8] Among these studies, the reaction with an alkenylative reagent is of particularly great interest because of its ability to be further functionalized.[8] However, most the olefinic coupling partners are either alkenyl metallic reagents or vinyl bromides, which are much less available or unstable, thus requiring multiple synthetic steps or tedious manipulations to facilitate this cascade reaction (Scheme 1a). The leverage of alkene without any prefunctionalization enables the domino Heck reaction to become an appealing approach for the assembly of molecular complexity from simple feedstocks with high atom economy.[9−11] Recently, the Glorius group developed a photoinduced Pd-catalyzed aryl bromide-tethered olefin dicarbofunctionalization with reactive styrene and acrylamides as coupling partners, enabling the expeditious synthesis of heterocyclic compounds. Because the reaction proceeded via the open-shell intermediate, the scope of olefins restricts the tri- and tetrasubstituted alkenes to stabilize the radical intermediate, and only two oxindoles with an olefinic substituent were accessible (Scheme 1a).[12]

Carbamoyl chloride, a stable and easily accessible feedstock derived from widespread secondary amine, is a good precursor for the expedient access to oxindole derivatives. Pioneering work by Grigg[13] and Takemoto,[14] carbopalladation-initiated cyclization of alkene-tethered carbamoyl chlorides, has emerged as an efficient approach to constructing oxindoles bearing all-carbon quaternary centers. Other elegant works involving

Scheme 1. Development for Domino Cyclization/Heck Reaction of Carbamoyl Chloride



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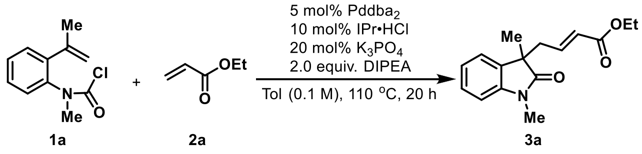
different termination reactions such as iodization,[15] borylation,[16] carbene insertion,[17a] alkynylation,[17b] and acylation[18] have also been reported by Tong and co-workers, Lautens and co-workers, Zhu and co-workers, and Wang and co-workers, respectively. Despite the advances, more useful reaction patterns still need to be continuously developed. Herein, we report a Pd-catalyzed two-sequence Heck-type reaction from carbamoyl chlorides and alkene feedstocks via intramolecular cyclization followed by intermolecular Heck reaction, allowing for the rapid assembly of a 3,3-disubstituted oxindole-bearing quaternary carbon center with broad functional group tolerance, which could serve as an advancement of the cyclization of *N*-(2-halophenyl)acrylamide and circumvent the use of prefunctionalized alkenyl organometallics or alkenyl halides (Scheme 1b, i). Moreover, the sequential Heck−1,4-Pd migration−Heck pattern was successfully applied to provide the hindered 3-arylated, all-carbon substituted oxindole synthesis when an aryl group was prefunctionalized on the tethered alkene moiety (Scheme 1b, ii).[7a,19] Additionally, the relay Heck sequence could be selectively incorporated with alkenols as the coupling component to introduce the aldehyde functionality at the remote site (Scheme 1b, iii).[20]

Initial attempts with our proposed protocol were carried out with model substrate carbamoyl chloride **1a** and ethyl acrylate **2a**. As outlined in Table 1, the reaction proceeded smoothly to afford the desired oxindole product **3a** in 84% GC yield with 5 mol % $Pd(dba)_2$ as the catalyst, 10 mol % IPr·HCl as the supporting ligand, and 2.0 equiv of DIPEA as the organic base, and an additional 0.2 equiv of inorganic base K_3PO_4 was necessary to liberate the free carbene ligand to give **3a** in 79% isolated yield (entry 1). The product yield dropped dramatically to 54% when DIPEA was replaced with K_3PO_4 (entry 2). Substoichiometric K_3PO_4 was also essential for high catalytic efficiency; the yield decreased to 53% with the omission of the K_3PO_4 (entry 3). The reaction could also proceed under ligand free conditions, albeit with 31% recovery of **3a** and 40% recovery of **1a** (entry 4), indicating the necessity of the IPr ligand. The lower efficiency of the reaction could be observed by using other common organic bases such as TMP and Cy_2NMe (entries 5 and 6, respectively). Meanwhile, the NHC-coordinated precatalyst PdCl(allyl)IPr, which was expected to furnish a better result, conversely caused a detrimental effect in the reaction (entry 7), probably due to the insufficient ratio of ligand to catalyst. The nickel catalyst possessed no reactivity (entry 8).[21]

Table 1. Optimization of Reaction Condition[a]

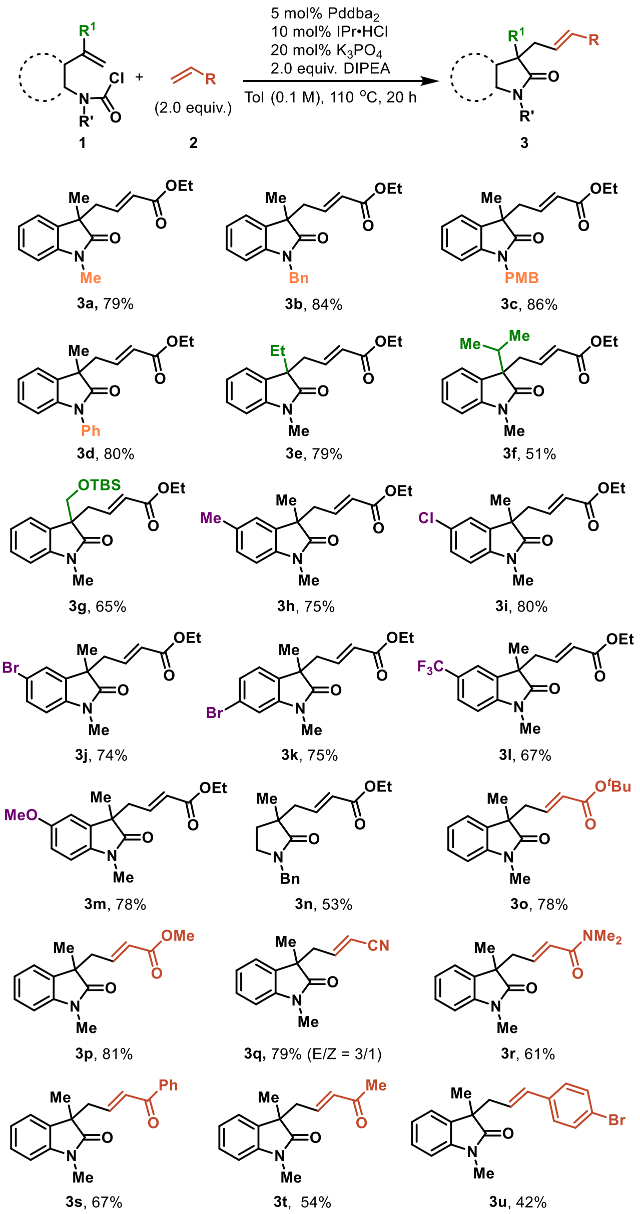


entry	deviation from above	**3a** (%)
1	none	84 (79)[b]
2	2.0 equiv of K_3PO_4, without DIPEA	54
3	without K_3PO_4	53
4	without ligand or K_3PO_4	31
5	TMP instead of DIPEA	63
6	Cy_2NMe instead of DIPEA	63
7	PdCl(allyl)IPr	12
8	$Ni(cod)_2$ instead of $Pd(dba)_2$	0

[a] Standard conditions: **1a** (1.0 equiv), **2a** (2.0 equiv), $Pd(dba)_2$ (5 mol %), IPr·HCl (10 mol %), K_3PO_4 (20 mol %), DIPEA (2.0 equiv), Tol (0.1 M), 110 °C, 20 h. [b] Isolated yield.

With the optimal conditions in hands, we sought to investigate the generality of the domino cyclization/intermolecular Heck reaction. As depicted in Scheme 2, diverse N-protecting groups such as Me, Bn, PMB, and Ph are well tolerated in this reaction (**3a**−**3d**, respectively). Substituents on the pendant alkene were also examined. Bulky alkylated groups, including isopropyl and CH_2OTBS-substituted olefins, could also participate in the reaction, affording the corresponding products in 51−79% isolated yield (**3e**−**3g**). Fascinatingly, halide substituent groups such as Cl and Br groups on the

Scheme 2. Substrate Scope of Sequential Cyclization Intermolecular Heck Reaction[a]

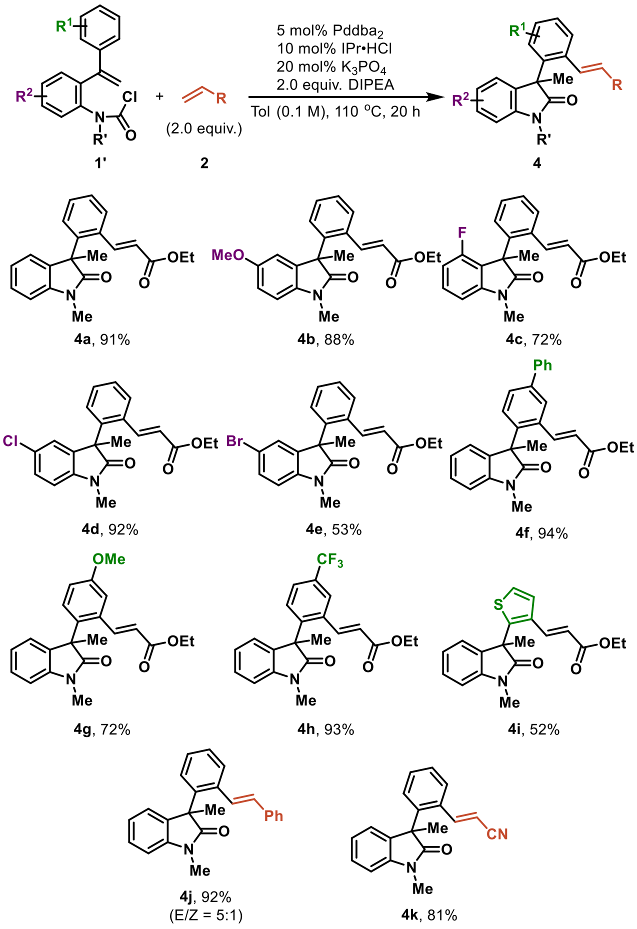


[a] Standard conditions: **1** (1.0 equiv), **2** (2.0 equiv), $Pd(dba)_2$ (5 mol %), IPr·HCl (10 mol %), K_3PO_4 (20 mol %), DIPEA (2.0 equiv), Tol (0.1 M), 110 °C, 11−57 h.

aromatic ring were accommodated with *para*-, *meta*-, and *ortho*-substituted carbamoyl chlorides, which could be utilized for further derivatization to form more functionalized oxindole scaffolds (**3i**−**3k**, respectively).[22] Meanwhile, both electron-donating and -withdrawing groups on the aromatic ring did not interfere with the formation of a productive alkene-tethered oxindole skeleton, generating the corresponding products in excellent yields (**3h**, **3l**, and **3m**). Carbamoyl chloride with a pendant alkylate alkene was also applicable in this transformation, delivering functional γ-lactam **3n** in a moderate yield. In addition, the scope of the olefins was also evaluated in this reaction. Both *tert*-butyl acrylate and methyl acrylate proceeded quite smoothly under the standard conditions, affording the desired product in a good isolated yield (**3o** and **3p**, respectively). Likewise, acrylonitrile (**3q**; E/Z = 3/1), acrylamide (**3r**), and vinyl ketones (**3s** and **3t**) were also investigated in this reaction, delivering moderate to good yields of the desired products. Styrene including bromide could also be tolerated, giving **3u** in a 42% isolated yield.

To our delight, when the substitution group on the alkene moiety of the starting material **1′** was switched to the aromatic groups, the reaction proceeded in the sequential carbamoylation−migratory insertion−1,4-Pd migration−Heck reaction manner, providing the arylated oxindoles **4** in excellent yields (Scheme 3). We began to explore the reaction of the phenyl-substituted starting material, with which the desired product **4a** was obtained in 91% isolated yield. Then the substrate scope of both the electrophiles and the olefins was investigated. Gratifyingly, carbamoyl chlorides bearing halogens such as F, Cl, and Br could be subjected to the standard conditions, delivering moderate to excellent yields of the products (**4c**−**4e**, respectively). Notably, the fluorine group *ortho* to the double bond provided the product without interfering with the insertion efficiency. Meanwhile, effects of the substituents on alkene were also examined. Both electron-donating and electron-withdrawing groups on the aromatic rings such as the phenyl group (**4f**), the methoxyl group (**4g**), and the trifluoromethyl group (**4h**) were tolerated without restricting the 1,4-Pd shift proficiency in this reaction. The heterocyclic thiophene-substituted alkene could also proceed via 1,4-Pd migration to provide **4i**, with a slight decrease in the yield. Other olefinic partners, including styrene and acrylonitrile, could be employed in this reaction efficiently to furnish intermolecular Heck products **4j** and **4k** in 92% (E/Z = 5/1) and 81% yields, respectively.

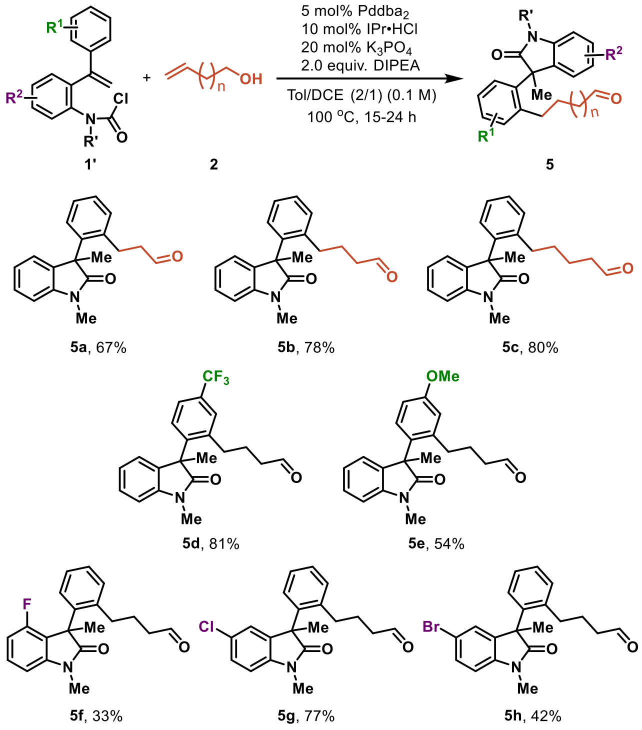
Scheme 3. Substrate Scope of Sequential Cyclization/1,4-Pd Shift/Heck Reaction[a]



[a] Standard conditions: **1′** (1.0 equiv), **2** (2.0 equiv), Pd(dba)$_2$ (5 mol %), IPr·HCl (10 mol %), K$_3$PO$_4$ (20 mol %), DIPEA (2.0 equiv), Tol (0.1 M), 110 °C, 12−21 h.

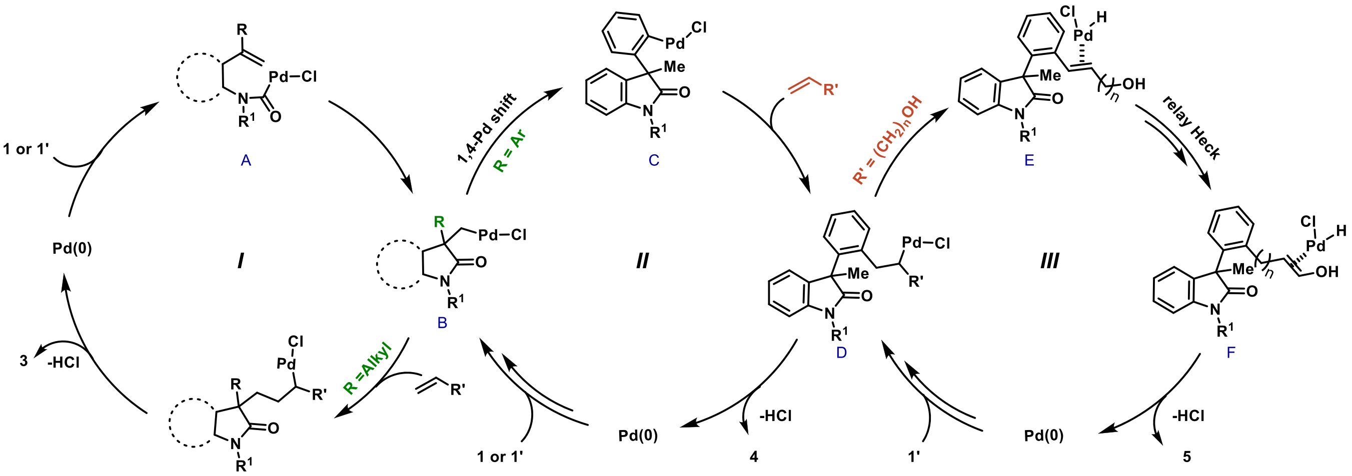
It would be challenging to incorporate the alcohol as the coupling partner, because the alcoholic functionality could not only serve as the transmetalation group with the palladium intermediate but also participate in the transesterification step with carbamoyl chloride. Attempts to interrogate various alkenols as the Heck reaction component also succeeded in providing the aldehyde-substituted oxindole product **5** (Scheme 4). The reaction proceeded in a carbamoylation−

Scheme 4. Substrate Scope of Sequential Cyclization/1,4-Pd Shift/Intermolecular Relay Heck Reaction[a]



[a] Standard conditions: **1′** (1.0 equiv), **2** (2.0 equiv), Pd(dba)$_2$ (5 mol %), IPr·HCl (10 mol %), K$_3$PO$_4$ (20 mol %), DIPEA (2.0 equiv), Tol/DCE (2/1, 0.1 M), 110 °C, 15−24 h.

Scheme 5. Plausible Mechanism



migratory insertion of alkene–1,4-Pd shift–relay Heck manner. In this transformation, allyl alcohol could proceed smoothly, providing **5a** in 67% isolated yield. In addition, the length of the chain between the alcohol and alkene minimally affects the efficiency of the relay Heck reaction. Excellent yields could be obtained with an increased chain length (**5b** and **5c**). Next, the electronic effect on the phenyl group linked to the alkene was also evaluated. Electron-withdrawing group CF_3 accelerated the reaction, while electron-donating substituent OMe provided a slightly decreased yield of the desired product (**5d** and **5e**). Synthetically versatile substituents on the oxindole backbones such as F, Cl, and Br groups were examined in this transformation. All of these groups could be employed to give the desired products in moderate to good yields (**5f**–**5h**, respectively); the fluorine group vicinal to the tethered alkene might affect the first insertion step, while the modest yield of **5f** is likely due to disfavored steric hindrance.

On the basis of the experimental results, we propose the following reaction pathways (Scheme 5). First, oxidative addition of carbamoyl chloride to Pd(0) formed **A**, which subsequently proceeded via the intramolecular migratory insertion into the tethered alkene to generate alkylpalladium species **B**. When the R group on **B** was an alkyl substituent, the existence of another olefinic counterpart led to the sequential intermolecular migratory insertion, followed by the β-H elimination to provide the oxindole product **3**, and the reactive Pd(0) intermediate was regenerated via the reductive elimination step (circle I). Moreover, when the R group on intermediate **B** was an aromatic ring, the reaction proceeded via path II. Intramolecular C–H activation of alkylpalladium with a phenyl group on an alkene resulted in a 1,4-Pd migration to afford intermediate **C**, which then could be trapped by alkene via intermolecular Heck reaction to furnish product **4**. Alternatively, when alkenols were used as the olefin counterpart to participate in this reaction, intermediate **E** was originally formed from species **D**, which then proceeded via the fast reinsertion of the Pd–H reactive intermediate to initiate the final relay Heck process. Aldehyde **5** was obtained to finish the whole domino process.

In summary, we have developed an efficient and intriguing protocol for the construction of various useful oxindole scaffolds via a Pd-catalyzed cascade intramolecular cyclization and versatile intermolecular Heck reaction of easily accessible carbamoyl chlorides with simple alkenes. The reaction can proceed through different pathways depending on the nature of the ingredient to afford 3,3-disubstituted oxindoles bearing an all-carbon quaternary center alkene and aldehyde functional group. This tranformation is distinguished by its multiple reactivities and broad functional group tolerance, which might establish a complementary approach to the synthesis of some useful pharmaceutical scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01197.

Detailed experimental procedures, characterization data, and copies of NMR spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **1b**–**1n**, **1′b**, **1′f**–**1′h**, **3a**–**3u**, **4a**–**4k**, **5a**–**5h**, and **6**–**11** (ZIP)

■ AUTHOR INFORMATION

Corresponding Authors

Jingping Qu – *Key Laboratory for Advanced Materials and Joint International Research Laboratory of Precision Chemistry and Molecular Engineering, Feringa Nobel Prize Scientist Joint Research Center, Frontiers Science Center for Materiobiology and Dynamic Chemistry, School of Chemistry and Molecular Engineering, East China University of Science & Technology, Shanghai 200237, China;* orcid.org/0000-0002-7576-0798; Email: qujp@dlut.edu.cn

Yifeng Chen – *Key Laboratory for Advanced Materials and Joint International Research Laboratory of Precision Chemistry and Molecular Engineering, Feringa Nobel Prize Scientist Joint Research Center, Frontiers Science Center for Materiobiology and Dynamic Chemistry, School of Chemistry and Molecular Engineering, East China University of Science & Technology, Shanghai 200237, China;* orcid.org/0000-0003-3239-6209; Email: yifengchen@ecust.edu.cn

Authors

Xianqing Wu – *Key Laboratory for Advanced Materials and Joint International Research Laboratory of Precision Chemistry and Molecular Engineering, Feringa Nobel Prize Scientist Joint Research Center, Frontiers Science Center for Materiobiology and Dynamic Chemistry, School of Chemistry and Molecular*

Engineering, East China University of Science & Technology, Shanghai 200237, China

Zaiquan Tang − *Key Laboratory for Advanced Materials and Joint International Research Laboratory of Precision Chemistry and Molecular Engineering, Feringa Nobel Prize Scientist Joint Research Center, Frontiers Science Center for Materiobiology and Dynamic Chemistry, School of Chemistry and Molecular Engineering, East China University of Science & Technology, Shanghai 200237, China*

Chengxi Zhang − *Key Laboratory for Advanced Materials and Joint International Research Laboratory of Precision Chemistry and Molecular Engineering, Feringa Nobel Prize Scientist Joint Research Center, Frontiers Science Center for Materiobiology and Dynamic Chemistry, School of Chemistry and Molecular Engineering, East China University of Science & Technology, Shanghai 200237, China*

Chenchen Wang − *Key Laboratory for Advanced Materials and Joint International Research Laboratory of Precision Chemistry and Molecular Engineering, Feringa Nobel Prize Scientist Joint Research Center, Frontiers Science Center for Materiobiology and Dynamic Chemistry, School of Chemistry and Molecular Engineering, East China University of Science & Technology, Shanghai 200237, China*

Licheng Wu − *Key Laboratory for Advanced Materials and Joint International Research Laboratory of Precision Chemistry and Molecular Engineering, Feringa Nobel Prize Scientist Joint Research Center, Frontiers Science Center for Materiobiology and Dynamic Chemistry, School of Chemistry and Molecular Engineering, East China University of Science & Technology, Shanghai 200237, China*

Complete contact information is available at:
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Notes

The authors declare no competing financial interest.

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