COMMUNICATIONS doi.org/10.1002/adsc.202100648 Advanced Synthesis & Catalysis

Copper-Catalyzed Chemo- and Diastereoselective 1,3-Dipolar Cycloaddition of Carbonyl Ylide and Aldehyde-Tethered-Cyclohexadienone to Access Polycyclic Systems

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Manuscript received: May 27, 2021; Revised manuscript received: July 24, 2021;
Version of record online: ■■, ■■

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202100648

Abstract: A copper-catalyzed tandem intermolecular ylide formation/intramolecular cycloaddition of diazo compounds and aldehyde-tethered-cyclohexadienones was reported, chemo- and diastereoselectively providing oxapolycyclic frameworks in moderate to excellent yields under mild conditions. This reaction creates two C–C bonds and one C–O bond with five stereocentres including two all-carbon quaternary centres. Moreover, the late-stage diversification of products can be realized via chemoselective substitutions.

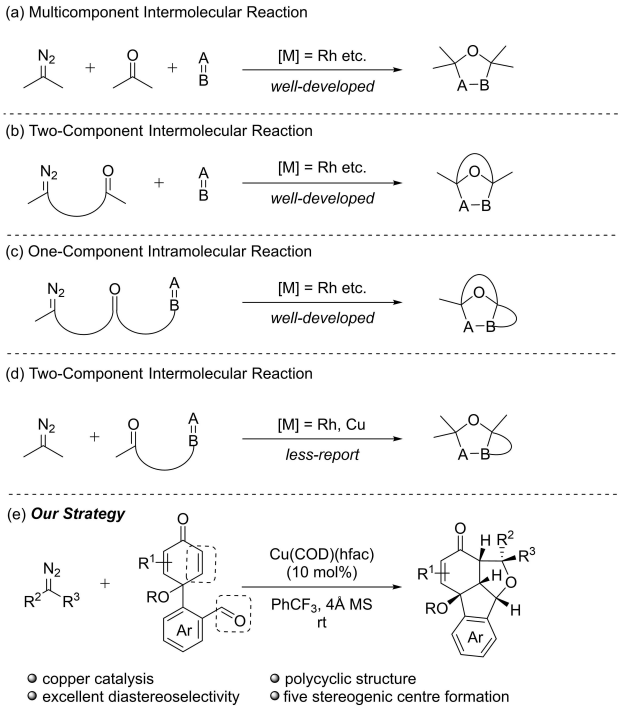
Keywords: copper catalysis; 1,3-dipolar cycloaddition; carbonyl ylide; polycyclic structure

Transition-metal-catalyzed inter- or intramolecular reactions of diazo compounds and Lewis bases are powerful tools to generate ylides, which are usually highly reactive species and readily undergo further tandem reactions for the creation of new chemical entities.[1] Particularly, carbonyl ylides formed by the transition-metal-catalyzed reaction of diazo compounds and carbon-oxygen double bonds are reactive intermediates and could undergo diverse transformations, among which the 1,3-dipolar cy-cloaddition of such carbonyl ylides has been studied extensively and used for the construction of complex oxapolycyclic systems containing embedded di- or tetrahydrofuran rings.[2]

The three-component intermolecular carbonyl ylide cycloaddition involving diazo compounds, aldehydes, and dipolarophiles is an effective method for the construction of functionalized oxygen heterocycles (Scheme 1a).[3] Nevertheless, it has been relatively restricted in terms of selectivity and substrate scope. In the last decades, great attentions have been paid to the intramolecular carbonyl ylide cycloaddition, including intramolecular ylide formation/intermolecular cycloaddition (Scheme 1b)[4] and intramolecular ylide formation/intramolecular cycloaddition (Scheme 1c),[5] for the synthesis of complex targets.

In contrast, analogous two component reactions involving tandem intermolecular ylide formation/intramolecular cycloaddition has been relatively limited (Scheme 1d). In 2001, Johnson and co-workers described an interesting example of rhodium-catalyzed intermolecular ylide for-mation/intramolecular cycloaddition of diazosulphone and alkynyl/alkenyl aldehydes, affording substituted furans or tetrahydrofurans.[6] Recently, Muthusamy et al. developed a copper-catalyzed tandem reaction of diazoamides and *O*-propargyl salicylaldehydes for the synthesis of spiro-indolofurobenzopyrans via intermolecular ylide formation/intramolecular cycloaddition process;[7] in comparison, Bakthadoss et al. reported a similar rhodium-catalyzed protocol of diazo dicarbonyl compounds and *O*-allylated salicylaldehydes for the construction of tricyclic chromeno/quinolino furan frameworks.[8] Despite these considerable advances, there was still not a general method for the two-component intermolecular ylide formation/intramolecular cycloaddition with broad scope and control over chemo- and diastereoselectivity.

On the other hand, these 1,3-dipolar cycloaddition of carbonyl ylide were commonly catalyzed by rhodium complexes.[1,2] Inspired by the former reports



Scheme 1. Previous Reports and Our Strategy.

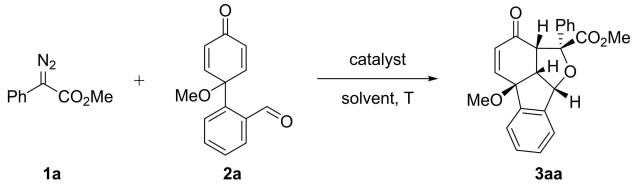
and in continuation with our interest in catalytic copper-carbene transformations for developing novel methodologies on polycyclic skeleton synthesis,[9] herein, we report a novel copper-catalyzed tandem intermolecular ylide formation/intramolecular 1,3-dipolar cycloaddition of diazo compounds and aldehyde-tethered-cyclohexadienones to access various oxapolycyclic systems with excellent chemo- and diastereoselectivities and moderate to excellent yields under mild conditions (Scheme 1e).

We first utilized phenyl diazoacetate **1a** and aldehyde-tethered-cyclohexadienone **2a** as model substrates to optimize the reaction conditions (Table 1). When the reaction was performed in methylene dichloride (CH_2Cl_2) at room temperature with $Rh_2(OAc)_4$ as the catalyst, the desired product **3aa** was obtained in 36% yield with moderate diastereoselectivity (entry 1).[10] The reaction was highly sensitive to moisture, and no desired product was detected without 4 Å MS (entry 2). Inspired by Muthusamy's report,[7] copper catalysts were extensively investigated, and gratifyingly, Cu(COD)(hfac) has been proven to be the best catalyst, affording the desired product **3aa** in 34% yield as single diastereomer (entries 3–5). Next, different solvents were screened. (Trifluoromethyl)benzene ($PhCF_3$) was the best choice, and the alternative aromatic solvents including toluene, xylenes, and chlorobenzene (PhCl) gave moderate yields,[11] whereas the other solvents were not suitable for the reaction (entries 6–10). Moreover, high temperature led to a lower yield (entry 11), and the reaction did not happen under low temperature (entry 12). Significantly, the yield of **3aa** was reduced to 27% in the absence of prestirring of the aldehyde with the copper complex (entry 13), and no product was isolated without slow addition of the diazo substrate (entry 14). Control experiment without copper catalyst yielded no product (entry 15). It is noteworthy that the carboxylic acid ligands of rhodium catalysts have obvious effect on the stereochemistry, which demonstrates that a Rh-ligated ylide intermediate is probably formed; while different copper catalysts with or without chiral ligands have no influence on the stereochemistry indicating that the reaction might take place via a metal-free ylide under copper catalysis (Supporting Information). It is proposed that the steric effect for the free carbonyl ylide resulted better diastereoselectivity, while the steric effect and ligated-metal for the metal-ligated carbonyl ylide would make the reaction complex with poor diastereocontrol.

With the optimal reaction conditions in hand,[12] we next set out to investigate the scope of diazo compounds (Table 2). Varying the ester group of diazo compounds to bulky ethyl or benzyl substitutent gave lower yields (**3aa**–**ca**). Then, the reaction of aldehyde-tethered-cyclohexadienone **2a** with different substituted aryl diazoacetates bearing electron-donating or electron-withdrawing substituents at the para- and meta-position of the aryl moiety all proceeded smoothly to furnish the desired products (**3da**–**oa**), while the yield sharply decreased for ortho-substituted diazo compounds, indicating that the steric effect is more significant than the electronic factor for this reaction (**3pa**–**qa**). Additionally, different di-substituted phenyl diazoacetates and bulky naphthyl diazoacetate were also well tolerated for the reaction (**3ra**–**ua**). When 3-diazo-oxindole substrate was applied to the reaction, an interesting spiro-oxindole fused hexacyclic framework was obtained in one step (**3va**–**wa**), which is attractive for medicinal chemistry.[13] Moreover, because the structure of diazo compound has a large impact on the reaction outcome,[14] other types of diazo compounds were further tested for this reaction. Gratifyingly, dimethyl 2-diazomalonate was suitable for this reaction, affording the desired product **3xa** in 47% yield. However, no target product **3ya** was detected from the reaction mixture when (1-diazoethyl) benzene was utilized. The structure and relative stereochemistry of **3aa** were unambiguously confirmed by X-ray diffraction analysis.[15]

Next, various substituted aldehyde-tethered-cyclohexadienone substrates were subjected to the optimized reaction conditions and generally showed somehow lower efficiency (Table 3). The influence of the R substituent was first investigated. Changing the R group of cyclohexadienones from methyl to ethyl or acetyl group had adverse effect on the reaction,

Table 1. Optimization of Reaction Conditions.[a]



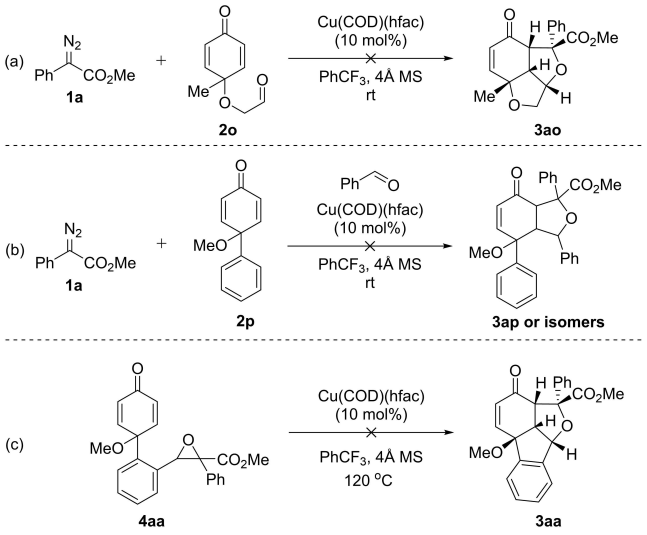
1a 2a 3aa

Entry	Catalyst	Solvent	Yield (%)[b]	dr[c]
1	$Rh_2(OAc)_4$	CH_2Cl_2	36	4:1
2[d]	$Rh_2(OAc)_4$	CH_2Cl_2	–	–
3	CuOTf	CH_2Cl_2	8	> 20:1
4	Cu(COD)(hfac)	CH_2Cl_2	34	> 20:1
5	$Cu(hfac)_2$	CH_2Cl_2	15	> 20:1
6	Cu(COD)(hfac)	dioxane	–	–
7	Cu(COD)(hfac)	toluene	53	> 20:1
8	Cu(COD)(hfac)	xylenes	48	> 20:1
9	Cu(COD)(hfac)	PhCl	64	> 20:1
10	Cu(COD)(hfac)	$PhCF_3$	71	> 20:1
11[e]	Cu(COD)(hfac)	$PhCF_3$	33	> 20:1
12[f]	Cu(COD)(hfac)	$PhCF_3$	–	–
13[g]	Cu(COD)(hfac)	$PhCF_3$	27	> 20:1
14[h]	Cu(COD)(hfac)	$PhCF_3$	–	–
15	–	$PhCF_3$	–	–

[a] Reaction conditions: a mixture of **2a** (0.3 mmol), catalyst ([Rh] 5 mol%, [Cu] 10 mol%) and 4 Å MS (300 mg) in solvent (1.0 mL) was prestirred for 2 h; then, a solution of **1a** (0.6 mmol) in solvent (2.0 mL) was injected over 2 h via an automatic syringe pump; the reaction was continued for 16 h at rt.
[b] Isolated yields.
[c] Determined by ^{1}H NMR. When no signals of minor diastereomers were detected in the crude and pure ^{1}H NMR, the diastereoselectivity is quoted as > 20:1.
[d] Without 4 Å MS.
[e] At 80 °C.
[f] At 0 °C.
[g] Without prestirring.
[h] **1a** (0.6 mmol) in $PhCF_3$ (2.0 mL) was added in one portion.

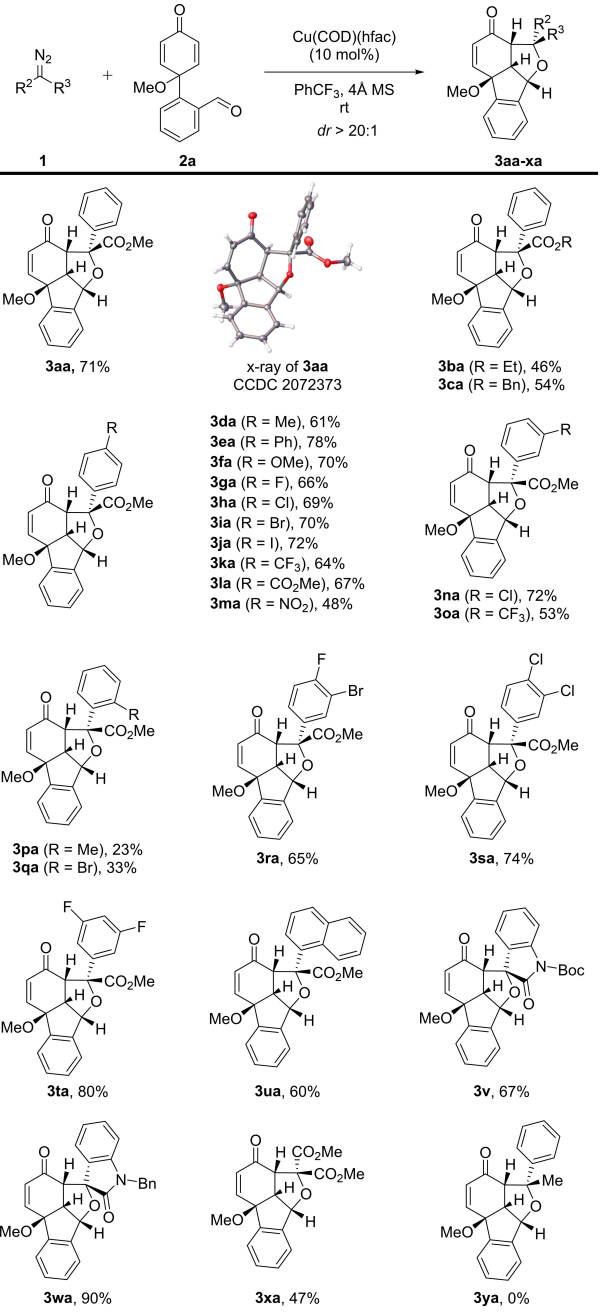
providing the corresponding products **3ab** and **3ac** in 42% and 40% yields, respectively. Then, the substitution pattern on the aryl moiety was examined. Substrates bearing electron-donating or electron-withdrawing substituents on the 3-, 4- or 5-position of the aryl moiety all proceeded smoothly to afford the corresponding products in moderate to excellent yields (**3ad–al**); the 2-substituted product was not obtained due to the unavailability of the corresponding cyclohexadienone substrate. To our delight, when the asymmetrical cyclohexadienone with a 3'-chloro group was employed, the expected product **3am** was obtained regioselectively in 49% yield. Unfortunately, the furan-derived cyclohexadienone was not applicable for the reaction (**3an**).

To further understand the tandem intermolecular ylide formation/intramolecular cycloaddition process, several control experiments were conducted (Scheme 2). When substrate **2o** was applied to the reaction, no desired product **3ao** was detected, which



Scheme 2. Control Experiments.

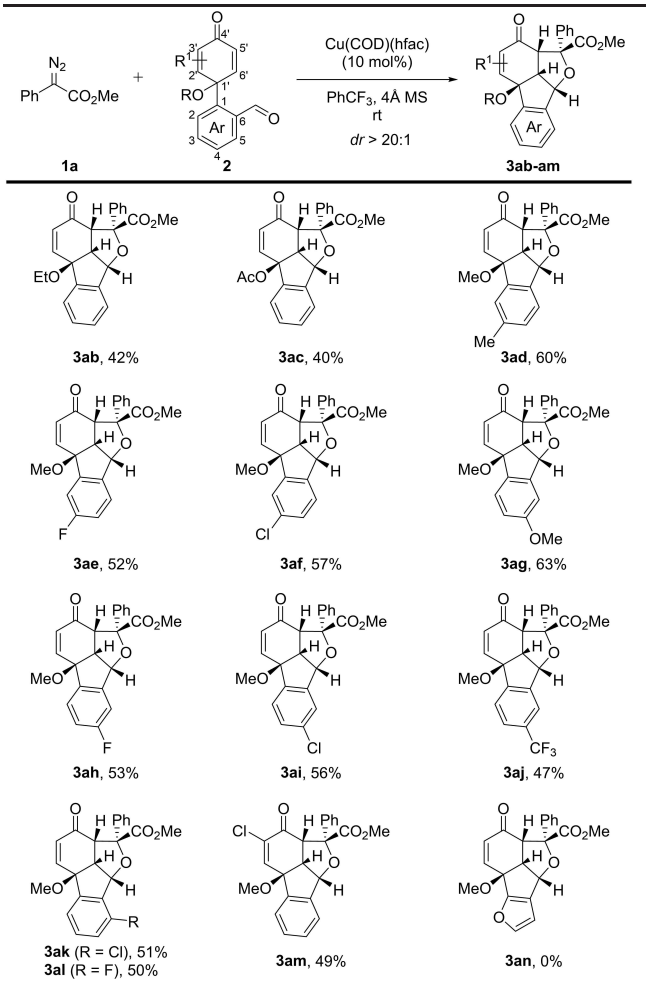
Table 2. Scope of Diazo Substrates.[a,b]



[a] Reaction conditions: a mixture of **2a** (0.3 mmol), Cu(COD)(hfac) (10 mol%) and 4 Å MS (300 mg) in $PhCF_3$ (1.0 mL) was prestirred for 2 h; then, a solution of **1** (0.6 mmol) in $PhCF_3$ (2.0 mL) was injected over 2 h via an automatic syringe pump; the reaction was continued for 16 h at rt.

[b] Isolated yields.

Table 3. Scope of Aldehyde-Tethered-Cyclohexadienone Substrates.[a,b]

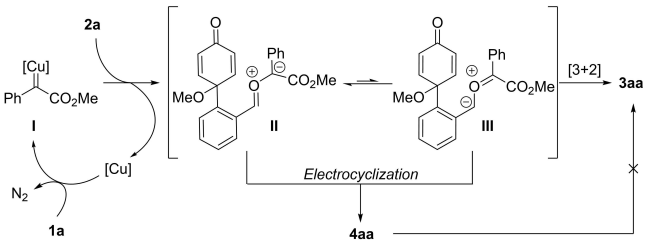


[a] Reaction conditions: a mixture of **2** (0.3 mmol), Cu(COD)(hfac) (10 mol%) and 4 Å MS (300 mg) in $PhCF_3$ (1.0 mL) was prestirred for 2 h; then, a solution of **1a** (0.6 mmol) in $PhCF_3$ (2.0 mL) was injected over 2 h via an automatic syringe pump; the reaction was continued for 16 h at rt.

[b] Isolated yields.

indicates that the aromatic linker is essential for this reaction and may stabilize the carbonyl ylide intermediate (Scheme 2a). Then, the three-component intermolecular cycloaddition involving diazo compound, cyclohexadienone, and benzaldehyde afforded no product **3ap** or related isomers (Scheme 2b). Based on the literature reports,[7,16] we tried to open the epoxide ring by heating to generate the carbonyl ylide, which in turn will undergo [3+2] cycloaddition. Accordingly, the epoxide **4aa** was tested under elevated temperature, however, no desired product **3aa** was isolated (Scheme 2c).

Based on the above results and related reports,[17] a plausible mechanism was illustrated in Scheme 3. The catalytic cycle starts with the formation of the copper-carbene **I** by the reaction of phenyl diazoacetate **1a** with copper catalyst. Interaction of the aldehyde group in cyclohexadienone **2a** with the copper-carbene **I**

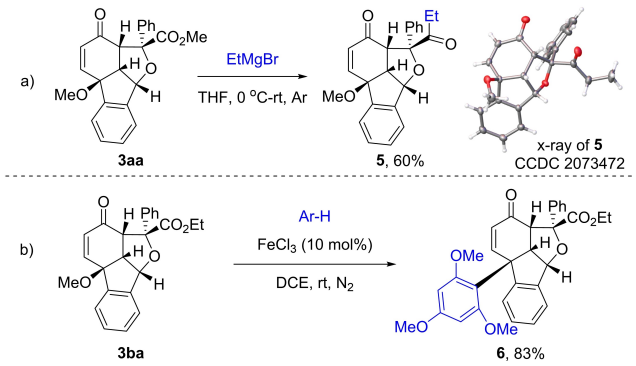


Scheme 3. Proposed Reaction Mechanism.

produces the free carbonyl ylide **II** and its polar-reversed resonance structure **III** with the release of copper catalyst. Here, the necessity of the aromatic linker could be explained by the stabilization of the ylide intermediate **III**. Then, the carbonyl ylide **III** undergoes Huisgen intramolecular 1,3-dipolar cycloaddition with the alkene dipolarophile would give the desired product **3 aa**. The carbonyl ylides **II**/**III** proceed via competitive electrocyclization to yield the epoxide side product **4 aa**.

The versatility of this copper-catalyzed protocol can be further exploited in chemoselective substitutions (Scheme 4). For examples, treatment of **3 aa** with EtMgBr in THF at 0 °C followed by quenching with water furnished the ketone product **5** in 60% yield;[15] the site-selective iron-catalyzed Friedel-Crafts arylation of **3 ba** with trimethoxybenzene proceeded smoothly to offer product **6** in 83% yield.[18]

In summary, we have developed a copper-catalyzed tandem intermolecular ylide formation/intramolecular cycloaddition of diazo compounds and aldehyde-tethered-cyclohexadienones to afford polycyclic structures in moderate to excellent yields under mild conditions. This reaction creates two C–C bonds and one C–O bond with five stereocentres including two all-carbon quaternary centers with high chemo- and diastereoselectivities. It is believed that the continued and renewed investigation on the copper-catalyzed 1,3-dipolar cycloaddition of carbonyl ylide will provide an economical alternative to diverse complex structures attractive for medicinal chemistry. Further studies based on this chemistry is in progress in our laboratory.



Scheme 4. Transformation of Products.

Experimental Section

General Procedure for the Preparation of Compounds 3

A solution of aldehyde-tethered-cyclohexadienones **2** (0.3 mmol, 1.0 equiv.), 4 Å MS (300 mg) and Cu(COD)(hfac) (10 mol%) in $PhCF_3$ (1.0 mL) was stirred at rt for 2 h. Then a solution of diazo compounds **1** (0.6 mmol, 2.0 equiv.) in $PhCF_3$ (2.0 mL) was injected via an automatic syringe pump over 2 h at rt and continued for another 16 h. The resulting mixture was filtered via a short pad of celite and washed with EtOAc. The combined organic phase was concentrated under reduced pressure and the residue was purified by flash chromatography (silica gel, EtOAc/hexanes as eluent) to afford the corresponding products **3**.

Acknowledgements

The authors are grateful for the financial support from the Natural Science Foundation of Guangdong Province (2018A030310680), the Research Foundation of Department of Education of Guangdong Province (2018KTSCX236, 2020KTSCX154, 2020KCXTD036), the Science Foundation for Young Teachers of Wuyi University (2019td09), and the College Students Innovation and Entrepreneurship Training Program of Wuyi University (2020CX08).

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[10] Although the diastereomers are not separable, the dr ratio could be easily determined via ^{1}H NMR. Please see Supporting Information for details.

[11] In general, aromatic solvents are suitable for this reaction. It is proposed that the higher polarity of $PhCF_3$ would contribute to the better result.

[12] After extensive optimizations, the main epoxide side reaction could not completely suppressed regardless of the catalytic system, which is a major reason for the general low efficiency of this reaction. However, pure **4aa** is difficult to isolate and could only be obtained by repeated preparative thin layer chromatography. Thus, the amount of **4aa and** others is not reported. By control experiments shown in Scheme 2c, **4aa** is quite stable to the copper catalyst and the reaction conditions.

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COMMUNICATIONS

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Adv. Synth. Catal. **2021**, *363*, 1 – 7

S. Peng*, H. Zhang, Y. Zhu, T. Zhou, J. He, N. Chen, M. Lang, H. Li, J. Wang*