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Pd(0)-Catalyzed Asymmetric Carbohalogenation: H-Bonding-Driven C(sp³)–Halogen Reductive Elimination under Mild Conditions

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ceptually novel elementary reaction. Its emergence broadens the horizons of transition-metal catalysis and provides new access to organohalides of versatile synthetic value. However, as the reverse process of facile oxidative addition of Pd(0) to organohalide, carbon-halogen reductive elimination remains elusive and practically difficult. Overcoming the thermodynamic disfavor inherent to $(X = I, Br) = \begin{cases} 10 \text{ mol\% Pd}(OAc)_2 \\ 20 \text{ mol\% FerroPhos} \\ 10 \text{ mol\% FerroPhos} \\ 2.0 \text{ equiv } [Et_3NH]^*[BF_4]^* \\ 10 \text{ mol\% FerroPhos} \\$

such an elementary reaction is frustrated by the high reaction temperature and requirement of distinctive ligands. Here, we report a general strategy that employs $[Et_3NH]^+[BF_4]^-$ as an H-bond donor under a toluene/water/ $(CH_2OH)_2$ biphasic system to efficiently promote $C(sp^3)$ -halogen reductive elimination at low temperature. This enables a series of Pd(0)-catalyzed carbohalogenation reactions, including more challenging and unprecedented asymmetric carbobromination with a high level of efficiency and enantioselectivity by using readily available ligands. Mechanistic studies suggest that $[Et_3NH]^+[BF_4]^-$ can facilitate the heterolytic dissociation of halogen-Pd^{II}C(sp³) bonds via a potential H-bonding interaction to reduce the energy barrier of $C(sp^3)$ -halogen reductive elimination, thereby rendering it feasible in an S_N^2 manner.

INTRODUCTION

Reductive elimination (RE) is a typical terminating elementary step for product formation and catalyst regeneration in numerous metal-catalyzed reactions.¹ Expanding the scope of such a fundamental reaction will no doubt broaden the horizons of transition-metal catalysis. As is the case, the newly emerging C-X (X = halogen) RE is particularly attractive since the resulting organohalide product is a class of versatile compounds in organic synthesis.² However, because of the reverse process of the facile and exergonic oxidative addition of an organohalide to the Pd(0) complex,³ the C-X RE is thermodynamically disfavored, rendering such an elementary reaction strikingly less prevalent and practically difficult (Scheme 1a,b).⁴ Nowadays, stoichiometric and catalytic reactions involving the challenging C-X RE strongly rely on the discovery and development of ligands with highly tailored electronic and/or steric properties. Seminal studies by Hartwig⁵ and Buchwald⁶ have established benchmarks for C(aryl)-X RE through the use of sterically hindered phosphorus ligands, which could be attributed to key species aryl-Pd^{II}-X with an extremely congested environment at the palladium center. This fundamental principle is further exemplified in the Lautens' Pd(0)-catalyzed carboiodination reactions, wherein bulky ligand QPhos has been proven to be essential.⁷ More recently, the Molandi group⁸ and our own group⁹ have disclosed that some specific electron-poor ligands are also able to promote C-X RE via reducing the electronic density of the corresponding Pd^{II} center. Despite these

advancements, there are only a limited number of capable ligands, and a few of them turned out to be general for different types of substrates.¹⁰ The high reaction temperature together with the time- and effort-consuming ligand identification have severely hampered the development of such Pd(0) catalysis involving the step of formidable C–X RE, especially in an asymmetric fashion (Scheme 1b).

As applications of this elementary reaction for conceptually novel access to organohalides continue to expand,⁴ the demand for increasingly active and mild catalytic systems has intensified, requiring a deeper understanding of the factors underlying the C–X RE mechanism. As a notable example, the Arndtsen group reported a light-promoted Pd(0)-catalyzed acyl chloride synthesis featuring a novel single-electron C(acyl)–Cl RE under ambient condition;¹¹ however, no applications for the formation of alkyl halide have been demonstrated. In addition, such a radical pathway is believed to be difficult in controlling stereochemistry and thus may not be suitable for asymmetric catalysis. We sought to develop a fundamentally different approach to rendering the classic twoelectron C–X RE more feasible and thus paving the way for

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Scheme 1. Challenges and Opportunities in Carbon Halogen Reduction Elimination



asymmetric catalysis. Computational studies have revealed that the X-M (M = Pd^{II} , Rh^{III}) bond dissociation of X-M-C(sp³) species is a crucial step in dominating the $C(sp^3)$ -X RE event no matter whether a concerted or stepwise mechanism is operative (Scheme 1c).¹² We accordingly realized that the reliability and reversibility of an ionic hydrogen bond (YH = H-bond donor)¹³ would render the H-bonding strategy ideally suited to tackle $C(sp^3)$ -X RE (Scheme 1c). The former feature would facilitate the heterolytic dissociation of the X-Pd^{II} bond via H-bonding interaction YH···X–Pd^{II}. In addition, unlike metal-type scavengers such as Ag⁺, the dynamic reversibility of YH…X⁻ would allow X⁻ to re-enter the catalytic cycle in due course to forge the C–X bond, furnishing an H-bonding-driven C-X RE (Scheme 1c). Such a simple Hbonding strategy could potentially reduce the energy barrier of C-X RE and open the door to the development of a milder catalytic system, which is vividly demonstrated in the efficient Pd(0)-catalyzed asymmetric carbohalogenations (Scheme 1d).

RESULTS AND DISCUSSION

Establishment of a Biphasic H-Bonding System. To test our H-bonding strategy, we chose the Pd(0)-catalyzed carboiodination of (Z)-1-iod-1,6-diene (1a) as the model case (Table 1). Under our previous conditions (10 mol % $Pd(OAc)_2$, 30 mol % DPPF, 110 °C, toluene), the reaction

Table 1. Establishment of an H-Bonding System^a

Ph—	-I _{nBu} 10 → 3	mol% Pd(OAc) ₂ 0 mol% DPPF	Ph
	N Ts toluene 1a	additive(s) e (4 mL), 60 ºC, 36 h	N Ts 2a
entry	ac	dditive(s)	isolated yield (%)
1	nc	additive	<5
2	Y	Y = 0, R = Ph	17
3		Y = S, R = Ph	8
4	H H	$Y = O, R = C_6 F_5$	39
5	[Et ₃ NH] ⁺ [BF ₄] ⁻		11
6	[Et ₃ NH] ⁺ [BF ₄] ⁻ + H ₂ O (1mL)		53
7	[Et ₃ N H] ⁺ [BF ₄] ⁻ + H ₂ O (1 mL) + EG (2 m		nL) 83
8	EG (2 mL)		33
9	H ₂	< 5	
10 ^b	[Et ₃ NH] ⁺ [BF ₄] ⁻ + H	mL) <mark>80</mark>	

^{*a*}Conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (10%), DPPF (30%), toluene (4 mL), and the indicated urea derivative (2.0 equiv) or $[Et_3NH]^+[BF_4]^-$ (2.0 equiv). ^{*b*}20% DPPF was used.

Scheme 2. Verification of the Reliability of a Biphasic H-Bonding System^a





^{*a*}The reactions were performed on the 0.2 mmol scale. Isolated yields were reported. ^{*b*}The reaction was conducted at 100 °C.

Ph-	Bu 10 mol% I	10 mol% Pd(OAc)₂, x mol% Ln toluene (4 mL), T (°C)				
N Ts 1a	additives =	$ \left[\begin{array}{c} 2.0 \text{ equiv } [\text{Et}_3\text{NH}]^{+}[\text{BF}_4]^{-} \\ \text{H}_2\text{O} \ (1 \text{ mL}), \text{ EG} \ (2 \text{ mL}) \end{array} \right] $	N Ts (S)-2a			
	30 mol% Ln T = 100 °C <i>w/o the additives</i>	30 mol% Ln T = 60 °C <i>w/o the additives</i>	20 mol% Ln T = 60 °C with the additives			
L13	30%, <5% ee	<5%, ND	41%, 23% ee			
L14	22%, 21% ee	<5%, ND	50%, 42% ee			
L15	47%, 66% ee	<5%, ND	58%, 78% ee			
L16	65%, 72% ee	8%, 91% ee	79%, 93% ee			
L17	<5%, ND	<5%, ND	<5%, ND			
L18	50%, 77% ee	10%, 86% <i>ee</i>	68%, 92% <i>ee</i>			
L19	<5%, ND	<5%, ND	<5%, ND			
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Scheme 3. Chiral Ligand Screening

of 1a afforded product 2a in 87% yield.¹⁴ Lowering the temperature to 60 °C led to no reaction (Table 1, entry 1), which served as a starting point for our study. We first employed urea-type H-bond donors since they are good acceptors of the halogen anion.¹⁵ To our delight, up to a 39% yield of 2a was isolated when 1,3-di(perfluorophenyl)urea was used (Table 1, entries 2–4), albeit with no further improve-

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ment after extensive screening. (See the Supporting Information for details.) Given the fact that urea derivatives can serve as competing ligands to disrupt the coordination environment of the metal catalyst,¹⁶ we turned our attention to ammonium-based H-bond donors.¹⁷ The initial attempt of using $[Et_3NH]^+[BF_4]^-$ afforded product 2a in only 11% yield (Table 1, entry 5), which was likely due to the poor solubility of this ammonium salt in nonpolar toluene. The addition of water as a cosolvent boosted the yield to 53% (Table 1, entry 6). Product 2a was finally obtained in 83% vield when additional ethylene glycol (EG) was introduced to form a biphasic system (Table 1, entry 7). EG was believed to serve as a second H-bond donor.¹⁸ Indeed, a 33% yield of product 2a could be obtained in the absence of water and ammonium salt (Table 1, entry 8). In contrast, only the use of water as an additive led to a trace amount of product 2a (Table 1, entry 9). Moreover, this biphasic H-bonding system could allow the reduction of DPPF loading from 30 to 20 mol % while maintaining the same level of isolated yield (Table 1, entry 10). This result further demonstrated the power of the H-bonding strategy since using 20 mol % DPPF has been shown to have no effect on the reaction of 1a in toluene at 110 $^{\circ}$ C.¹⁴

To further verify the reliability of the newly developed biphasic H-bonding system for $C(sp^3)-X$ RE, we examined some other Pd(0)-catalyzed carbohalogenations (Scheme 2). Fortunately, the unprecedented carbobromination of 1-bromo-1,6-diene (3a), which involves a more challenging $C(sp^3)$ -Br RE compared with the iodine version,^{12a,19} was also achieved to give product 4a in 56% yield, although increased catalyst loading (20 mol % Pd(OAc)₂/40 mol % DPPF) and a higher temperature (80 °C) were required (Scheme 2a). The absence of $[Et_3NH]^+[BF_4]^-$ and H_2O/EG led to only a trace amount of 4a even at 110 °C. Moreover, the benefit of this system could be successfully extended to aryl halide substrates. Lautens and co-workers have found that high temperature (>90 °C) is a prerequisite for the efficient Pd(0)/QPhos-catalyzed carboiodonation of aryl iodide 5a.^{7a} We also found that, under the Lautens' catalytic system, lower temperature (60 °C) indeed sharply reduced the yield of product 6a (ca. 10%) along with undesired product 6a' (15% yield) (Scheme 2b). To our delight, the use of our biphasic H-bonding system could significantly improve the yield of 6a to 67%. The reaction of highly active substrate 5b under this biphasic system gave product 6b in 84% yield. The carbobromination of aryl bromide substrate 5c could also be realized at higher temperature (100 °C), delivering product 6c in 52% yield (Scheme 2b).

Pd(0)-Catalyzed Asymmetric Carbohalogenation. With the establishment of the reliable biphasic system, we then turned our attention to its potential with respect to the Pd(0)-catalyzed asymmetric carbohalogenation of (Z)-1-halo-1,6-dienes. In 2019, the Zhang group came up with its own chiral ligand, L1, to realize the version of Lautens' carboiodination with high enantioselctivity for the first time.^{20a} Simultaneously, Xu et al. utilized chiral phosphoramidite ligand L2 to achieve an interesting asymmetric isomerization of 3-(2-iodoaryl)cyclobutanone, which involves the step of $C(sp^3)$ –I RE.^{20b} To the best of our knowledge, no precedent exists for the asymmetric carbobromination. In our hands, chiral ligands L1 and L2 used in these two reactions failed to promote the carboiodination of 1a, and ligands L3-L12 with diverse chiral skeletons were also proven to be futile. (For the structures of L1-L12, see Table S3.) With the Scheme 4. Substrate Scope of Asymmetric Carboiodination



Scheme 5. Substrate Scope of Asymmetric Carboiodination







success of DPPF in racemic reactions, well-known chiral FerroPhos ligands²¹ L13–L19 were then tested (Scheme 3). Even so, a dilemma still arose where high temperature was

necessary for a good yield and low temperature was essential for high enantioselectivity (Scheme 3). It was not until the use of a biphasic system that such a puzzle was completely solved.

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Scheme 8. Effect of Additional NaI on the Reaction Performance

Ph-		10 mol% Pd(OAc) ₂ 20 mol% DPPF		Ph	<u>_</u>
	N Ts 1a (0.2 mmol)	[Et ₃ NH] ⁺ [BF ₄] ⁻ (2.0 equiv), 60 °C toluene (4 mL), H ₂ O (1 mL), EG (2 mL)		N Ts 2a	
	entry	additive(s)	t (h)	2a	
	1	2.0 equiv Nal	24	No Reaction	
	2	2.0 equiv Nal ◄ hen 1.02 equiv Ag ₂ O ◄	····· 24 ∉ 36	64%	

Scheme 9. Effect of $[Et_3NH]^+[BF_4]^-$ on the Reactions under the Heterogenous and Homogenous Systems



Among them, ligand L16 was optimal, which afforded product (S)-2a in 79% yield and 93% ee.

Next, we investigated the substrate scope of Pd(0)/L16catalyzed asymmetric carboiodination under the biphasic Hbonding system. This asymmetric catalytic system was found to be robust and could be applicable to a range of (Z)-1-iodo-

1,6-dienes. The results are summarized in Scheme 4. Substrate 1b with an NNs linkage shows activity similar to that of 1a, affording product 2b in 77% yield and 94% ee. A wide range of phenyl substituents on the vinyl iodide moiety $(R^1 \text{ group})$ were well tolerated, giving products 2c-2i in moderate to good yields and with high enantioselectivity (86%-94% ee). Substrates 1h and 1i with an alkyl substituent also reacted smoothly to give products 2h and 2i in ca. 50% yield with high enantioselectivity. The relatively lower yields might stem from the reluctant oxidative addition of their vinyl iodides to the Pd(0) catalyst. Moreover, the reaction was found to tolerate a wide range of alkyl substituents on the alkene part, affording products 2j-20 with high ee. Substrates 11 and 1m show relatively lower reactivity, likely due to the sterichindrance imposed by cyclohexyl and benzyl groups. An alkyl chain with both BzO and TBSO groups was also compatible, as exemplified by the isolation of products 2p-2s. Substrates 1t-1w bearing other functional groups, such as ester, chloride, and amino groups as well as glycol acetal, reacted well under optimal conditions, providing products 2t-2w in moderate to good yields and with high enantioselectivity. While the reaction could be extended to substrates 1x and 1y with an O linkage, the enantioselectivity sharply dropped to 55 and 35%, respectively. On the other hand, substrate 1z with a $C(CO_2Me)_2$ linkage exhibited good reactivity to deliver product 2z in 70% yield with 87% ee.

Subsequently, we evaluated the potential of the biphasic system toward the asymmetric carbobromination of (Z)-1bromo-1,6-diene 3 (Scheme 5). Although this system was also applicable to substrate 3b, the reaction became very sluggish and the desired carbobromination product, 4b, was isolated in 15% yield even though a greater catalyst loading (20 mol %) and higher temperature (80 °C) were employed. We believed that, in addition to more challenging $C(sp^3)$ -Br RE, a relatively inferior oxidative addition of Pd(0) to vinyl bromine appears to be a second adverse factor in the carbobromination reaction. We therefore exploited an electron-richer ligand, L18, to overcome the reluctant oxidative addition, which indeed afforded product 4b in 43% yield with 94% ee. Although a relatively higher catalyst loading was employed, this reaction, to our knowledge, represents the first example of catalytic asymmetric carbobromination. We then briefly examined the scope of asymmetric carbobromination by using ligand L18. Gratefully, corresponding products 4c-4f were isolated in moderate yields and with excellent enantioselectivity (Scheme 5).

To demonstrate the robustness of this process, the reaction of laa was conducted on a 1 mmol scale under standard conditions, and product 2aa was still obtained in 58% yield and 86% ee (Scheme 6). In an attempt to explore the elaboration of product 2aa, the intramolecular Friedel-Crafts reaction was examined. With the use of trifluoromethanesulfonic acid as a solvent, bridged bicycle 5 was easily isolated in 72% yield with 87% ee. Moreover, product 2a underwent an $S_N 2$ reaction with 2-iodo-N-methylbenzamide to give compound 6, which was useful for the construction of fused bicycle 7. Chiral spirocycle 9 (96% ee) could also be obtained from product 2v via Bocgroup deprotection and subsequent S_N^2 reaction. These chemical manipulations clearly demonstrated that both alkene and alkyl iodide groups of the carboiodination products are convenient handles for constructing structurally complex compounds (Scheme 6).

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Scheme 10. DFT Calculations and Establishment of the S_N2-Type Mechanism on the Step of C(sp³)-I RE

Mechanistic Considerations. On the basis of our previous studies,¹⁴ a general reaction mechanism is proposed (Scheme 7). First, the oxidative addition of 1a to the Pd(0) catalyst generates alkenyl–Pd^{II}–I intermediate **A**. Next, migratory insertion of the tethered alkene gives rise to alkyl–Pd^{II}–I intermediate **B**, which is the enantio-determining step (EDS). Finally, intermediate **B** undergoes $C(sp^3)$ –I RE to give product (*S*)-2a and regenerate the Pd(0) catalyst. Under the biphasic system, $[Et_3NH]^+[BF_4]^-$ would develop a potential H-bond with the iodide in intermediate **B** to accelerate $C(sp^3)$ –I RE, therefore rendering the reaction more facile. To interrogate how and when these additives influenced the carbohalogenation reaction, we carried out several mechanistic studies.

First, we prepared a known X-Pd^{II}–C(sp³) complex, (Ph₃P)₂Pd(Me)I.²² This complex was found to be very stable, and no decomposition was observed even after it was incubated in toluene at 60 °C for 36 h. Thus, PhI was introduced with the hope of capturing any Pd(0) species generated from the reductive elimination of (Ph₃P)₂Pd(Me)I. When the mixture of PhI (10.0 equiv) and (Ph₃P)₂Pd(Me)I was subjected to toluene at 60 °C, no reaction was observed and (Ph₃P)₂Pd(Me)I was recovered in nearly quantitative yield (eq 1). In sharp contrast, once the biphasic system was



employed, the reaction produced a 27% yield of (Ph₃P)₂Pd-(Ph)I along with a 63% yield of recovered (Ph₃P)₂Pd(Me)I (eq 2). These results clearly demonstrate a critical role of the biphasic system on the key step of $C(sp^3)$ -I RE.Then, two more control experiments on NaI testing were conducted (Scheme 8). It is known that additional NaI has no negative impact on carboiodonation under the previously established H-bond-donor-free conditions.^{19a,23} However, the introduction of NaI (2.0 equiv) into the current biphasic system completely shut down the reaction of 1a (Scheme 8, entry 1). Notably, this reaction was retriggered when the iodide in the aqueous phase was removed by the addition of Ag₂O (1.02 equiv), resulting in the isolation of product 2a in 64% yield (Scheme 8, entry 2). These findings could be interpreted as the additional iodine anion being capable of outcompeting the interaction of $[Et_3NH]^+[BF_4]^-$ with intermediate **B**. We believe that this interaction is most likely to be an H-bonding interaction, although we cannot provide more direct evidence at this stage.

Finally, we analyzed the sample consisting of toluene- d_s , H_2O , EG, and $[Et_3NH]^+[BF_4]^-$ by means of ¹H NMR. To our surprise, there is no presence of EG and $[Et_3NH]^+[BF_4]^-$ in toluene- d_s , strongly implying that the proposed H-bonding interaction would take place on the liquid–liquid interphase. Nevertheless, the biphasic system was found to be essential to the reaction outcome, especially to maintain a consistent enantioselectivity. As shown in Scheme 9a, increased loading of $[Et_3NH]^+[BF_4]^-$ improved the yield of **2a** significantly but had little effect on the enantioselectivity when the reaction of **1a** was performed in the toluene/H₂O/EG biphasic system. Surprisingly, opposite enantioselectivity was observed, albeit with a low value when a homogeneous system, dioxane/H₂O/EG, was instead employed under otherwise identical conditions (Scheme 9a). In principle, the ammonium salt

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Notes

The authors declare no competing financial interest.

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was able to develop H-bonds with intermediates A and B (Scheme 9b). The former would become apparent and lead to the formation of H-bonding adduct A' due to a much higher concentration of $[Et_3NH]^+$ in the case of a homogeneous system. As a result, the kinetically facial migratory insertion in the EDS would be interrupted, so intermediate C' was generated as the major diastereoisomer, which was responsible for the observed opposite enantioselectivity. On the other hand, the toluene/H₂O/EG biphasic system was believed to place a threshold on the concentration of $[Et_3NH]^+$ so that it imposed minor ramification on the EDS while promoting the C(sp³)–I RE via H-bonding adduct C (Scheme 9b).

To better understand the role of H-bonding in the $C(sp^3)$ -I RE, a preliminary computational study was carried out, which disclosed that the stepwise-type RE is favored over the concerted one. (For details, see Figure S7.) Moreover, the free energy of I-Pd^{II} bond heterolytic dissociation is 41.3 kcal/mol, and the energy barrier of $C(sp^3)$ -I RE is as high as 41.7 kcal/ mol via transition state TS1 in the absence of [Et₃NH]⁺[BF₄]⁻ (Scheme 10a). In the presence of $[Et_3NH]^+[BF_4]^-$, the Hbonding interaction is exergonic by 2.0 kcal/mol and the elongation of the I-Pd^{II} bond is indicative (2.835 Å vs 2.774 Å), which facilitates I-Pd^{II} bond dissociation at as low as 5.3 kcal/mol free energy. This may also contribute to the stabilization of the resulting $[alkyl-Pd]^+$ by $[BF_4]^-$ (Pd-F: 2.267 Å). The reductive elimination via transition state TS2 requires an overall activation energy of 34.9 kcal/mol, which is the turnover-determining step in the whole catalytic cycle (Figure S7). Taken together, the computational study clearly pointed out that the H-bonding interaction is able to greatly reduce the reaction barrier of $C(sp^3)$ -I RE ($\Delta\Delta G = -6.8$ kcal/mol). Moreover, transition state TS2 implies S_N2-type mechanism $C(sp^3)$ -I RE, which was confirmed by the stereochemical outcome of the reaction of (Z)-1a-D under optimal conditions (Scheme 10b). However, more studies are still needed to establish the working mode of H-bonding and to elucidate the mechanism of the challenging $C(sp^3)$ -I RE.

CONCLUSIONS

We have developed a unique strategy to enable Pd(0)catalyzed carbohalogenation reactions at much lower temperature. This strategy features simple operation with the addition of $[Et_3NH]^+$ salt as the H-bond donor under the toluene/ H_2O/EG biphasic system. These advantages allow us to easily achieve asymmetric carboiodination and carbobromination with high levels of reaction efficiency and enantioselectivity by using the readily available chiral FerroPhos ligand. The putative H-bonding interaction between the $[Et_3NH]^+$ and $X-Pd^{II}-C(sp^3)$ species significantly enhances $X-Pd^{II}$ bond heterolytic dissociation, which plays an essential role in the reduction of the $C(sp^3)-I$ RE reaction barrier. We hope that the newly developed biphasic system would open up a new avenue to stimulate the potential of palladium catalysis in the asymmetric synthesis of organohalides via $C(sp^3)-X$ RE.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c10797.

Experimental procedures, characterization data of products, and calculation details (PDF)

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