Palladium-Catalyzed Interceptive Decarboxylative Addition of Allyl Carbonates with Carbonyl Group

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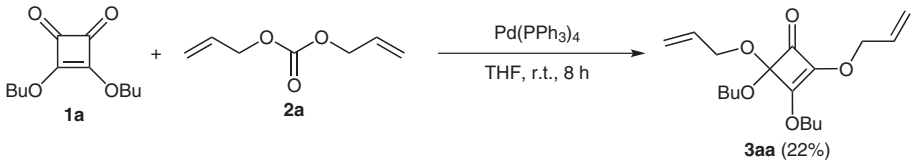
Abstract: The first palladium-catalyzed interceptive decarboxylative 1,4-addition of allyl carbonates with squarates is reported. Interestingly, the C-3 carbonyl group of N-substituted isatins undergoes smooth decarboxylative 1,2-addition with allyl carbonates. This transformation offers a straightforward method for the synthesis of spiro-oxepane-fused 2-oxindole.

Key words: palladium, allylation, conjugate addition, allyl complexes, spiro compounds, metathesis

The development of efficient methods to construct organic frameworks continues as a challenge in both academic as well as industrial research applications. Since the ground-breaking work of Tsuji,[1] Saegusa,[2] and Trost,[3] palladium-catalyzed decarboxylative allylation has emerged as an important method for the construction of new carbon–carbon bonds. Intensive research efforts have been devoted to transition-metal-catalyzed intramolecular decarboxylative allylation by many research groups.[4] Recent advances toward interceptive decarboxylative allylation include the reactions of allyl-β-keto esters,[5] allylcarbonates,[6] allyl carbamates,[7] and allyl diphenylglycinate esters[8] with electrophilic olefins. Hayashi and coworkers have extended the palladium-catalyzed IDcA to malonate-derived valerolactones.[9]

We have recently disclosed our success on palladium-catalyzed allylation reactions of isatylidenes[10] and heptafulvenes.[11] Nucleophilic allylation of carbonyl groups have attracted attention of a number of organic chemists.[12] Yamamoto et al. reported the first palladium-catalyzed allylation of aldehydes using bis-π-allylpalladium intermediates.[13] Allylation of carbonyl groups using iridium,[14] indium,[15] zinc,[16] and other metal reagents[17] have been extensively studied. In 2004, Schaus and co-workers reported the palladium(0)-catalyzed decarboxylative aldol reaction of allyl-β-keto esters and aldehydes.[18] But there are only limited reports on palladium-catalyzed intermolecular decarboxylative coupling with carbonyl groups.[9c,8b] This fact combined with our interest in allylation using π-allyl–palladium complex prompted us to investigate its reactivity on activated ketones such as squarates and isatins. Herein, we report the catalytic interceptive decarboxylative 1,4-addition of allylcarbonates with squarates and 1,2-addition of carbonyl group of acenaphthenequinone and isatins.

Squarates, fascinating and versatile C-4 synthons, offer the prospect of serving as useful starting materials for the synthesis of a wide variety of compounds.[19] The monoaddition and two-fold addition to the carbonyl group of squarates by organolithium and Grignard reagents to synthesize polycyclic compounds are well documented in the literature.[20] But there are only few reports on palladium-catalyzed reactions involving squarates.[19d,21] Our initial studies involved the treatment of dibutyl squarate (**1a**) and diallylcarbonate **2a** in the presence of $Pd(PPh_3)_4$ (5 mol%) in THF at room temperature. The reaction afforded 1,4-addition product 2,4-bis(allyloxy)-3,4-dibutoxycyclobut-2-enone (**3aa**) in 22% yield (Scheme 1). The structure of the 1,4-addition product was characterized by usual spectroscopic analysis,[22] and the regiochemistry was con-



Scheme 1 Decarboxylative 1,4-addition of diallylcarbonate with dibutyl squarate

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firmed by HMBC spectral analysis.[23] To the best of our knowledge this is the first report on palladium-catalyzed decarboxylative 1,4-addition of allyl carbonates to squarate.

With this promising result in hand, we investigated the generality of this reaction under the best conditions identified for the conversion of dibutyl squarate **1a** into cyclobutenone derivative **3aa**.[23] The developed method was successfully applied to other alkyl squarates **1b**,**c**. The scope of the reaction was substantially expanded by utilizing various allyl carbonates **2a**–**c**. All the reactions proceeded smoothly at room temperature to produce the desired ketals **3aa**–**cc** in moderate yields (Table 1). Regioselective 1,4-addition achieved using the alkyl squarate **1b**,**c**, but the 1,4-addition is not observed for isopropyl squarate **1d**. The branched isopropyl group placed at the olefinic carbon makes the 1,4-conjugate addition difficult.[20f] This palladium-catalyzed synthesis of ketals is milder than the existing methods for acetalization, which mostly involve acidic reagents.[24]

Table 1 Decarboxylative 1,4-Addition of Allyl Carbonates with Squarates[a]

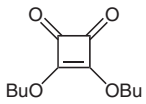
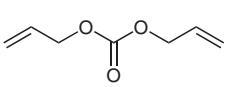
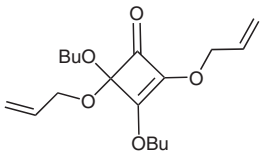
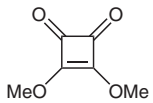
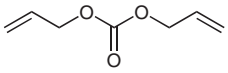
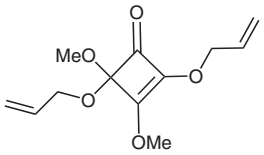
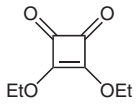
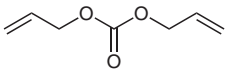
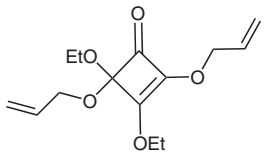
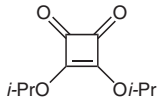
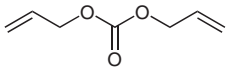
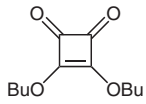
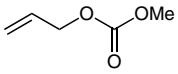
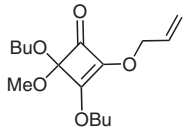
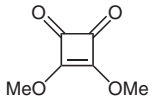
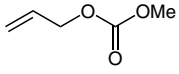
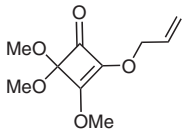
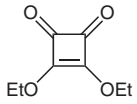
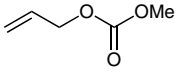
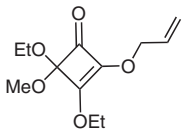
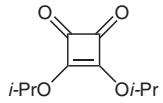
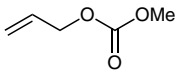
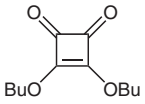
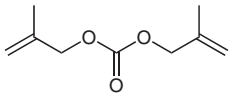
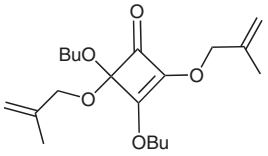
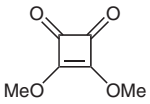
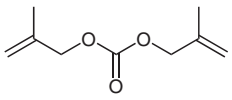
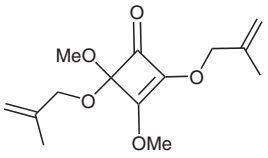
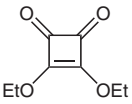
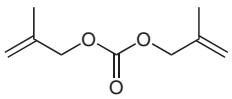
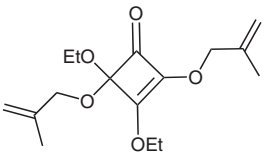
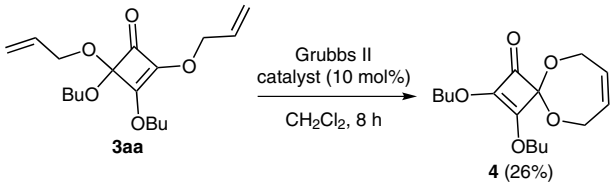
Entry	Squarate	Allyl carbonate	Product	Yield (%)
1	 **1a**	 **2a**	 **3aa**	42[b] (62)[c]
2	 **1b**	 **2a**	 **3ba**	59[b] (74)[c]
3	 **1c**	 **2a**	 **3ca**	21[b] (69)[c]
4	 **1d**	 **2a**	n.r.[d]	
5	 **1a**	 **2b**	 **3ab**	18[b] (67)[c]
6	 **1b**	 **2b**	 **3bb**	45[b] (75)[c]
7	 **1c**	 **2b**	 **3cb**	29[b] (63)[c]

Table 1 Decarboxylative 1,4-Addition of Allyl Carbonates with Squarates[a] (continued)

Entry	Squarate	Allyl carbonate	Product	Yield (%)
8	 **1d**	 **2b**	n.r.[d]	
9	 **1a**	 **2c**	 **3ac**	36[b] (69)[c]
10	 **1b**	 **2c**	 **3bc**	43[b] (73)[c]
11	 **1c**	 **2c**	 **3cc**	44[b] (71)[c]

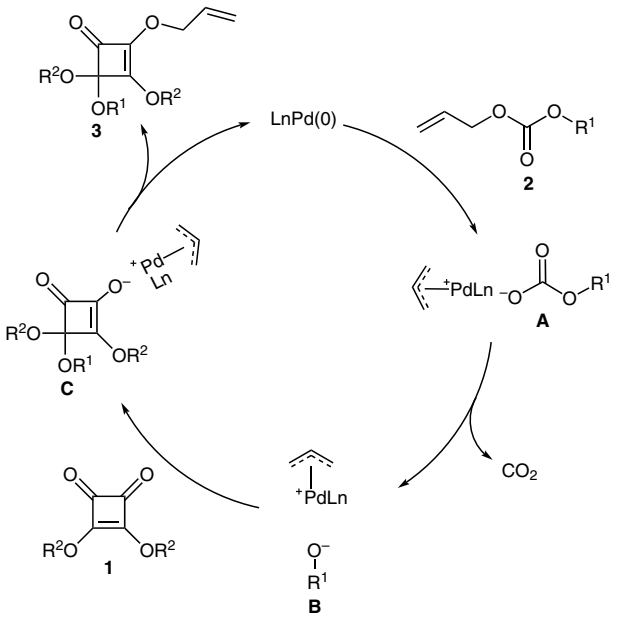
[a] Reaction conditions: squarate (1.0 equiv), allyl carbonate (2.0 equiv), catalyst (10 mol%), CH_2Cl_2 (2 mL), r.t., 12 h.
[b] Isolated yield.
[c] Yield based on recovered starting material.
[d] n.r. = no reaction.

We have carried out a straightforward synthetic transformation of 2,4-bis(allyloxy)-3,4-dibutoxycyclobut-2-enone (**3aa**). The ring-closing metathesis of compound **3aa** with Grubbs second-generation catalyst afforded spiro-4,7-dihydro-1,3-dioxepine-fused 2-butenone derivative **4** in 26% yield (Scheme 2). The formation of product **4** is presumed to form through the allyloxy rearrangement followed by ring-closing metathesis.[23]

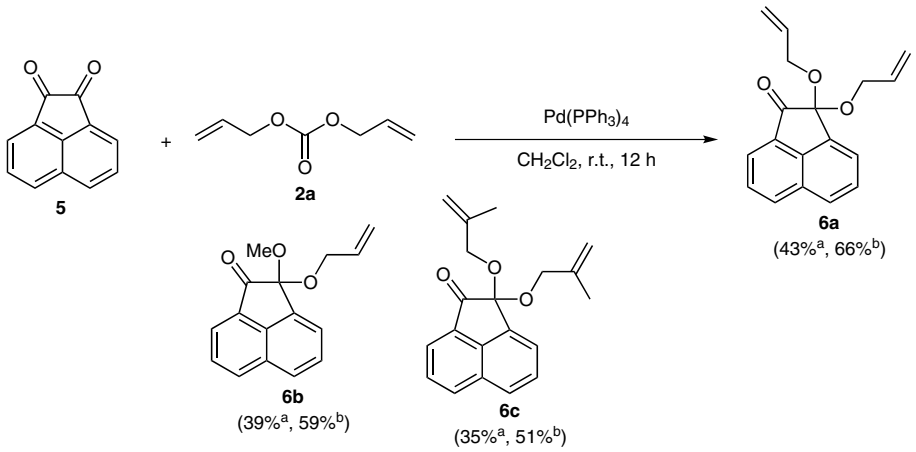


Scheme 2 Ring-closing metathesis of bisallyloxy cyclobutenone

Based on the results, we propose a plausible mechanism as illustrated in Scheme 3. The catalytic cycle is initiated by the oxidative addition of palladium(0) to allyl carbonate **2** followed by decarboxylation to generate π-allyl–palladium complex **B**.[1,6] The alkoxy anion undergoes 1,4-addition with squarate **1** to give cationic π-allyl–palladium complex **C** having the oxyanion of squarate as the counterion. Reductive elimination of **C** results in the formation of allylated product **3** and regenerates the catalyst.



Scheme 3 Proposed catalytic cycle



Scheme 4 Decarboxylative addition of allyl carbonate with acenaphthenequinone. [a] Isolated yield. [b] Yield based on recovered starting material.

To examine the possibility of interceptive decarboxylative 1,2-addition we carried out the reaction of allyl carbonates with electrophilic acenaphthenequinone under the similar conditions. Allyl carbonates **2a**–**c** reacted smoothly with **5** to furnish the corresponding ketals **6a**–**c** in moderate yields (Scheme 4).

With a view to study the generality of 1,2-addition of allylcarbonates, we turned our attention to the functionalization of carbonyl group of isatins. Isatins have been widely used as precursors of spiro-oxindoles and many natural products.[25] In an initial attempt, we carried out the reaction of 1-ethyl isatin (**7a**) with diallyl carbonate **2a** in the presence of 5 mol% $Pd(PPh_3)_4$ in THF at room temperature. The C-3 carbonyl group underwent smooth allylation–oxyallylation to afford 3,3-bis(allyloxy)-1-ethylindolin-2-one (**8aa**) in 57% yield (Scheme 5). The structure of the product was established by NMR analysis, mass spectrometry, and unambiguously confirmed by single-crystal X-ray analysis of one of the derivatives **8da** (Figure 1).[26]

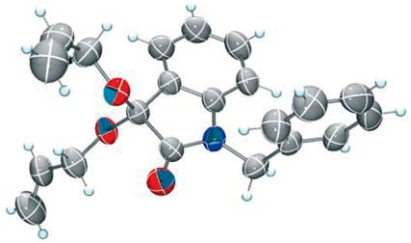


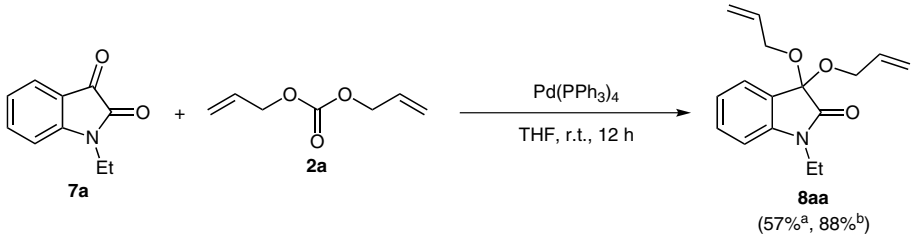
Figure 1 ORTEP view of compound **8da**

The method was also proved to be very convenient and general for the palladium-catalyzed decarboxylative 1,2-addition of allyl carbonates **2a**–**c** with the C-3 carbonyl group of a range of isatins **7a**–**d**. The reactions proceeded very efficiently under the same catalytic conditions to furnish the desired 1,2-addition products **8aa**–**dc** in good yields (Figure 2).

The reaction of isatin **9** with diallyl carbonate **2a** was conducted under similar conditions. The reaction afforded 1-allylindoline-2,3-dione (**10**) in 52% yield along with 1-allyl-3,3-bis(allyloxy)indolin-2-one (**8ca**) in 8% yield (Scheme 6). From our investigations, it is noticeable that the C-3 functionalization occurs only in the N-protected isatin.

Finally, the synthetic utility of this chemistry is highlighted by the synthesis of spiro-dioxepine-fused 2-oxindole (Scheme 7). Ring-closing metathesis of **8aa** using Grubbs first-generation catalyst afforded dioxepine-fused spiro-oxindole in 76% yield. It is noteworthy that spirocyclic oxindole compounds are valuable pharmaceuticals.[25] Spiro-oxindoles have been reported to possess a wide range of biological activities such as progesterone receptor modulators,[27] anti-HIV,[28] anticancer,[29] antimalarial,[30] and MDM2 inhibitor.[31]

In summary, we have developed for the first time a palladium-catalyzed interceptive decarboxylative 1,4-addition of allyl carbonates to squarates. Interceptive decarboxylative 1,2-addition of allyl carbonates with acenaphthenequinone and N-substituted isatins also described. Furthermore, the ring-closing metathesis of the 1,2-addi-



Scheme 5 Decarboxylative addition of diallyl carbonate with 1-ethyl isatin. [a] Isolated yield. [b] Yield based on recovered starting material.

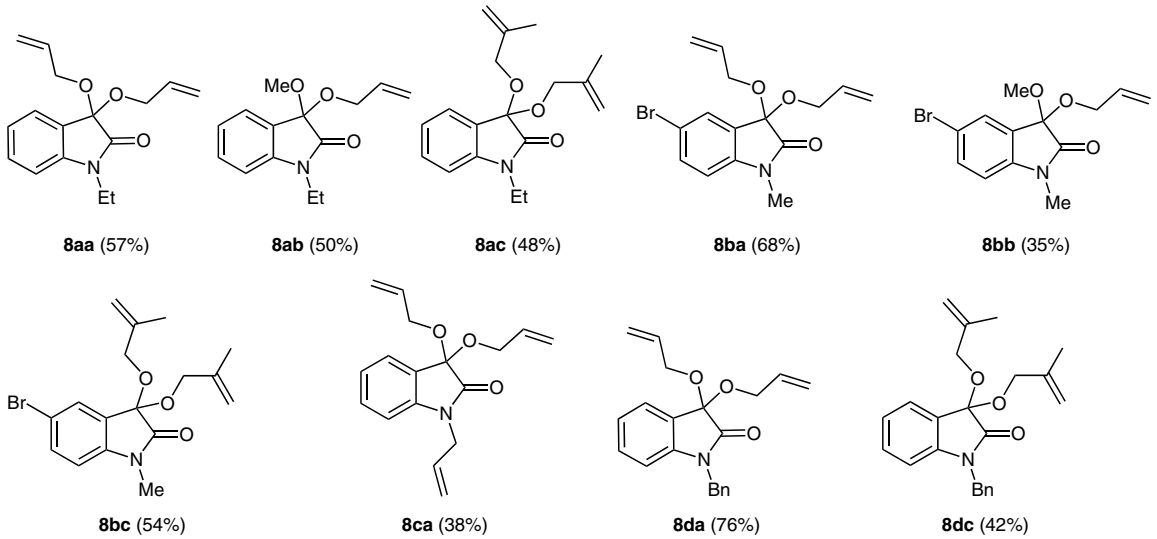
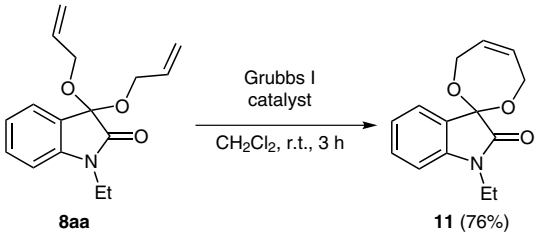


Figure 2 Decarboxylative 1,2-addition of allylcarbonates with N-substituted isatin. *Reagents and conditions*: isatin (1.0 equiv), allylcarbonate (2.0 equiv), catalyst (5 mol%), THF (2 mL), r.t., 12 h.



Scheme 7 Ring-closing metathesis of bisallyloxy 2-oxindole

tion product of isatin furnished the corresponding spirodioxepine-fused 2-oxindole in good yield. Investigations to broaden the scope of this chemistry to other activated carbonyl groups are currently in progress.

Typical Procedure for the Palladium-Catalyzed Decarboxylative Allylation of Dibutyl Squarate

Dibutyl squarate (**1a**, 40 mg, 0.18 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.018 mmol) were taken in a Schlenk tube, degassed, and diallyl carbonate **2a** (50 mg, 0.35 mmol) was added followed by CH_2Cl_2 (2 mL). Argon gas was purged into the reaction mixture and stirred at r.t. for 12 h. The reaction was monitored by TLC. The solvent was removed under reduced pressure, and the residue on silica gel (100–200 mesh) column chromatography using 3% EtOAc in hexane afforded **3aa** in 42% yield (24 mg), and the unreacted dibutyl squarate (13 mg) was recovered.

Typical Procedure for the Ring-Closing Metathesis of 2,4-Bis(allyloxy)-3,4-dibutoxycyclobut-2-enone (3aa)

2,4-Bis(allyloxy)-3,4-dibutoxycyclobut-2-enone (**3aa**, 43 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (6 mL). To this, Grubbs second-generation catalyst (12 mg, 0.013 mmol) was added and stirred at r.t. for 8 h. The reaction was monitored by TLC. The solvent was evaporated in vacuo, and the residue on silica gel (100–200 mesh) column chromatography using 5% EtOAc in hexane afforded the product **4** in 26% (10 mg) yield.

Typical Procedure for the Ring-Closing Metathesis of 3,3-Bis(allyloxy)-1-ethylindole-2-one (8aa)

3,3-Bis(allyloxy)-1-ethylindolin-2-one (**8aa**, 25 mg, 0.09 mmol) was dissolved in CH_2Cl_2 (4 mL). To this, Grubbs first-generation catalyst (4 mg, 0.0046 mmol) was added and stirred at r.t. for 3 h. The reaction was monitored by TLC. The solvent was evaporated in vacuo, and the residue on silica gel (100–200 mesh) column chromatography using 10% EtOAc in hexane afforded the product **11** in 76% (17 mg) yield.

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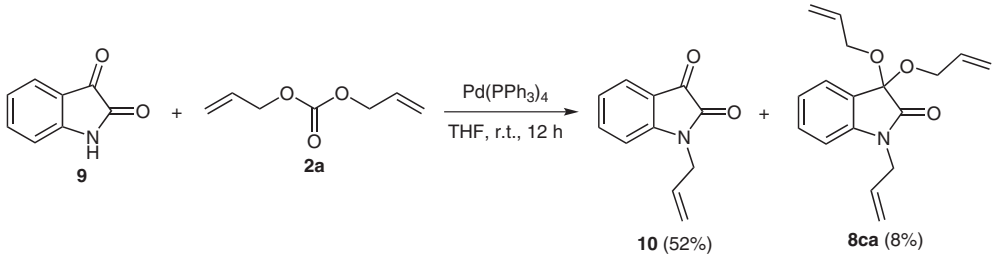

Scheme 6 Decarboxylative addition of diallyl carbonate with isatin

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(22) **Spectral Data of 3aa**
R_f = 0.61 (EtOAc–hexane, 3:7). IR (neat): 2961, 2935, 2874, 1778, 1638, 1460, 1331, 1061 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.98–5.91 (m, 2 H), 5.39–5.15 (m, 4 H), 4.77 (d, *J* = 5.5 Hz, 2 H), 4.40 (t, *J* = 6.5 Hz, 2 H), 4.27 (d, *J* = 5.5 Hz, 2 H), 3.71 (t, *J* = 6.5 Hz, 2 H), 1.75 (quin, *J* = 7.0 Hz, 2 H), 1,58 (quin, *J* = 7.0 Hz, 2 H), 1.47–1.36 (m, 4 H), 0.96 (t, *J* = 7.5 Hz, 3 H), 0.91 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 184.9, 167.4, 137.1, 134.3, 132.6, 118.8, 116.8, 108.2, 73.3, 71.2, 66.6, 65.5, 31.9, 31.5, 19.2, 18.7, 13.8, 13.6. ESI-HRMS: *m/z* calcd for $C_{18}H_{28}O_5Na$ $[M + Na]^+$: 347.18344; found: 347.18249.

(23) See the Supporting Information.

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