JOC The Journal of Organic Chemistry

Article

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Selective Pinacol-Coupling Reaction using a Continuous Flow System

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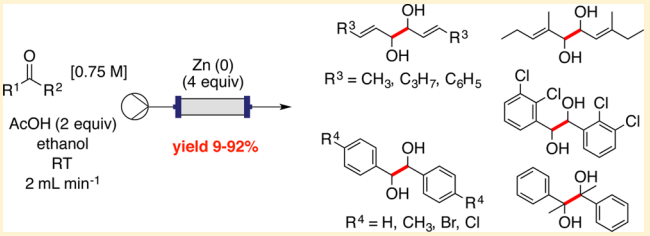
Supporting Information

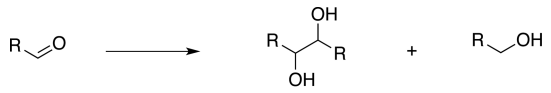
ABSTRACT: The first continuous flow pinacol coupling reaction of carbonyl compounds was successfully achieved within only 2 min during a single pass through a cartridge filled with zinc(0). The optimized method allowed the efficient production of gram-scale value-added compounds with high productivity. The developed methodology is efficient for aromatic or α,β-unsaturated aldehydes but gives moderate results for more stable acetophenone derivatives. Moreover, the flow method displayed better results in terms of yield and selectivity in comparison to the corresponding batch methodology.



INTRODUCTION

Pinacol coupling of carbonyl compounds is of particular interest within all C−C coupling methods because of the synthetic potential of pinacol derivatives.[1] Following pioneer works reported by Fitting,[2] this reaction still finds many applications for constructing biologically important products or useful synthetic intermediates.[3] Many batch methodologies for pinacol coupling reactions have been developed using low-valent metals in excess such as the Zn−Cu couple,[4] Mg,[5] Mn,[6] Zn,[7] In,[8] Sm,[9] Al,[10] Ga,[11] and other metals.[12] Ti, V, or Zr complexes have also been widely used to promote this reaction.[13] In the framework of green chemistry, our research group focused on this particular reaction and several batch sustainable methodologies have been reported: (i) micellar catalysis under sonication,[14] (ii) use of commercially available acidic resins[15] or use of only acidic water.[16] Due to our interest and the first encouraging results, a continuous flow system for selective pinacol coupling reactions was envisaged. In fact, in the past few years, the use of heterogeneous flow systems in synthetic organic chemistry has been widely explored due to many expected advantages such as very efficient heat transfer in comparison with batch methodologies, good monitoring of temperature, and enhanced mass transfer.[17] This innovative approach also permits the integration of several steps into one single streamlined process, thus shortening the time from research to pilot scale and production.[18] Concerning the pinacol coupling reaction, our goal was to enhance the selectivity for pinacol coupling versus side reactions thanks to an intimate contact between the metal and the substrates. In fact, from our experiments, the limiting step for pinacol coupling relies on the meeting of ketyl radicals, allowing the formation of the C−C bond. As a consequence, the main observed side product came from direct reduction of the carbonyl compound **1** to the corresponding alcohol **3** (Scheme 1). Our goal was to design efficient and selective coupling reactions in a flow system under green conditions.

Scheme 1. Pinacol Coupling Reaction and Reduction Side Reaction



1 **2** **3**

RESULTS AND DISCUSSION

In the present work, a continuous flow system was used. All reactants were dissolved in ethanol and pumped into the system with an HPLC pump (0.5−20 mL min^{-1}) at room temperature. The solution was then flowed into a cartridge filled with zinc(0) powder. The cartridge possesses an internal diameter of 15 mm and a length of 100 mm. In our case, the piston was placed to allow a fixed useful volume of 4 mL containing the immobilized catalyst and potential additives (Figure 1).

In the first case, in order to ensure the good solubility of all reactants, ethanol was selected as the solvent for the continuous flow reaction and Zn(0) was packed. Crotonaldehyde (**1a**) was chosen as the model substrate and diluted in ethanol (0.75 M) in the presence of 2 equiv of acetic acid as activator. Acetic acid was selected due to its use in to previously reported works for its high promoting ability at room temperature.[16] The solution was pumped at a 2 mL min^{-1} flow rate at room temperature, and the resulting solution was collected and analyzed (Table 1, entry 1). After a single pass, 83% of the substrate **1a** was

Received: August 22, 2016
Published: October 25, 2016

DOI: 10.1021/acs.joc.6b02069
J. Org. Chem. 2016, 81, 11065−11071

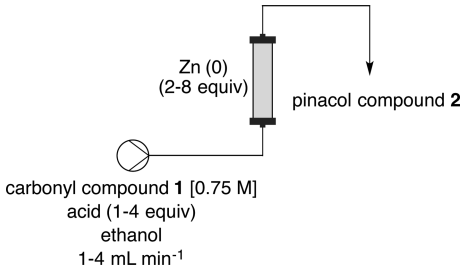
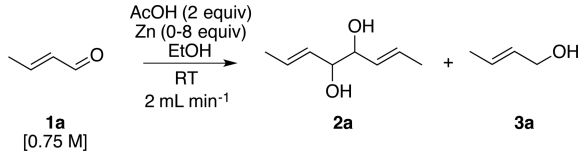


Figure 1. Experimental setup of the flow system.

Table 1. Screening of Zinc Amount[a]



entry	amt of Zn (equiv)	conversn (%)	yield (%) 2a	yield (%) 3a	relative sel[b] (%)	global sel[c] (%)	*dl*/*meso* for **2a**
1	2	83	75	4	95	90	45/55
2	0	0	0	0			
3	3	85	77	4	95	91	40/60
4	4	96	81	5	94	84	40/60
5	8	94	83	7	92	88	40/60

[a]Reaction conditions: crotonaldehyde (**1a**, 6 mmol) and AcOH (2 equiv) were diluted in ethanol (8 mL) and flowed through a cartridge filled with a variable amount of zinc dust at 2 mL min^{-1} at room temperature. [b]Relative selectivity is defined as the ratio between **2a** and **2a** + **3a**. [c]Global selectivity is defined as the ratio between **2a** and conversion.

converted and 75% of the corresponding pinacol **2a** was obtained. Only 4% of alcohol **2a** was observed in the resulting solution. Under such conditions, the reaction in flow is highly selective. As expected, in the absence of zinc, the reaction did not occur (Table 1, entry 2). Increasing the amount of zinc to 3 equiv allowed a weak improvement in conversion and yield in **2a** with an excellent selectivity (Table 2, entry 3). However, when more zinc was in contact with the solution, the conversion increased but favored the alcohol formation (Table 2, entries 4 and 5). As a compromise, the amount of zinc was fixed at 4 equiv to reach a total conversion (96%) and other parameters were screened to manage the selectivity of the reaction.

In a second instance, different acid sources and quantities were screened and compared. Liquid acids were directly diluted in ethanol in the presence of crotonaldehyde (**1a**). Insoluble acids were packed in the cartridge in the presence of Zn(0). Two systems were attempted: (i) the first consisted of grinding the supported acid with zinc and packing them together; (ii) the second consisted of placing the supported acid before and after the layer of zinc (Figure 2). All results are gathered in Table 2.

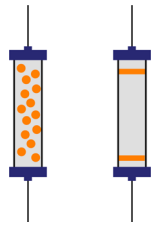
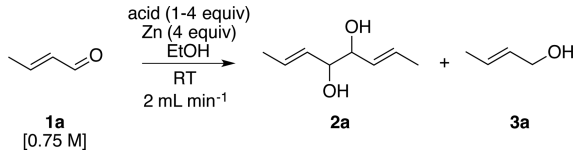


Figure 2. Different packings of Zn(0) (gray) and AmberlystH15 (orange).

Decreasing the amount of acetic acid (1 vs 2 equiv) slowed the reaction rate and only 80% conversion was obtained (entry 2). Moreover, 64% of pinacol **2a** was recovered at the end of the process, suggesting that some product could be retained on the metal and did not elute in the collection sample. As the acid is known to break down the chelates at the end of the reaction, a low acid concentration should be insufficient for recovering all formed products. Increasing the quantity of acetic acid (4 vs 2 equiv) boosted the conversion and allowed a better 87% yield in pinacol **2a** (Table 2, entry 3). However, as previously described, it also favored the formation of the alcohol **3a** in 10%

Table 2. Influence of Acid Sources and Quantities[a]



entry	acid source	amt of acid (equiv)	conversn (%)	yield (%) 2a	yield (%) 3a	relative sel[b] (%)	global sel[c] (%)	*dl*/*meso* for **2a**
1	AcOH	2	96	81	5	94	84	40/60
2	AcOH	1	80	64	4	94	80	45/55
3	AcOH	4	98	87	10	90	89	40/60
4	H_2SO_4	2	95	30	65	31	31	40/60
5	CH_3SO_3H	2	96	70	26	73	73	45/55
6	AmberlystH15	2[d]	30	22	8	73	73	40/60
7	AmberlystH15	1 + 1[e]	15	11	4	73	73	40/60
8	H_2SO_4@SiO_2 (33 wt %)	2[d]	35	20	15	57	57	40/60

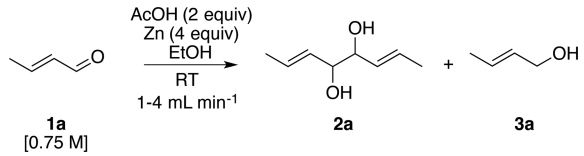
[a]Reaction conditions: crotonaldehyde (**1a**, 6 mmol) and acid were diluted in ethanol (8 mL) and flowed through a cartridge filled with zinc dust (4 equiv) at 2 mL min^{-1} at room temperature. [b]Relative selectivity is defined as the ratio between **2a** and **2a** + **3a**. [c]Global selectivity is defined as the ratio between **2a** and conversion. [d]The supported acid was ground with zinc, and the resulting mixture was filled in the cartridge. [e]Zinc was packed between two layers of the supported acid separated by porous frits.

DOI: 10.1021/acs.joc.6b02069
J. Org. Chem. 2016, 81, 11065−11071

yield. It is notable that all formed products are recovered in the collection sample (98% conversion for 97% recovered products), which proved the importance of a sufficient quantity of acid to recover them from zinc. Using 2 equiv of sulfuric acid boosted the reaction, but in favor of the direct reduction product **3a** (Table 2, entry 4). This strong acid allowed the recovery of all formed products at the end of the reaction. Liquid methanesulfonic acid was also strongly active in the reaction, but with a high 25% amount of alcohol formed (Table 2, entry 5). In order to vary the nature of the acid, some supported acids were used. AmberlystH15, a strongly acidic resin stable at room temperature, was mixed with zinc, and the resulting mixture was packed in the cartridge. To our disappointment, the conversion of the reaction after a single pass was low (only 30%) even if the selectivity was good (Table 2, entry 6). Using a triple-layer system (acid/zinc/acid) decreased the conversion of the overall process but maintained the same selectivity (Table 2, entry 7). Using sulfuric acid supported on silica gel gave moderate conversion and yield with low selectivity (Table 2, entry 8). As a consequence, Zn(0) (4 equiv) and acetic acid (2 equiv) in a continuous flow process at room temperature were kept as standards for further optimization.

In a third time, the flow rate was varied between 1 and 4 mL min^{-1} for 4 equiv of packed zinc dust in the presence of acetic acid (2 equiv). This modification affected the residence time and also the productivity in pinacol **2a** (Table 3). Indeed, the

Table 3. Influence of Flow Rate Variation[a]



entry	residence time (min)	conversn (%)	yield (%) 2a	yield (%) 3a	relative sel[b] (%)	global sel[c] (%)	*dl*/*meso* for **2a**
1	4	95	70	15	82	74	40/60
2	2	96	81	5	94	84	45/55
3	1.33	79	64	4	94	81	40/60
4	1	89	76	5	94	85	40/60

[a]Reaction conditions: crotonaldehyde (**1a**, 6 mmol) and AcOH (2 equiv) were diluted in ethanol (8 mL) and flowed through a cartridge filled with zinc dust (4 equiv) at room temperature. [b]Relative selectivity is defined as the ratio between **2a** and **2a** + **3a**. [c]Global selectivity is defined as the ratio between **2a** and conversion.

faster the flow rate, the lower the residence time but the higher the productivity. With a continuous flow of 2 mL min^{-1}, 96% conversion was obtained with a good 84% selectivity for pinacol product **2a** (Table 3, entry 2). Only 5% of alcohol **3a** was observed after a single pass. When the residence time was doubled, the conversion was still high but a large amount of alcohol **3a** (15%) was obtained (Table 3, entry 1). A long contact with zinc seems to favor the direct reduction process. When the flow rate was increased, the conversion decreased but the selectivity remained the same as that for a 2 mL min^{-1} rate. It is possible that the carbonyl compound did not have enough contact time with zinc to efficiently react. As a consequence, a 2 mL min^{-1} flow rate was chosen as a compromise among conversion, yield, and selectivity.

As the reaction was not complete at the end of the first run, the collected solution was reinjected in a second cartridge filled with fresh zinc Zn(0) (4 equiv) (Figure 3). To ensure the

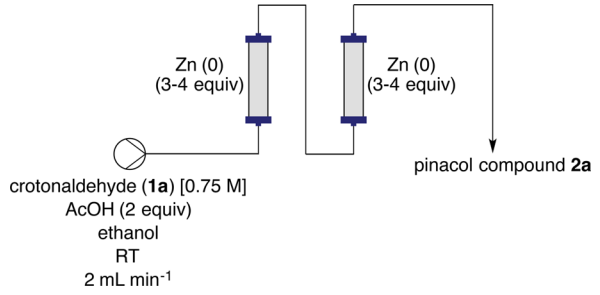
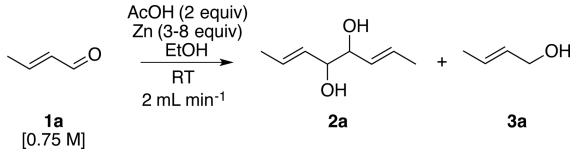


Figure 3. Experimental setup of the flow system using two cartridges.

recovery of all formed products at the end of the two passes, a solution of AcOH in ethanol was flowed. As expected, the conversion after passage through the two cartridges was total and a good 85% yield in pinacol **2a** was obtained (Table 4,

Table 4. Effect of a Double Pass on the Reaction[a]



entry	no. of cartridges	amt of Zn (equiv)	conversn (%)	yield of **2a** (%)	global sel[b] (%)	*dl*/*meso* for **2a**
1	0	4	96	81	84	40/60
2	1	4 + 4	100	85	85	45/55
3	0	3	85	77	91	40/60
4	1	3 + 3	100	91	91	40/60

[a]Reaction conditions: crotonaldehyde (**1a**, 6 mmol) and AcOH (2 equiv) were diluted in ethanol (8 mL) and flowed through a cartridge filled with zinc dust Zn(0) at 2 mL min^{-1} at room temperature. At the end of the process, a AcOH/ethanol mixture was flowed to recover all formed products. [b]Global selectivity is defined as the ratio between **2a** and conversion.

entry 2). When the same system was used with 3 equiv of zinc, the conversion was still total and an excellent 91% yield in pinacol **2a** was obtained (Table 4, entry 4). A 5% amount of alcohol **3a** was observed, accompanied by some minor side products.

To finish, the recyclability of the zinc cartridge was evaluated. An initial amount of 8 equiv of zinc dust was packed in the cartridge, and some freshly prepared solutions of crotonaldehyde (**1a**) in AcOH/ethanol were flowed through the catalyst bed (Figure 4).

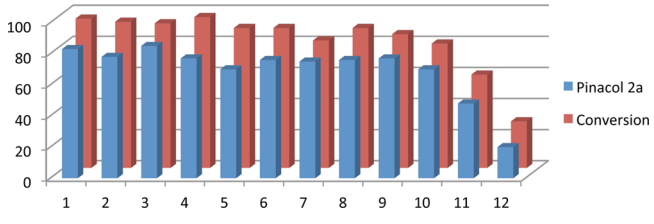
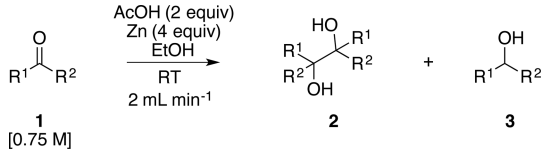


Figure 4. Recycling of the packed catalyst over time for 12 consecutive runs.

DOI: 10.1021/acs.joc.6b02069
J. Org. Chem. 2016, 81, 11065−11071

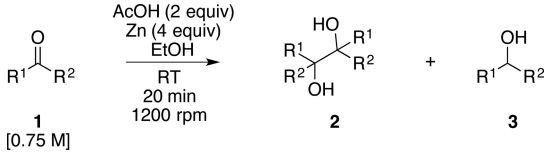
Table 5. Scope of the Continuous Flow Process in a Single Pass[a]



		substrate			yield (%)				
entry	compd	R^1	R^2	conversn (%)	**2**	**3**	global sel[b] (%)	relative sel[c] (%)	*dl*/*meso* for **2**
1	**a**	(*E*)-$CH_3CH{=}CH-$	H	96	81	5	84	94	40/60
2	**b**	(*E*)-$C_3H_7CH{=}CH-$	H	80	70	9	87	89	35/65
3[d]	**b**	(*E*)-$C_3H_7CH{=}CH-$	H	100	88	11	88	88	35/65
4	**c**	(*E*)-$C_2H_5CH{=}C(CH_3)-$	H	50	40	nd[e]	80		0/100
5	**d**	(*E*)-$C_6H_4CH{=}CH-$	H	95	85	6	89	93	60/40
6	**e**	C_6H_5	H	100	68	32	68	68	30/70
7[f]	**f**	4-Br-C_6H_4	H	100	92	2	92	98	25/75
8	**g**	4-CH_3-C_6H_4	H	100	92	<5	92	>95	50/50
9[g]	**h**	4−Cl-C_6H_4	H	55	20	33	36	38	25/75
10	**i**	2,3-$(Cl)_2$-C_6H_4	H	48	15	28	31	31	15/85
11	**j**	C_6H_5	CH_3	10	9	1	90	90	55/45
12	**k**	C_6H_5	C_6H_4	0	0	0			
13	**l**	$CH_3CH_2CH_2-$	H	0	0	0			

[a]Reaction conditions unless specified otherwise: aldehyde or ketone (**1**, 6 mmol) and AcOH (2 equiv) were diluted in ethanol (8 mL) and flowed through a cartridge filled with zinc dust (4 equiv) at 2 mL min^{-1} at room temperature. [b]Global selectivity is defined as the ratio between **2a** and conversion. [c]Relative selectivity is defined as the ratio between **2** and **2** + **3**. [d]The collection sample was reinjected in a second zinc cartridge (Zn(0) 4 equiv). [e]nd = not determined. [f]The reaction medium was diluted to 24 mL of EtOH. [g]The reaction medium was diluted to 32 mL of EtOH.

Table 6. Comparison with Batch Conditions using AcOH/EtOH[a]



		substrate			yield (%)			
entry	compd	R^1	R^2	conversn (%)	**2**	**3**	global sel[b] (%)	relative sel[c] (%)
1	**a**	(*E*)-$CH_3CH{=}CH-$	H	100	99	1	99	99
2	**b**	(*E*)-$C_3H_7CH{=}CH-$	H	60	20	31	33	39
3	**d**	(*E*)-$C_6H_4CH{=}CH-$	H	90	42	42	50	50
4	**e**	C_6H_5	H	60	8	49	13	14
5	**g**	4-CH_3-C_6H_4	H	38	7	27	18	21

[a]Reaction conditions: carbonyl compound (**1**, 6 mmol) and AcOH (2 equiv) in the presence of zinc (Zn(0), 4 equiv) were diluted in ethanol (8 mL) and stirred (1200 rpm) at room temperature for 20 min. [b]Global selectivity is defined as the ratio between **2a** and conversion. [c]Relative selectivity is defined as the ratio between **2** and **2** + **3**.

Until the 10th run, conversions were high and yields in **2a** were good at between 70 and 85% with an average value of 75%. After the 10th run, conversion began to decrease dramatically and lower amounts of pinacol **2a** were observed. This decrease in yield and conversion was accompanied by the physical disappearance of zinc dust in the cartridge. In fact, after 10 runs, a great deal of zinc dust had reacted and was converted to white zinc salts poorly soluble in ethanol. Under these flow conditions, the pinacol coupling reaction was realized with less than 1 equiv of zinc per run, which is a good result in comparison with all reported batch methods.

The optimized conditions, carbonyl compound (6 mmol) diluted in ethanol (8 mL) in the presence of AcOH (2 equiv) flowed through a packed zinc bed (4 equiv) at a flow rate of 2 mL min^{-1} at room temperature, were then applied to some various carbonyl compounds in a single pass (Table 5). The first scope was realized on *α*,*β*-unsaturated compounds with a long linear chain ((*E*)-hex-2-enal (**1b**)) and branched chain ((*E*)-2-methylpent-2-enal (**1c**)) (Table 5, entries 2−4). The pinacol coupling of aldehyde **1b** afforded the desired product in 70% yield and 80% conversion. The selectivity for coupling was very good, and only 9% of alcohol **3b** was obtained (Table 5, entry 2). These results are slightly above those obtained for crotonaldehyde (**1a**) in a single pass, probably due to the steric hindrance of the aliphatic chain. As previously shown, a second pass through another zinc bed has been realized and, as expected, the conversion is total and led to pinacol **2b** in 88% yield with high selectivity (Table 5, entry 3). The greatly hindered substrate **1c** reacted with a moderate 50% conversion but with a high selectivity for pinacol coupling **2c** (Table 3, entry 4). Aromatic *α*,*β*-unsaturated aldehyde **1d** reacted well under flow conditions and gave 85% yield in pinacol product **2d** accompanied by only 6% of cinnamyl alcohol **3d**. Some aromatic aldehydes **1d**−**k**, well-known for their reactivity in

DOI: 10.1021/acs.joc.6b02069
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reductive coupling, were then submitted to the optimized flow conditions. It is notable that benzaldehyde (**1e**) was totally converted to 68% of pinacol **2e** and 32% of benzyl alcohol (**3e**) (Table 5, entry 6). 4-Bromobenzaldehyde (**1f**) was then successfully submitted to the continuous flow process, with an excellent 92% yield in pinacol **2f** (Table 5, entry 7). The same result was observed for 4-tolualdehyde (**1g**), with excellent yield and selectivity (Table 5, entry 8). Aromatic aldehydes bearing chlorine groups displayed a moderate reactivity in favor of the direct reduction products **3h,i** (Table 5, entries 9 and 10). It is noteworthy that the use of aldehydes **1f,h** having respectively a bromine and chlorine atom made it necessary to dilute the solution. Acetophenone (**1j**) reacted slowly under such flow conditions, giving only 9% of the desired pinacol product **2j**. This result can be attributed to the steric hindrance and the lower reactivity of aromatic ketones in comparison with aldehydes (Table 5, entry 11). As envisioned, a much more hindered benzophenone (**1k**) or aliphatic aldehyde (**1l**) did not react under such conditions (Table 5, entries 12 and 13).

In terms of comparison, the batch reaction was carried out with some relevant examples (Table 6). Crotonaldehyde (**1a**), which is highly reactive and possesses a short aliphatic chain, reacted with an excellent selectivity for pinacol coupling (Table 6, entry 1). (*E*)-Hex-2-enal (**1b**) showed a dramatic decrease in results under batch conditions in comparison with the flow conditions, with a majority of alcohol **3b** formed at the end of the process (Table 6, entry 2). The same tendency was observed when cinnamaldehyde (**1d**), benzaldehyde (**1e**), and 4-tolualdehyde (**1g**) were used as substrates, with lower selectivities under batch conditions than in continuous flow process (Table 6, entries 3−5). These results confirmed that, under our conditions, the continuous flow process favored the pinacol coupling of the substrates, probably due to an intimate contact between zinc and formed ketyl radicals.

CONCLUSION

The first highly selective continuous flow pinacol coupling reaction in acidic medium has been developed using an HPLC-type pump and a cartridge filled with the adequate reductor. The optimized conditions allowed the formation of pinacol products for α,β-unsaturated and aromatic aldehydes with a residence time of 2 min. The cartridge is filled with cheap zinc metal (Zn(0)), which can be used at less than 1 equiv per substrate for high conversion and productivity.

EXPERIMENTAL SECTION

General Information. All commercially available products and solvents were used without further purification. Reactions were monitored by TLC (Kieselgel 60F254 aluminum sheet) with detection by UV light or potassium permanganate acidic solution. Column chromatography was performed on silica gel 40−60 μm. Flash column chromatography was performed on an automatic apparatus, using silica gel cartridges. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz/54 mm ultralong hold. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to TMS as an internal standard. Coupling constants (J) are quoted in hertz. Comparisons with known or reported compounds and 2D methods (HMBC and HSQC experiments) have been used to confirm the NMR peak assignments.

General Procedure for the Synthesis of Pinacol Products 2. The desired carbonyl compound (**1**; 6 mmol) was dissolved in ethanol (8 mL) in the presence of acetic acid (2 equiv, 685 mg). The resulting solution was pumped at room temperature by an HPLC-type pump and flowed through a packed zinc dust (4 equiv) cartridge (intern diameter 15 mm, length 100 mm, useful volume 4 mL) at a 2 mL min^{-1} flow rate. At the end of the process, 8 mL of pure ethanol was flowed through the system. Ethanol was then evaporated, and the crude product was purified over a column of silica gel and eluted with a gradient of cyclohexane/ethyl acetate to give the pinacol products **2**.

*(2E,6E)-Octa-2,6-diene-4,5-diol (dl and meso) (**2a**)*..[19,15,16] Table 5, entry 1, colorless oil (346 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.65 (t, J = 6.5 Hz, 6H, CH_3), 2.55−2.47 (bs, 2H, OH), 3.84 (d, J = 4.7 Hz, 2H, C*H*−OH, *dl form*), 3.99 (d, J = 6.2 Hz, 2H, C*H*−OH, *meso form*), 5.45−5.36 (m, 2H, CH=CH), 5.73−5.66 (m, 2H, CH=CH). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ ppm: 17.9 (2 × CH_3), 75.6 (CH), 75.8 (CH), 128.9 (CH=CH), 129.1 (CH=CH), 129.4 (CH=CH), 129.8 (CH=CH). MS (ESI): 143.10 [M + H]$^+$, 165.11 [M + Na]$^+$.

*(4E,8E)-Dodeca-4,8-diene-6,7-diol (dl and meso) (**2b**)*..[20,15,16] Table 5, entry 2, colorless oil (417 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.85−0.79 (m, 6H, 2 CH_3), 1.36−1.30 (m, 4H, 2 CH_2), 1.99−1.93 (m, 4H, 2 CH_2), 2.82 (brs, 2H, OH), 3.81 (d, J = 8.4 Hz, 2H, C*H*−OH, *dl form*), 4.00 (d, J = 8.4 Hz, 2H, C*H*−OH, *meso form*), 5.42−5.32 (m, 2H, C*H*=CH), 5.68−5.61 (m, 2H, C*H*=CH). *dl*-**2b**: ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ ppm: 13.6 (CH_3), 22.2 (CH_2), 34.4 (CH_2), 76.1 (CH), 128.8 (CH=CH), 134.2 (CH=CH). *meso*-**2b**: ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 13.6 (CH_3), 22.2 (CH_2), 34.4 (CH_2), 75.6 (CH), 128.0 (CH=CH), 134.5 (CH=CH). MS (ESI): 199.16 [M + H]$^+$, 221.17 [M + Na]$^+$.

*(3E,7E)-4,7-Dimethyldeca-3,7-diene-5,6-diol (meso) (**2c**)*.[16] Table 5, entry 4, colorless oil (238 mg, 40% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.92 (t, 6H, 2 CH_3), 1.59 (s, 6H, 2 CH_3), 2.00 (quint, J = 7.6 Hz, 4H, 2 CH_2), 2.36 (bs, 2H, 2 OH), 3.97 (s, 2H, 2 C*H*−OH), 5.41 (td, 2H, 2 C*H*=C). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 11.8 (CH_3), 13.9 (CH_3), 20.8 (CH_2), 78.8 (CH), 130.7 (*C*H=C), 133.0 (CH=*C*). HRMS (ESI): found 221.1508; calculated 221.1517 for $C_{12}H_{22}O_2Na$.

*(1E,5E)-1,6-Diphenylhexa-1,5-diene-3,4-diol (dl and meso) (**2d**)*..[14,21a] Table 5 entry 5, white solid (679 mg, 85% yield). Mp: 112−114 °C [lit. 106−155 °C]. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.63 (bs, 2H, OH), 4.29 (dd, J = 11.4, 5.4 Hz, 2H, C*H*−OH, *dl form*), 4.46 (dd, J = 9.4, 3.8 Hz, 2H, C*H*−OH, *meso form*), 6.35−6.26 (m, 2H, CH=CH), 6.76−6.70 (m, 2H, CH=CH), 7.43−7.22 (m, 10H, CHAr). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 75.8 (CH, *meso form*), 75.9 (CH, *dl form*), 126.6 (CH), 126.7 (CH), 127.1 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.6 (2 CH), 132.7 (CH), 133.0 (CH), 136.4 (C_{IV}), 136.5 (C_{IV}). MS (ESI): 267.13 [M + H]$^+$, 289.12 [M + Na]$^+$.

*1,2-Diphenylethane-1,2-diol (dl and meso) (**2e**)*..[21a−c] Table 5, entry 6, white solid (594 mg, 68% yield). Mp: 120−122 °C [lit. 119−159 °C]. *dl*-**2e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.32 (bs, 2H, OH), 4.61 (s, 2H, C*H*−OH), 7.23−7.02 (m, 10H, CHAr). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 79.0 (CH−OH), 126.9 (2 CHAr), 127.9 (CHAr), 128.1 (2 CHAr), 139.8 (C_{IV}). *meso*-**2e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.32 (bs, 2H, OH), 4.74 (s, 2H, C*H*−OH), 7.23−7.02 (m, 10H, CHAr). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 78.0 (CH−OH), 127.1 (2 CHAr), 128.1 (CHAr), 128.2 (2 CHAr), 139.7 (C_{IV}). MS (ESI): 215.10 [M + H]$^+$, 237.11 [M + Na]$^+$.

*1,2-Bis(4-bromophenyl)ethane-1,2-diol (dl and meso) (**2f**)*.[21] Table 5, entry 7, white solid (1.026 g, 92% yield). Mp: 159−161 °C. *dl*-**2f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.02−1.97 (bs, 2H, OH), 4.53 (s, 2H, C*H*−OH), 6.90 (d, J = 8.4 Hz, 4H, CHAr), 7.30 (d, J = 8.4 Hz, 4H, CHAr). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 79.1 (CH), 128.1 (C_{IV}), 127.1 (2 CHAr), 128.1 (C_{IV}), 128.2 (2 CHAr), 139.7 (C_{IV}). *meso*-**2f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.02−1.97 (bs, 2H, OH), 4.75 (s, 2H, C*H*−OH), 6.99 (d, J = 8.4 Hz, 4H, CHAr), 7.34 (d, J = 8.4 Hz, 4H, CHAr). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ppm: 78.0 (CH), 126.9 (2 CHAr), 127.9 (C_{IV}), 128.1 (2 CHAr), 139.8 (C_{IV}). MS (ESI): 370.92 (50%) [M + H]$^+$, 372.92 (100%), 374.92 (50%).

*1,2-Bis(4-methylphenyl)ethane-1,2-diol (dl and meso) (**2g**)*..[21a−c] Table 6 entry 8, beige solid (669 mg, 92% yield). Mp: 165−166 °C [*litt* 161−180 °C]. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 2.22 (s, 6H, 2 CH_3), 2.26 (s, 6H, 2 CH_3), 4.57 (s, 2H, C*H*−OH *dl form*), 4.65 (s, 2H, C*H*−OH *meso form*), 7.10−6.93 (m, 8H, CHAr). ^{13}C{^{1}H} NMR

DOI: 10.1021/acs.joc.6b02069
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(100 MHz, $CDCl_3$) δ ppm: 21.2 (4 CH_3), 78.1 (CH−OH *meso form*), 78.8 (CH−OH *dl form*), 126.9 (2 CHAr), 127.1 (2 CHAr), 128.8 (2 CHAr), 129.0 (2 CHAr), 137.0 (2 C_{IV}), 137.5 (C_{IV}), 137.8 (C_{IV}). MS (ESI): 243.13 $[M + H]^+$, 267.12 $[M + Na]^+$.

1,2-Bis(4-chlorophenyl)-1,2-ethanediol (dl and meso) (**2h**).[14−16,21c] Table 5, entry 9, white solid (mg, % yield). Mp: 146−149 °C. *dl*-**2h**: ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.62 (s, 2H, C*H*−OH), 7.02 (d, J = 8.4 Hz, 4H, 2 CHAr), 7.21 (d, J = 8.4 Hz, 4H, 2 CHAr). *meso*-**2h**: ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 4.84 (s, 2H, C*H*−OH), 7.113 (dd, J = 8.4, 1.6 Hz, 4H, 2 CHAr), 7.23 (m, 4H, CHAr). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 77.2 (CH *meso form*), 78.6 (CH *dl form*), 128.4 (CHAr), 128.4 (CHAr), 128.4 (CHAr), 128.9 (CHAr), 131.6 (C_{IV}), 133.9 (C_{IV}), 137.8 (C_{IV}), 137.9 (C_{IV}). MS (ESI): 283.02 (100%), 285.02 (64%) $[M + H]^+$.

1,2-Bis(2,3-dichlorophenyl)ethane-1,2-diol (dl and meso) (**2i**)..[14,6a,21,22] Table 5 entry 9, white solid (158 mg, 15% yield). Mp: 178−180 °C. *dl*-**2i**: ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.19 (bs, 2H, OH), 5.38 (s, 2H, C*H*−OH), 7.26 (t, J = 8.0 Hz, 2H, CHAr), 7.43 (dd, J = 8.0, 1.6 Hz, 2H, CHAr), 7.62 (dd, J = 8.0, 1.6 Hz, 2H, CHAr). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 73.0 (CH), 127.2 (CHAr), 127.3 (CHAr), 130.1 (CHAr), 131.5 (C_{IV}), 133.2 (C_{IV}), 139.7 (C_{IV}). *meso*-**2i**: ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 2.19 (bs, 2H, OH), 5.64 (s, 2H, C*H*−OH), 7.11 (t, J = 8.0 Hz, 2H, CHAr), 7.18 (dd, J = 7.9, 1.7 Hz, 2H, CHAr), 7.35 (dd, J = 8.0, 1.6 Hz, 2H, CHAr). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 72.3 (CH), 126.9 (2 CHAr), 129.8 (CHAr), 129.8 (C_{IV}), 132.5 (C_{IV}), 138.5 (C_{IV}). MS (ESI): 352.94 (100%), 350.94 (78%), 354.94 (48%) $[M + H]^+$.

2,3-Diphenylbutane-2,3-diol (dl and meso) (**2j**)..[14,16,21b,23] Table 5 entry 10, white solid (66 mg, 9% yield). Mp: 128−129 °C. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.50 (s, 6H, CH_3 *dl form*), 1.58 (s, 6H, CH_3 *meso form*), 2.49 (bs, 2H, OH *dl and meso forms*), 7.26−7.20 (m, 10H, CHAr *dl and meso forms*). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ ppm: 24.9 (CH_3 *dl form*), 25.0 (CH_3 *meso form*), 78.6 (C_{IV} *meso form*), 78.8 (C_{IV} *dl form*), 126.8 (CHAr), 126.9 (2 CHAr), 127.0 (CHAr), 127.1 (2 CHAr), 127.2 (2 CHAr), 127.3 (2 CHAr), 143.3 (C_{IV}), 143.7 (C_{IV}). MS (ESI): 243.13 $[M + H]^+$, 267.12 $[M + Na]^+$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02069.

^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was performed, in partnership with the SAS PIVERT, within the framwork of the French Institute for the Energy Transition (Institut pour la Transition Energétique (ITE) PIVERT (www.institut-pivert.com) selected as an Investment for the Future ("Investissements d'Avenir"). This work was supported, as part of the Investments for the Future, by the French Government under the reference number ANR-001-01.

■ REFERENCES

(1) (a) Meciarova, M.; Toma, S.; Babiak, P. *Chem. Pap.* **2001**, *55*, 302. (b) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. (c) Morcillo, S. P.; Miguel, D.; Campana, A. G.; Alvares de Cienfuegos, L.; Justicia, J.; Cuerva, J. M. *Org. Chem. Front.* **2014**, *1*, 15. (d) Hirao, T. *Pure Appl. Chem.* **2005**, *77*, 1539. (e) Terra, B. S.; Macedo, F., Jr. *Arkivoc* **2012**, 134. (f) Steel, P. G. *J. Chem. Soc., Perkin Trans 1* **2001**, 2727. (g) Chatterjee, A.; Joshi, N. N. *Tetrahedron* **2006**, *62*, 12137. (h) Li, J.-T.; Wang, S.-X.; Chen, G.-F.; Li, T.-S. *Curr. Org. Synth.* **2005**, *2*, 415. (i) Zhao, H.; Li, D. J.; Deng, L.; Liu, L.; Guo, Q. X. *Chem. Commun.* **2003**, 506. (j) Sun, J.; Dai, Z.; Li, C.; Pan, X.; Zhu, C. *J. Organomet. Chem.* **2009**, *694*, 3219. (k) Aspinall, H. C.; Greeves, N.; Hin, S. L. F. *Tetrahedron Lett.* **2010**, *51*, 1558. (l) Buchammagari, H.; Toda, Y.; Hirano, M.; Hosono, H.; Takeuchi, D.; Osakada, K. *Org. Lett.* **2007**, *9*, 4287. (m) Kim, Y. J.; Kim, S. M.; Hosono, H.; Yang, J. W.; Kim, S. W. *Chem. Commun.* **2014**, *50*, 4791.

(2) Fitting, R. *Justus Leibigs Ann. Chem.* **1859**, *110*, 23.

(3) (a) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 61. (b) Avalos, M.; Babiano, R.; Cintas, P.; Jimenze, J. L.; Palacios, J. C. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 159.

(4) Delair, P.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1989**, 398.

(5) (a) Zhang, W.-C.; Li, C.-J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3131. (b) Mecarova, M.; Toma, S. *Green Chem.* **1999**, *1*, 257. (c) Zhang, W.-C.; Li, C.-J. *J. Org. Chem.* **1999**, *64*, 3230. (d) Maekawa, H.; Yamamoto, Y.; Shimada, H.; Yoneruma, K.; Nishiguchi, I. *Tetrahedron Lett.* **2004**, *45*, 3869. (e) Fürstner, A.; Csuk, R.; Rohrer, C.; Weidmann, H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1729.

(6) (a) Li, C.-J.; Meng, Y.; Yi, X.-H. *J. Org. Chem.* **1997**, *62*, 8632. (b) Rieke, R. D.; Kim, S.-H. *J. Org. Chem.* **1998**, *63*, 5235.

(7) (a) Trost, B. M.; Aponick, A. *J. Am. Chem. Soc.* **2006**, *128*, 3931. (b) Hazarika, B. K.; Dutta, D. K. *Synth. Commun.* **2011**, *41*, 1088. (c) So, J.-H.; Park, M.-K.; Boudjouk, P. J. *J. Org. Chem.* **1988**, *53*, 5871.

(8) Lim, H. J.; Keum, G.; Kang, S. B.; Chung, B. Y.; Kim, Y. *Tetrahedron Lett.* **1998**, *39*, 4367.

(9) Matsukawa, S.; Hinakubo, Y. *Org. Lett.* **2003**, *5*, 1221.

(10) (a) Yuan, S.-Z.; Wang, Z.-Y.; Li, Z. *Chin. J. Chem.* **2006**, *24*, 141. (b) Mitoma, Y.; Hashimoto, I.; Simion, C.; Tashiro, M.; Egashira, N. *Synth. Commun.* **2008**, *38*, 3243. (c) Bhar, S.; Panja, C. *Green Chem.* **1999**, *1*, 253. (d) Schreibmann, A. A. P. *Tetrahedron Lett.* **1970**, *11*, 4271 and references therein.

(11) Wang, Z. Y.; Yuan, S. Z.; Zha, Z. G.; Zhang, Z. D. *Chin. J. Chem.* **2003**, *21*, 1231.

(12) (a) Halterman, R. L.; Porterfield, J. P.; Mekala, S. *Tetrahedron Lett.* **2009**, *50*, 7172. (b) Hirao, T. *Pure Appl. Chem.* **2005**, *77*, 1539. (c) Steel, P. G. *J. Chem. Soc., Perkin Trans 1* **2001**, 2727. (d) Arai, S.; Sudo, Y.; Nashida, A. *Chem. Pharm. Bull.* **2004**, *52*, 287.

(13) (a) Oller-Lopez, J. L.; Campana, A. G.; Cuerva, J. M.; Oltra, J. E. *Synthesis* **2005**, *15*, 2619. (b) Clerici, A.; Porta, O. *J. Org. Chem.* **1982**, *47*, 2852. (c) Askham, F. R.; Carroll, K. M. *J. Org. Chem.* **1993**, *58*, 7328. (d) Hirao, T.; Asahara, M.; Muguruma, Y.; Ogawa, A. *J. Org. Chem.* **1998**, *63*, 2812. (e) Hirao, T.; Hatano, B.; Imamoto, Y.; Ogawa, A. *J. Org. Chem.* **1999**, *64*, 7665.

(14) Billamboz, M.; Len, C. *ChemSusChem* **2015**, *8*, 1664.

(15) Sotto, N.; Billamboz, M.; Chevrin-Villette, C.; Len, C. *J. Org. Chem.* **2015**, *80*, 6375.

(16) Billamboz, M.; Sotto, N.; Chevrin-Villette, C.; Len, C. *RSC Adv.* **2015**, *5*, 46026.

(17) (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*. Oxford University Press: Oxford, U.K., 2000. (b) *Beilstein J. Org. Chem.* **2011**, *7*, thematic issue on flow chemistry. (c) Wiles, C.; Watts, P. *Green Chem.* **2012**, *14*, 38. (d) Yoshida, J.; Kim, H.; Nagaki, A. *ChemSusChem* **2011**, *4*, 331. (e) Vaccaro, L.; Lanari, D.; Marrocchi, A.; Strappaveccia, G. *Green Chem.* **2014**, *16*, 3680. (f) Luis, S. V.; Garcia-Verdugo, E. *Chemical Reactions and Processes under Flow Conditions*; RSC Publishing: Cambridge, U.K., 2010. (g) Frost, C. G.; Mutton, L. *Green Chem.* **2010**, *12*, 1687. (h) Noël, T.; Buchwald, S. L. *Chem. Soc. Rev.* **2011**, *40*, 5010. (i) Gemoets, H. P. L.; Hessel, V.; Noël, T. *Org. Lett.* **2014**, *16*, 5800. (j) Yalgin, H.; Luart, D.; Len, C. *J. Flow Chem.* **2016**, *6*, 80.

(18) (a) *Microreactors: New Technology for Modern Chemistry*; Ehrfield, W., Hessel, V., Lçwe, H., Eds.; Wiley-VCH: Weinheim, Germany, 2000. (b) Wiles, C.; Watts, P. *Eur. J. Org. Chem.* **2008**, *2008*, 1655. (c) Illg, T.; Löb, P.; Hessel, V. *Bioorg. Med. Chem.* **2010**, *18*, 3707. (d) Watts, P.; Haswell, S. J. *Drug Discovery Today* **2003**, *8*, 586. (e) *Microreactors in Organic Synthesis and Catalysis*; Wirth, T., Ed.;

DOI: 10.1021/acs.joc.6b02069
J. Org. Chem. 2016, 81, 11065−11071

Wiley-VCH: Weinheim, Germany, 2008. (f) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300. (g) Sahoo, H. R.; Kralj, J. G.; Jensen, K. F. *Angew. Chem.* **2007**, *119*, 5806. (h) Hartman, R. L.; McMullen, J. P.; Jensen, K. F. *Angew. Chem.* **2011**, *123*, 7642. (i) Wiles, C.; Watts, P. *Green Chem.* **2012**, *14*, 38.

(19) (a) Yasuda, M.; Tsuruwa, K.; Azuma, T.; Arulananda Babu, S.; Baba, A. *Tetrahedron* **2009**, *65*, 9569. (b) Handa, Y.; Inanaga, J. *Tetrahedron Lett.* **1987**, *28*, 5717.

(20) Shimizu, M.; Goto, H.; Hayakawa, R. *Org. Lett.* **2002**, *4*, 4097.

(21) (a) Griffith, J. C.; Jones, K. M.; Picon, S.; Rawling, M. J.; Kariuki, B. M.; Campbell, M.; Tomkinson, N. C. O. *J. Am. Chem. Soc.* **2010**, *132*, 14409. (b) Wang, K.; Wang, S. X.; Gao, M.-Z.; Li, J.-T. *Synth. Commun.* **2006**, *36*, 1391. (c) Takenaka, N.; Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 13198. (d) Jeong, K. S.; Kim, Y. S.; Kim, Y. J.; Lee, E.; Yoono, J. H.; Park, W. H.; Park, Y. W.; Jeon, S.-J.; Kim, Z. H.; Kim, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 8134.

(22) Li, C.-J.; Meng, Y.; Yi, X.-H.; Ma, J.; Chan, T.-H. *J. Org. Chem.* **1998**, *63*, 7498.

(23) Uchiyama, M.; Matsumoto, Y.; Nakamura, S.; Ohwada, T.; Kobayashi, N.; Yamashita, N.; Matsumiya, A.; Sakamoto, T. *J. Am. Chem. Soc.* **2004**, *126*, 8755.

DOI: 10.1021/acs.joc.6b02069
J. Org. Chem. 2016, 81, 11065−11071