

# A Diastereoselective One-Pot, Three-Step Cascade toward $\alpha$ -Substituted Allylboronic Esters

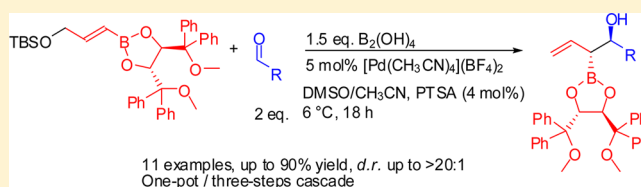
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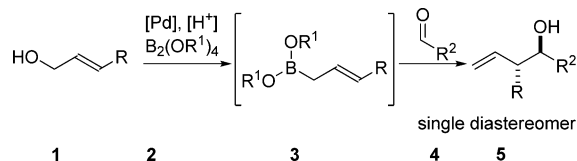
## Supporting Information

**ABSTRACT:** A new highly diastereoselective synthesis of chiral  $\alpha$ -substituted allylboronic esters, based on a one-pot, three-step cascade, is presented. The palladium- and acid-cocatalyzed reaction cascade involves a desilylation of a TBS-protected allylic alcohol, borylation, and addition of an allyl group to an aldehyde. Herein we present the first application of a TBS-protected allylic alcohol in a palladium-catalyzed borylation/allylation reaction.



In the past several years, the direct activation of allylic alcohols in palladium-catalyzed transformations has attracted a high level of interest. Given the advantages of these unactivated substrates over more active species like allylic carbonates, halides, and esters, with regard to stability and availability, they are clearly the more preferable substrates.<sup>1</sup> Among others, Szabó and co-workers published a number of procedures toward the catalytic borylation of unactivated allylic alcohols **1** via application of diboronic species **2** as the boron source, leading to allylboronic acids or esters **3** as highly active and valuable products or intermediates for further transformations.<sup>2</sup> The same group also showed that such allylboronic acid intermediates **3** could be transformed into more stable derivatives, like tetrafluoro borates.<sup>2c</sup> Also, allylboronic acids directly react with electrophiles such as aldehydes **4** or ketones<sup>2a,3</sup> to form homoallylic alcohols **5** with impressive diastereoselectivity (Scheme 1).<sup>2a,b,e</sup>

**Scheme 1. Palladium-Catalyzed Transformation of Allylic Alcohols to Allylboronates and Their Addition to Aldehydes Developed by the Szabó Group**



Asymmetric versions of such palladium-catalyzed allylic substitution/allyl addition reactions, using nonactivated allylic alcohols, are particularly rare.<sup>1b,e,4</sup> In 2009, our group published the synthesis of  $\alpha$ -substituted, enantiomerically pure allylboronic esters **6–8** via palladium-catalyzed carbonyl allylation reactions starting from an allylic mesylate **10** (Scheme 2).<sup>5</sup> This three-step method comprises a few drawbacks, namely, the lengthy synthesis of the very reactive and therefore unstable

mesylate **10**, the application of toxic  $\text{SnCl}_2$  as the metal source, and the partially unsatisfying diastereomeric ratios of the products.

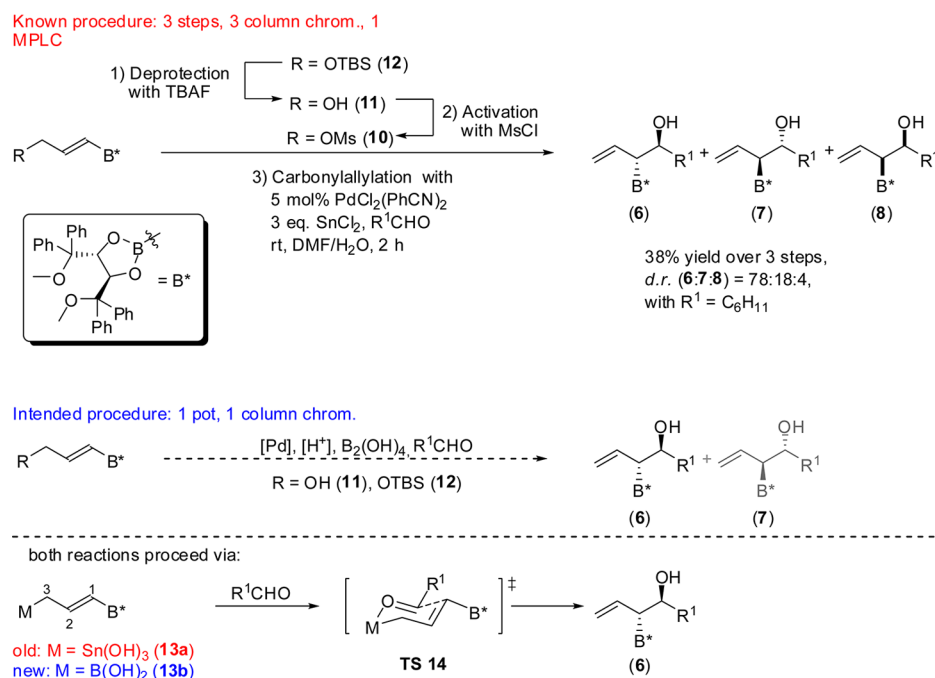
Inspired by Szabó's results, we decided to develop an improved synthetic approach toward allylboronates **6–8**, avoiding the aforementioned pitfalls. Therefore, it was envisaged to use tetrahydroxy diboron (**2a**) as a boron source and allylic alcohol **11** or silyl ether **12** as the starting material of choice to reduce the number of steps and to avoid handling of unstable compounds. With the choice of this mode of action, a number of advantages arise. First, toxic allyl tin intermediate **13a** would be substituted with nontoxic allylboronate **13b**. Second, one might achieve a better diastereoselectivity of the allyl addition step by means of formation of a more compact transition state **TS 14** because of the shorter B–O coordination in comparison to the Sn–O complexation (Scheme 2).

Proposed intermediate **13b** represents a member of the group of highly valuable, chiral, 1,3-bifunctionalized allylmetal reagents, precisely 1,3-diboron compounds,<sup>6</sup> with highly desirable applications<sup>7</sup> in double allylboration reactions as shown by Roush,<sup>7a–8</sup> Soderquist,<sup>6c</sup> and others.<sup>7h,i</sup> In our previous publications, we demonstrated that the chiral  $\alpha$ -substituted allylboronic esters **6–8** showed unrivaled stability and are versatile reagents for natural product synthesis.<sup>8</sup> Unlike other examples of 1,3-diboron reagents, we are therefore able to isolate, purify, and store allylboronates **6–8** after the first allyl addition, thus also obtaining these reagents in absolutely enantio- and diastereomerically pure form.

The desired reaction was probed by applying the reaction conditions published by Szabó's group.<sup>2a</sup> Reacting allylic alcohol **11** in a DMSO/MeOH (1:1) mixture with tetrahydroxy diboron (**2**) and cyclohexyl carbaldehyde (**4a**) and 5 mol % tetrakisacetonitrile palladium(II) tetrafluoroborate {[Pd-

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Scheme 2. Palladium-Catalyzed Carbonyl Allylation toward Enantiomerically Pure,  $\alpha$ -Substituted Allylboronic Esters 6–8Table 1. Optimization of Carbonyl Allylation Reaction Conditions<sup>a</sup>

entry	R	[Pd]	[acid]	solvent	temp (°C)	conv <sup>b</sup> (%)	dr <sup>b</sup>
1	OH	Pd(CH <sub>3</sub> CN) <sub>4</sub> (BF <sub>4</sub> ) <sub>2</sub>	—	A	20	— <sup>c</sup>	—
2	OH	Pd(CH <sub>3</sub> CN) <sub>4</sub> (BF <sub>4</sub> ) <sub>2</sub>	—	B	20	>90	6:1
3	OH	Pd(CH <sub>3</sub> CN) <sub>4</sub> (BF <sub>4</sub> ) <sub>2</sub>	PTSA	B	20	>95	6:1
4	OTBS	Pd(CH <sub>3</sub> CN) <sub>4</sub> (BF <sub>4</sub> ) <sub>2</sub>	PTSA	B	20	>95	6:1
5	OH	Pd(dba) <sub>2</sub>	—	B	20	0	—
6	OH	Pd(dba) <sub>2</sub>	PTSA	B	6	70 <sup>d</sup> / <sup>e</sup> >95 <sup>e</sup>	10:1
7	OTBS	Pd(dba) <sub>2</sub>	PTSA	B	6	70 <sup>d</sup> / <sup>e</sup> >95 <sup>e</sup>	10:1
8	OTBS	Pd(CH <sub>3</sub> CN) <sub>4</sub> (BF <sub>4</sub> ) <sub>2</sub>	PTSA	B	6	>95	10:1
9	OTBS	Pd(CH <sub>3</sub> CN) <sub>4</sub> (BF <sub>4</sub> ) <sub>2</sub>	PTSA	B	0	30	10:1
10	OAc	Pd(CH <sub>3</sub> CN) <sub>4</sub> (BF <sub>4</sub> ) <sub>2</sub>	PTSA	B	6	30	10:1
11	Cl	Pd(CH <sub>3</sub> CN) <sub>4</sub> (BF <sub>4</sub> ) <sub>2</sub>	PTSA	B	6	0	—

<sup>a</sup>Reactions were performed on a 0.08 mmol scale using 0.5 mL of the solvent mixture. <sup>b</sup>Conversions and diastereomeric ratios (6:7) were determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>c</sup>Full decomposition of starting materials was observed. <sup>d</sup>After 18 h. <sup>e</sup>After 42 h.

(CH<sub>3</sub>CN)<sub>4</sub>(BF<sub>4</sub>)<sub>2</sub> as a precatalyst (Table 1, entry 1) led to complete decomposition of the starting material and produced a complex product mixture. A short solvent screening, including DMSO, MeOH, CH<sub>3</sub>CN, THF, toluene, diethyl ether, and mixtures of them, revealed a DMSO/CH<sub>3</sub>CN (1:1) mixture as the solvent of choice (results not shown). Under these conditions, a high level of conversion (>90%), determined by <sup>1</sup>H NMR analysis of the crude reaction mixture, was observed after 18 h at room temperature (entry 2). The tested solvents were neither dried nor degassed prior to use because it was found that intensely dried solvents showed a much lower extent of conversion and that degassing of solvents did not have any influence on the reaction outcome. This shows that a small amount of water is necessary for the reaction to take place, a finding that is in perfect agreement with those published previously.<sup>2a,9</sup> Nevertheless, recrystallization of tetrahydroxy

diboron<sup>2a</sup> prior to use proved to be necessary concerning its oxidation after a short storage time. At this point, the influence of a Brønsted acid was also studied. The experiments showed that application of 4 mol % PTSA improved the reaction and led to an excellent level of conversion of >95% (entry 3). These conditions were transferred to TBS-protected allylic alcohol 12, which is the direct precursor of allylic alcohol 11, and we were very pleased to find full conversion with cyclohexyl carbaldehyde (entry 4). To the best of our knowledge, this is the first report of an application of a TBS-protected allylic alcohol in a palladium-catalyzed transformation. Other Pd catalysts were tested next (see the Supporting Information for more details), and experiments revealed that employment of significantly cheaper bis(dibenzylideneacetone) palladium(0) [Pd(dba)<sub>2</sub>] is also possible. However, this precatalyst was found to be less reactive and led to full conversion only after 42 h.

Additionally, it was found that Pd(dba)<sub>2</sub> cannot activate allylic alcohol **11** and that addition of an acid was necessary to obtain any conversion (entries 5 and 6). To enhance the diastereomeric ratio, the temperature was reduced to 6 °C. Again, both reactions showed full conversion after 18 and 42 h, respectively, but the diastereomeric ratio could be increased from 6:1 (entry 7) to 10:1 (entry 8). Further decreasing the temperature to 0 °C did not lead to a better diastereoselectivity but resulted in a much slower reaction rate (entry 9). Application of such optimized reaction conditions to substrates containing a leaving group, such as acetate **15** or chloride **16**, revealed a quite slow conversion in the case of allyl acetate **15** (entry 10) and no conversion of allyl chloride **16** (entry 11).

With the optimal reaction conditions in hand, we turned our attention to the substrate scope. To compare our new method with the previously described carbonyl allylations,<sup>5a,b</sup> we chose to examine a number of aldehydes listed in Table 2.

Table 2. Probing the Scope of the Carbonyl Allylation<sup>a</sup>

entry	R	product	yield <sup>b</sup> (%)	dr <sup>c</sup>
1	Ph	<b>6a</b>	86	>20:1
2	3,4-F <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>6b</b>	84	>20:1
3	C <sub>6</sub> F <sub>5</sub>	<b>6c</b>	83	>20:1
4	furfuryl	<b>6d</b>	57	>20:1
5	CO <sub>2</sub> Et	<b>6e</b>	56	20:1
6	PhCH=CH ( <i>E</i> )	<b>6f</b>	72	>20:1
7	PhCH <sub>2</sub> CH <sub>2</sub>	<b>6g</b>	90	10:1
8	(CH <sub>3</sub> ) <sub>2</sub> CH	<b>6h</b>	75	15:1
9	(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> CH	<b>6i</b>	89	15:1
10	C <sub>6</sub> H <sub>11</sub>	<b>6j</b>	82	10:1
11	H <sup>d</sup>	<b>6k/7k</b>	84	1:1.7

<sup>a</sup>Reactions were performed on a 0.16 mmol scale using 1.0 mL of the solvent mixture. <sup>b</sup>Yield of isolated and purified major diastereomer **6**. <sup>c</sup>Diastereomeric ratios (**6**:**7**) were determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>d</sup>Reaction performed on a 1.20 mmol scale; paraformaldehyde was used.

With the optimized reaction conditions, heteroaromatic and unsaturated aldehydes (entries 1–6) show perfect diastereoselectivity (dr ≥ 20:1) because of their sterically demanding nature. As expected, aliphatic aldehydes (entries 7–10) show a slightly decreased but still very good diastereoselectivity (dr = 10–15:1). Only formaldehyde (entry 11) shows moderate diastereoselectivity [dr = 1.7:1 (**7k**:**6k**)]. However, to the best of our knowledge, this is the first example in which facial selectivity, using the smallest aldehyde, was observed at all. It is worth mentioning that with this aldehyde the reaction could be scaled up to a 1.2 mmol scale without any loss of reactivity. Neutral and electron-deficient aldehydes show good to very good yields (entries 1–3 and 6–11); electron-rich aldehydes such as furfural (entry 4) show only moderate conversion, and formation of byproducts, as protodeboronation of intermediate allylboronic acid **13b**, was observed. Ethyl glyoxalate (entry 5) was found to be a troublesome substrate; the commercially available solution, containing 40% toluene was found not to be suitable because the toluene interfered with the reaction and the redistilled ethyl glyoxalate showed only moderate yield, probably because of the fast oligomerization of the aldehyde.

Any attempts to decrease the catalyst load to 2.5 mol % [Pd(CH<sub>3</sub>CN)<sub>4</sub>](BF<sub>4</sub>)<sub>2</sub> or even 1 mol % [Pd(CH<sub>3</sub>CN)<sub>4</sub>](BF<sub>4</sub>)<sub>2</sub> led to a significant decrease in the reaction rate and were therefore rejected. In contrast to these findings, the concentration of PTSA seemed to have only a minor influence on the reaction rate. Tested concentrations between 1 and 20 mol % PTSA showed full conversion after 18 h at 6 °C in all cases (see the Supporting Information for details). However, a NMR study of the reaction course with 20 mol % [Pd(CH<sub>3</sub>CN)<sub>4</sub>](BF<sub>4</sub>)<sub>2</sub> and 20 mol % PTSA gave full conversion after only approximately 3 h (see the Supporting Information for details) without a significant increase in the level of decomposition products.

Some of the reactions have also been tested applying the cheaper but less active Pd(dba)<sub>2</sub> precatalyst as shown in Table 3. After 42 h, all reactions were found to reach full conversion

Table 3. Carbonyl Allylation Applying the Pd(dba)<sub>2</sub> Catalyst<sup>a</sup>

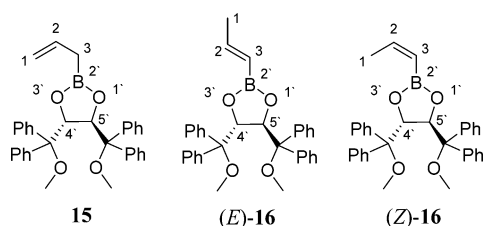
entry	R	product	yield <sup>b</sup> (%)	dr <sup>c</sup>
1	Ph	<b>6a</b>	88	>20:1
2	CO <sub>2</sub> Et	<b>6e</b>	42	20:1
3	(CH <sub>3</sub> ) <sub>2</sub> CH	<b>6h</b>	79	15:1
4	C <sub>6</sub> H <sub>11</sub>	<b>6j</b>	42	10:1
5	furfuryl	<b>6d</b>	0	–
6	PhCH=CH ( <i>E</i> )	<b>6f</b>	0	–

<sup>a</sup>Reactions were performed on a 0.16 mmol scale using 1.0 mL of the solvent mixture. <sup>b</sup>Yield of isolated and purified major diastereomer **6**. <sup>c</sup>Diastereomeric ratios (**6**:**7**) were determined by <sup>1</sup>H NMR analysis of the crude reaction mixture.

and the yields of isolated products as well as diastereomeric ratios were comparable to those of the reactions shown in Table 2.

A drawback of the Pd(dba)<sub>2</sub> precatalyst is its incompatibility with certain substrates such as furfuraldehyde (entry 5) or cinnamyl aldehyde (entry 6) most probably because of the coordination of these substrates to the catalyst, which inhibited the reaction and led to a lower level of conversion with a large amount of decomposition products. Any attempt to separate the borylation and the allylation reaction by adding the aldehyde after complete borylation failed. The double borylated intermediate **13b** reacts so fast with an aldehyde during the reaction course that it could not be observed by means of <sup>1</sup>H NMR when the reaction was performed in a NMR tube in a reaction monitoring study (see the Supporting Information). When the reaction was conducted without addition of aldehyde, only protodeboronation products **15**, (*E*)-**16**, and (*Z*)-**16** were isolated as a 1:0.2:0.1 mixture of three inseparable isomers as shown in Figure 1.

In conclusion, we report the first acid- and Pd-cocatalyzed deprotection/borylation/allyl addition sequence for TBS-protected allylic alcohols. We therefore have been able to expand the substrate scope of such reactions toward even less activated compounds, thus avoiding an additional deprotection step. In comparison to the previously published method for the synthesis of allylboronates **6**–**8**,<sup>5b</sup> a number of advantages arise. The method presented here is a more environmentally friendly



**Figure 1.** Protodeboronation products **15**, (*E*)-**16**, and (*Z*)-**16** that were formed when the reaction was conducted without the addition of an aldehyde.

and safe reaction because of the application of nontoxic tetrahydroxy diboron instead of toxic  $\text{SnCl}_2$  as the metalation reagent. A one-pot, three-step procedure facilitates the synthesis of valuable building blocks by reducing the number of isolation and purification steps and by utilization of nondried solvents and atmospheric conditions. Additionally, the reaction proceeds with strongly improved yields and diastereoselectivities. The synthetic value of such  $\alpha$ -substituted, chiral allylboronic esters for natural product synthesis was already shown by our group in previous reports. Especially allylboronates **6k** and **7k**, which were synthesized on a synthetically useful scale and are can be separated by means of MPLC, are highly valuable reagents for the enantioselective synthesis of dihydro- $\alpha$ -pyrones. They have been used, for example, in the selective synthesis of both enantiomers of Rugulactone, Goniotalamin or Massoia lactone.<sup>8</sup> With this more convenient protocol available, the reagents should become even more generally applicable in future applications.

## EXPERIMENTAL SECTION

In a reaction vessel, TBS-protected allylic alcohol **12** (100 mg, 0.16 mmol) and  $\text{B}_2(\text{OH})_4$  were dissolved in 1.0 mL of a DMSO/ $\text{CH}_3\text{CN}$  (1:1) mixture at room temperature. Subsequently, aldehydes **2a–k** (0.32 mmol, 2 equiv), PTSA [stock solution in a DMSO/ $\text{CH}_3\text{CN}$  mixture (1:1), 0.01 g/mL, 0.1 mL, 0.04 equiv], and the indicated catalyst [ $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$  (stock solution in dry  $\text{CH}_3\text{CN}$ , 0.1 g/mL, 35  $\mu\text{L}$ , 0.05 equiv) or  $\text{Pd}(\text{dba})_2$  (stock solution in dry DMSO, 0.01 g/mL, 452  $\mu\text{L}$ , 0.05 equiv)] were added. The closed vessel was placed in a shaker in a refrigerator, and the reaction was conducted at 6 °C. After the indicated period of time (18 or 42 h), the conversion as well as the diastereomeric ratio was analyzed by means of  $^1\text{H}$  NMR analysis of the crude reaction mixture. The reaction mixture was diluted with 30 mL of  $\text{CH}_2\text{Cl}_2$ , and 3 g of silica gel was added. The solvents were removed under reduced pressure, and the so adsorbed products were purified via column chromatography (pentane/diethyl ether, 90:10  $\rightarrow$  70:30) to afford allylboronic esters **6** mostly in diastereomerically pure form as colorless foams. In the case of the reaction with formaldehyde (paraformaldehyde was applied) (**2k**), a 1.7:1 (**7k/6k**) mixture of the two diastereoisomers was isolated. Separation using MPLC afforded diastereomerically pure compounds **6k** and **7k**. The spectroscopic data ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, including copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra, IR,  $[\alpha]_D^{20}$ ) of allylboronates **6a–k**<sup>5b</sup> and **7k**<sup>5b</sup> as well as those of **10**,<sup>5b</sup> **11**,<sup>5b</sup> and **12**<sup>10</sup> have been published previously. Spectroscopic data for all products are in full agreement with those previously reported.<sup>5a,b</sup>

**Protodeboronation Compounds 15 and 16.** Signals for **15**:  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  1.14 (dd,  $J = 16.0, 8.0$  Hz, 1 H, 3- $\text{H}_a$ ), 1.21 (dd,  $J = 16.0, 7.1$  Hz, 1 H, 3- $\text{H}_b$ ), 2.94 (s, 6 H,  $\text{OCH}_3$ ), 4.68 (m, 1 H,  $J = 1$  Hz), 4.70 (m, 1 H, 1- $\text{H}_E$ ), 5.24 (s, 2 H, 4'-H and 5'-H), 5.34 (dddd,  $J = 15.6, 10.5, 8.0, 7.1$  Hz, 1 H, 2-H), 7.20–7.35 (m, arom. CH). Signals for (*E*)-**16**:  $^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  1.62 (d,  $J = 6.4$  Hz, 1 H, 1-H), 2.91 (s, 6 H,  $\text{OCH}_3$ ), 4.99 (d,  $J = 17.8$  Hz, 1 H, 3-H), 5.25 (s, 2 H, 4'-H and 5'-H), 6.09 (dq,  $J = 17.8, 6.4$  Hz, 1 H, 2-H), 7.20–7.35 (m, arom. CH). Signals for (*Z*)-**16**:  $^1\text{H}$  NMR (600 MHz,

DMSO- $d_6$ )  $\delta$  1.50 (d,  $J = 6.9$  Hz, 1 H, 1-H), 2.91 (s, 6 H,  $\text{OCH}_3$ ), 4.85 (d,  $J = 13.6$  Hz, 1 H, 3-H), 5.25 (s, 2 H, 4'-H and 5'-H), 6.25 (dq,  $J = 13.6, 6.9$  Hz, 1 H, 2-H), 7.20–7.35 (m, arom. CH). Signals for **15**:  $^{13}\text{C}$  NMR (151 MHz, DMSO- $d_6$ )  $\delta$  17.2 (C-3), 51.3 ( $\text{OCH}_3$ ), 77.1 (C-4' and C-5'), 82.6 ( $\text{CPh}_2\text{OMe}$ ), 114.7 (C-1), 127.3, 127.4, 127.7, 127.9, 128.0, 129.1 (arom. CH), 133.5 (C-2), 140.5, 140.6 (arom.  $\text{C}_{\text{ipso}}$ ).  $^{13}\text{C}$  NMR signals belonging to (*E*)-**16** and (*Z*)-**16** are too weak to be fully characterized.

## ASSOCIATED CONTENT

### Supporting Information

Detailed catalyst and acid screening, a NMR study of the reaction course, and copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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