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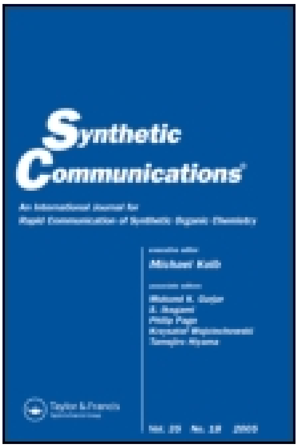

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Hydroarylation of Styrenes with Electron-Rich Arenes Over Acidic Ion-Exchange Resins

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Accepted author version posted online: 18 Mar 2014.Published online: 29 May 2014.

To cite this article: Jingyun Wen , Haofei Qi , Xiangjin Kong , Ligong Chen & Xilong Yan (2014) Hydroarylation of Styrenes with Electron-Rich Arenes Over Acidic Ion-Exchange Resins, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:13, 1893-1903, DOI: 10.1080/00397911.2013.876547

To link to this article: http://dx.doi.org/10.1080/00397911.2013.876547

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Synthetic Communications®, 44: 1893–1903, 2014
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ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2013.876547

HYDROARYLATION OF STYRENES WITH ELECTRON-RICH ARENES OVER ACIDIC ION-EXCHANGE RESINS

Jingyun Wen, Haofei Qi, Xiangjin Kong, Ligong Chen, and Xilong Yan
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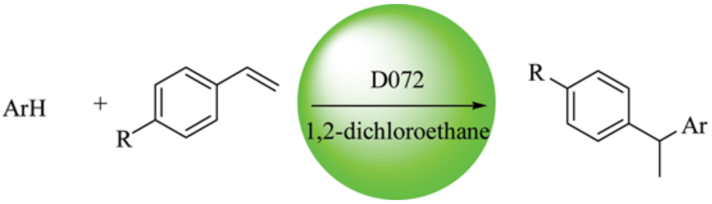
GRAPHICAL ABSTRACT



Abstract *A series of acidic cation-exchange resins were used for the hydroarylation of resorcinol with styrene, in which resin D072 exhibited the excellent catalytic performance in this reaction with 99% conversion of styrene and 90% selectivity of 4-(1-phenylethyl) resorcinol. It was applied to the hydroarylation of various electron-rich arenes with styrenes, and the hydroarylated products were quantitatively obtained. This catalyst could be used for four consecutive runs with slight decrease in activity. The hydroarylation of resorcinol with styrene over resin D072 in a fixed bed was completed effectively with 94% selectivity and 99% conversion, and this green continuous process is potentially applicable to large-scale productions.*

Keywords Acidic cation-exchange resin; fixed-bed reactor; Friedel–Crafts hydroarylation; green chemistry; heterogeneous catalyst

INTRODUCTION

Friedel–Crafts hydroarylation is one of the most fundamental and useful transformations for carbon–carbon bond formation and is widely applied to the synthesis of pharmaceuticals, agrochemicals, dyes, and fine and bulk chemicals. Recently, Lewis acids such as $FeCl_3$,[1] $BiCl_3$,[2] and $Bi(OTf)_3$[3] and Brønsted acids such as sulfonic acid,[4] phosphoric acid,[4] or I_2[5] have been used to catalyze the hydroarylation

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Received September 12, 2013.

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of styrenes for the synthesis of a variety of 1,1-diarylalkanes in good yields. Although these catalysts work reliably with a variety of substrates, they are accompanied by serious corrosion of equipment, complicated workup procedures, consumption of large amount of acids and bases, and large amounts of wastewater, which is unfriendly to the environment. Furthermore, wastewater treatment is an ongoing and expensive issue in large-scale chemical processes.

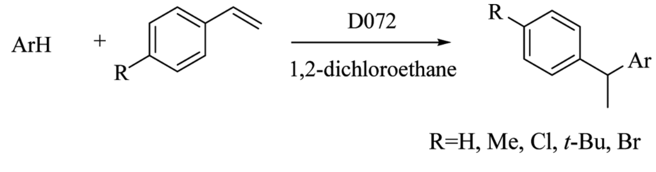
Efforts recently have been made to develop heterogeneous catalysts for this reaction, for example, $KHSO_4$,[6] 3D nanoporous FeAl-KIT-5,[7] H-β-zeolite,[8] acidic ionic liquids,[9] ion-containing mesoporous aluminosilicate,[10] aluminum-exchanged tungstophosphoric acid,[11] molybdenum complexes,[12,13] Ir-Cp complexes,[14] palladium complex,[15] Amberlyst-15,[16,17] and the like. However, the disadvantages limit their application in large-scale productions.

Acidic cation-exchange resins have been recognized as very promising candidates to manage the handicaps of homogeneous catalysts and solid catalysts as alternatives because of their advantages such as low cost, environmental friendliness, reusability, noncorrosiveness, and excellent physical characteristics including high surface area, large pore volume, and uniform pore-size distribution. However, no examples of immobilized resin systems for hydroarylation in a fixed-bed reactor are found in the literature.

The establishment of a green continuous process for this important reaction would be desirable. Therefore, we have investigated various cheap and readily available acidic cation-exchange resins that may prove to be catalytically active in hydroarylation. It was found that resin D072 exhibited the best catalytic performance. Thus, further efforts have been made to it to ensure that it is an efficient catalyst that has potential to be used in a fixed-bed reactor (Scheme 1).

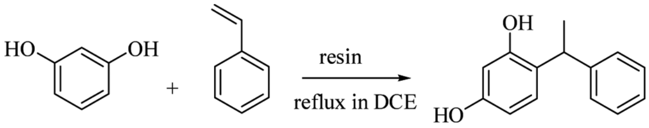
RESULTS AND DISCUSSION

The well-known Friedel–Crafts alkylation is a typical aromatic electrophilic substitution, in which the formation of carbocation is crucial to this reaction. Traditional Brønsted acids protonate the alkenes to produce reactive carbocations. Acidic resins belong to solid Brønsted acids, which can provide H^+ to catalyze the reaction. Therefore, a number of acidic resins were selected for the model reaction of resorcinol with styrene in 1,2-dichloroethane (DCE) to give 4-(1-phenylethyl) resorcinol as the target product (Table 1). The by-product was double-substituted resorcinol, which was 4.6-di(1-phenylethyl)resorcinol. 4-(1-Phenylethyl)resorcinol was reported to be one of the most efficient tyrosinase inhibitors, due to its safety and effectiveness at low concentration, which has the potential to be used as a whitening cosmetic.[18]



Scheme 1. General hydroarylation of arenes with styrenes.

Table 1. Hydroarylation of resorcinol with styrene[a]



Entry	Resin	Conv. (%)[b]	Yield (%)[c]	Sel.[d]
1	D072	99	89	90:10
2	NKC-9	99	84	85:15
3	D061	99	83	84:16
4	D062	98	75	77:23
5	D401	3	3	
6	D114	2	2	—
7	D113	2	2	—
8	D151	1	1	—
9	D152	2	2	—
10	D001-CC	1	1	—
11	100 × 7	1	1	—

[a] Reaction condition: 15 mmol of resorcinol, 5 mmol of styrene, 30 wt% (based on styrene) of catalyst, reflux in DCE for 4 h.
[b] HPLC conversion of styrene.
[c] HPLC yield of the product.
[d] Single/double substituted isomers were determined by ^{1}H NMR and ^{13}C NMR.

It is obvious that resin's acidity has an important influence on the hydroarylation. All sulfonic acidic resins such as D072, NKC-9, D061, and D062 can effectively catalyze this reaction (Table 1, entries 1–4), in which resin D072 exhibited the excellent catalytic performance in both conversion and selectivity. However, with

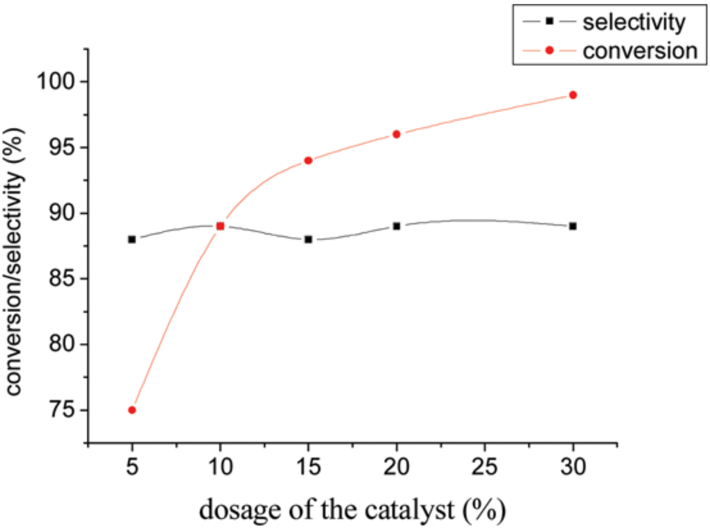
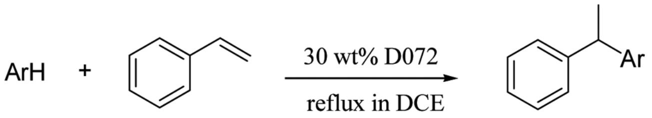
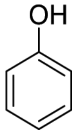
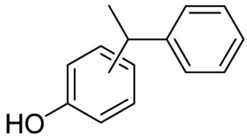
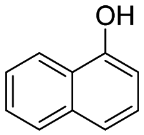
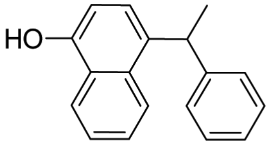
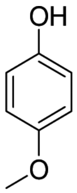
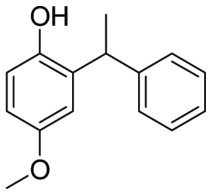
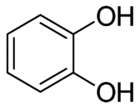
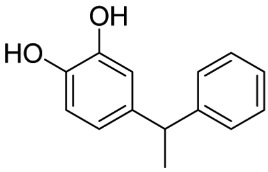
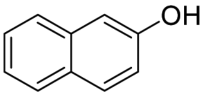
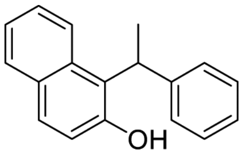
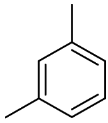
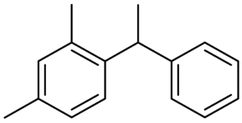
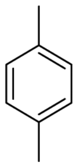
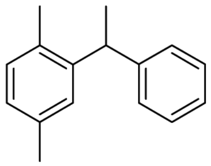


Figure 1. Hydroarylation of resorcinol with styrene in the presence of D072.

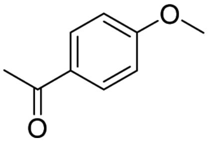
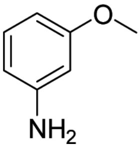
Table 2. Resin D072 catalyzed the reaction of styrene with various aromatics[a]



Entry	Arene	Product[b]	Conv. (%)[c]	Yield (%)[d]	Sel.[e]
1			100	92	60:40
2			100	68	68:32
3			99	83	84:16
4			97	82	85:15
5			100	67	67:33
6[f]			100	25	25:75
7[f]			100	12.5	1:7

(*Continued*)

Table 2. Continued

Entry	Arene	Product[b]	Conv. (%)[c]	Yield (%)[d]	Sel.[e]
8		—	100	0	—
9		—	0	—	—

[a] Reaction conditions: 15 mmol arene, 5 mmol (substituted) styrene, 30 wt% D072, reflux in DCE, 4 h.
[b] Main product.
[c] HPLC conversion of styrene.
[d] HPLC yield of products.
[e] Main product: other isomers.
[f] The selectivity was detected by ^{1}H NMR.

carboxylic resins as catalysts, nearly no alkylated product was detected, due to their poor protonation ability (Table 1, entries 5–11).

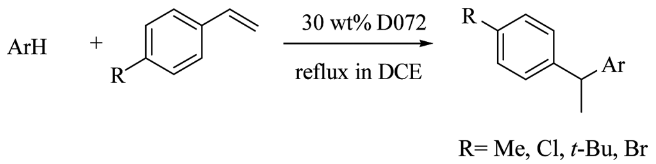
D072 is sulfonic resin with the appearance of light camel in color and spherical particles, its surface area is 77 m^2/g, the pore volume is 0.27 mL/g, the concentration of H^+ is greater than 4.8 mmol/g, and the average pore size is 56 nm. All these parameters make it appropriate for the catalyst of the hydroarylation.

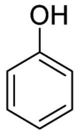
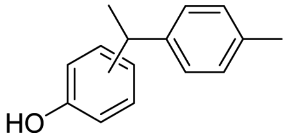
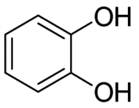
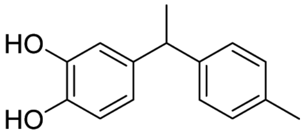
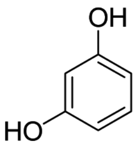
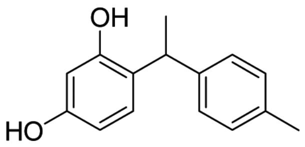
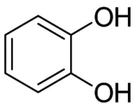
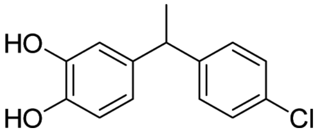
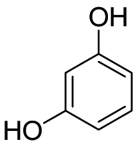
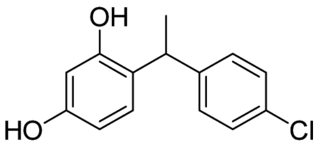
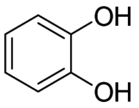
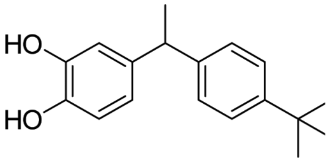
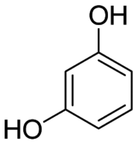
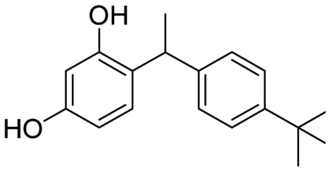
The effect of dosages of D072 was investigated, as shown in Figure 1. With the increase of the catalyst's dosage from 5 to 30 wt%, the conversion of styrene increased from 75% to 99% and the selectivity for the target product remained unchanged. With 30 wt% of D072, significant conversion and selectivity could result. Therefore, 30 wt% of D072 was used in this reaction.

To explore the scope and limitations of this reaction, various aromatic compounds were employed as the substrate to react with styrene. Under the optimized condition styrene almost fully reacted with the electron-rich arenes to give the corresponding alkylated products (Table 2, entries 1–5); however, arenes with weaker electron-donating groups were ineffective (Table 2, entries 6–8) because most of styrene reacted itself to afford the alkylated styrene and few desirable products were obtained. Furthermore, perhaps the basic group of aniline blocked acidic centers of the resin, and neither the desired product nor alkylated styrene were obtained (Table 2, entry 9).

Then, *para*-chloro, bromo, methyl, and *tert*-butyl substituted styrenes were examined, and all of them reacted well as hydroarylation reagents to give the corresponding products with satisfactory yield and selectivity (Table 3, entries 1–9). Additionally, take hydroarylation of styrenes with pyrocatechol for example, and the ratio of 4-substituted isomer with 3-substituted isomer was different (Table 3, entries 2, 4, 6, 8; Table 2, entry 4). This may depend on the stability of carbocation. The introduction of electron-donating group to the benzene ring could enhance the

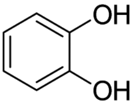
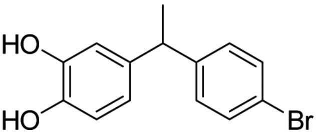
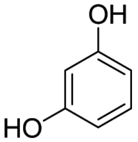
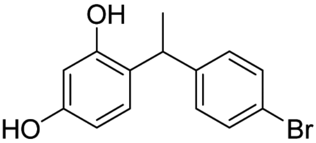
Table 3. Resin D072 catalyzed the reaction of styrenes with various aromatics[a]



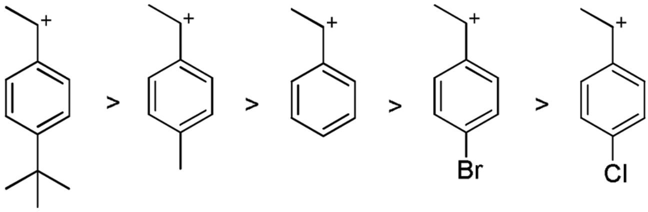
Entry	Arene	Product[b]	Conv. (%)[c]	Yield (%)[d]	Sel.[e]
1			100	91	67:33
2			100	90	90:10
3			100	93	93:7
4			100	81	81:19
5			96	95	>99:1
6			100	94	94:6
7			99	99	100

(*Continued*)

Table 3. Continued

Entry	Arene	Product[b]	Conv. (%)[c]	Yield (%)[d]	Sel.[e]
8			100	83	83:17
9			100	96	96:4

[a] Reaction conditions: 15 mmol arene, 5 mmol (substituted) styrene, 30 wt% D072, reflux in DCE for 4 h.
[b] Main product.
[c] HPLC conversion of styrene.
[d] HPLC yield of products.
[e] Main product : other isomers.



Scheme 2. Stability of the carbocations.

stability of the carbocation: the greater the stability, the better the selectivity. However, the introduction of electron-withdrawing group could reduce the stability of the carbocation. Therefore the stability of these carbocations is shown in Scheme 2. The experimental results demonstrated the selectivity of these target products was consistent with the stability of carbocations.

Next, the reusability of resin D072 was investigated in the model reaction of resorcinol with styrene. After each run, the catalyst was filtered from the reaction mixture and reused for four runs without any activation. As shown in Table 4, the activity remained unchanged in the first three runs, but in the fourth cycle, the activity of the reused catalyst started declining while the conversion remained high. The catalyst (fresh and reused) has been characterized by using scanning electron microscopy (SEM) analysis; after the first run, the morphology of the catalyst was same with the fresh (Figs. 2a and 2b). When the catalyst was used for four runs (Figs. 2c and 2d), the morphology almost had no changes, and the number and size of protuberances on the wrinkles seemed unchanged. This indicated that the catalyst was chemically stable.

Finally, the implementation of the resin in a continuous system is the ultimate goal of large-scale application. Hence, we integrated the loaded resin D072 beads in a fixed catalyst bed, which was then continuously fed with a preheated solution of

Table 4. Reuse of resin D072[a]

Run	Conv. (%)[b]	Yield (%)[c]	Sel.[d]
1	99	85	86:14
2	99	87	88:12
3	99	87	88:12
4	99	83	84:16

[a] Reaction condition: 15 mmol of resorcinol, 5 mmol of styrene, 30 wt% (based on styrene) of catalyst, reflux in DCE for 4 h.

[b] HPLC conversion of styrene.

[c] HPLC yields of product.

[d] Single/double substituted isomer were determined by ^{1}H NMR and ^{13}C NMR.

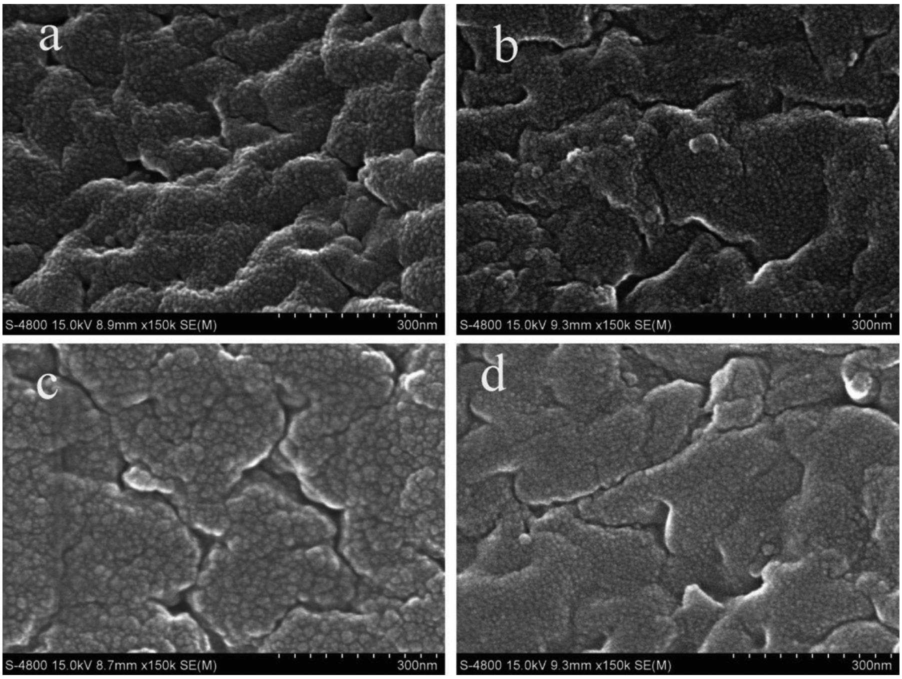


Figure 2. SEM images of resin D072 before (a) and after (b) the first run and before (c) and after (d) the fourth run.

resorcinol and styrene in DCE. Unlike batch conditions, the temperature should not be too high due to vaporization of solvent in continuously conditions. Thus most resorcinol was absorbed in resin and styrene flowed out with solvent; therefore, the desirable product was not detected in the outcoming flow. Then, the reaction temperature was set to 72 °C; surprisingly, styrene almost fully reacted, and the outcoming flow was monitored by HPLC for 9 h and samples were taken at intervals. As shown in Table 5, resin D072 showed good activity and selectivity in the fixed bed. To our delight, the selectivity (up to 94%) of the catalyst was significantly improved compared to the batch conditions. This was a tandem reaction; it was inevitable to

Table 5. Continuous flow conditions[a]

Time (h)	Conv. (%)[b]	Yield (%)[c]	Sel.[d]
3	99	93	94:6
4	99	93	94:6
5	99	93	94:6
6	99	92	93:7
7	99	93	94:6
8	99	92	93:7
9	99	93	94:6

[a] Reaction conditions: flow rate 0.3 mL/min, temperature 72 °C.

[b] HPLC conversion of styrene.

[c] HPLC yields of product 1.

[d] Single/double substituted isomer were determined by ^{1}H NMR and ^{13}C NMR.

produce the double substituted by-product. In batch conditions, the dosage of the catalyst was less than that of continuous conditions, and therefore the reaction time was much longer, which could promote the occurrence of further alkylation of the product. Compared with the batch conditions, as the product continuously flowed out of the fixed-bed reactor, the product's retention time in the reactor was much shorter. This made it difficult to be further alkylated, and therefore the selectivity for the product was greater.

To explore the general applicability of the established continuous conditions, greater concentrations of the mixture of phenol (14.1 g, 0.15 mol) and styrene (5.2 g, 0.05 mol) in DCE (174 mL) were constantly fed to the fixed-bed reactor at a rate of 0.3 mL/min. The outgoing flow was monitored by HPLC, styrene reacted adequately with phenol, and the ratio of *p*-substituted isomer with *o*-substituted isomer was 1:1, which was different from the batch conditions. The yield of the overall single-substituted products was 90%, similar to that with batch conditions.

CONCLUSION

In summary, we have developed a simple and efficient method for hydroarylation of various electron-rich arenes and styrenes with promising yields using resin D072 as a green and heterogeneous catalyst. The catalyst is commercially available, inexpensive, and reusable, and it has been successfully applied to the continuous flow conditions with greater selectivity than batch conditions. This green continuous process is potentially applicable to large-scale productions.

EXPERIMENTAL

General Procedure for the Hydroarylation

Batch conditions. Styrene (5 mmol, 0.52 g) was added to a mixture of resorcinol (15 mmol, 1.65 g) and resin (0.156 g, 30 wt%) in 10 mL of DCE, and the solution was stirred under reflux for 4 h. After the completion, the mixture was allowed to cool down to ambient temperature, and the catalyst was separated by filtration. The organic layer was washed with water (10 mL × 3) to remove the unreacted resorcinol, then dried with anhydrous magnesium sulfate, and concentrated under vacuum to give the viscous dark yellow oil. The residue was purified by flash chromatography (silica, eluant: petroleum/ethyl acetate/methanol) to get pure single-substituted and double-substituted products respectively.

Continuous conditions. A preheated solution of resorcinol (15 mmol) and styrene (5 mmol) in DCE (150 mL) was fed continuously with a syringe pump (flow rate 0.3 mL/min) over a catalyst bed consisting of 40 mL D072; the reaction temperature was 72 °C. The outlet of the reactor was sampled at intervals. The crude mixtures were directly analyzed by HPLC. The more detailed HPLC analysis conditions and spectroscopic data of the new compounds are provided in the Supplementary Information.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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