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Synthesis of Aryl-Substituted 1,4-Benzoquinone *via* Water-Promoted and $In(OTf)_3$-Catalyzed *in situ* Conjugate Addition-Dehydrogenation of Aromatic Compounds to 1,4-Benzoquinone in Water

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Abstract: Mono- and diaryl-substituted 1,4-quinones were synthesized by the $In(OTf)_3$-catalyzed conjugate addition of aromatic *C*-nucleophiles to 1,4-quinone derivatives followed by *in situ* dehydrogenation in water. Water was found to be beneficial to the reaction. The regioselectivity of the addition reaction in water was also examined.

Keywords: arylation; benzoquinone; C–C bond formation; homogeneous catalysis; indium; water as solvent

Introduction

Substituted 1,4-benzoquinone derivatives exist widely in nature and exhibit various important biological activities,[1] including antitumor and antibiotic activities,[2] inhibition of HIV-1 reverse transcriptase,[3] antidiabetic activities,[4] and others. Among these derivatives, aryl-substituted 1,4-quinones are found in many natural products. For example, belamcandaquinones A and B isolated from the seed of a medicinal plant, *Belamcanda chinests,* were used as a specific cyclooxygenase inhibitor.[5] Common synthetic methods for aryl-substituted 1,4-quinone compounds include the Meerwein arylation reaction of quinone with diazonium salts,[6] oxidation of aromatic compounds,[7] transition metal-catalyzed coupling reactions,[8] and photochemical reactions of acetylenes with $Fe(CO)_5$.[9] All these methods have certain limitations, such as the need for precious metals to act as catalysts, the use of a great amount of reagents, or polymerizations and low yields as a result of performing the reaction under intensive reaction conditions. Recently, it was reported by Yadav[10] and Pirrung[11] that a Lewis acid can catalyze the conjugate addition reaction of indole compounds with 1,4-benzoquinone to give 3-indolylquinone compounds. Such a reaction can also be catalyzed by some Brønsted acids.[12] On the other hand, Chan and co-workers[13] reported the synthesis of 4-hydroxycoumarin derivatives by the reaction of 4-hydroxycoumarins with *p*-benzoquinone. Although conjugate additions of simple non-conjugated carbonyl compounds by using aromatic compounds as *C*-nucleophiles have been studied extensively, there were few examples of conjugate addition of aromatic *C*-nucleophiles to benzoquinones for the synthesis of aryl-substituted benzoquinone compounds.[14] Recently, aqueous organic reactions have received considerable attention in view of their synthetic efficiency and environmental friendliness.[15] As part of our continuing interest in performing $In(OTf)_3$-catalyzed addition reactions of aromatic *C*-nucleophiles in water,[16] herein we report an $In(OTf)_3$-catalyzed conjugate addition of aromatic compounds to 1,4-benzoquinones followed by *in situ* dehydrogenation in water to give aryl-substituted benzoquinone compounds.

Results and Discussion

When 3-methoxy-*N,N*-dimethylaniline (**1a**) was reacted with 1,4-benzoquinone (**2a**) (**1a**/**2a** = 1:2) in the presence of a catalytic amount of $In(OTf)_3$ (5 mol %) in organic solvents such as CH_3CN, CH_2Cl_2 or THF, the yields

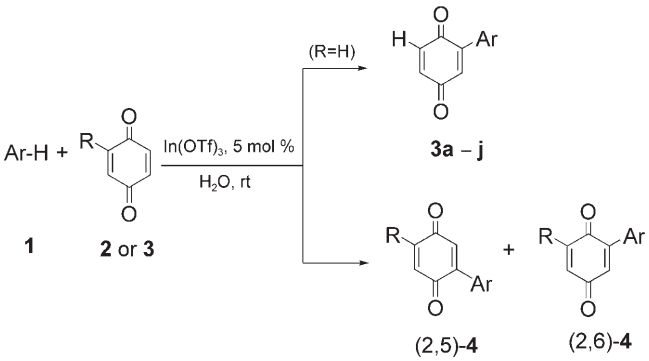
Table 1. $In(OTf)_3$-catalyzed reactions of **1a** with **2a** in various solvents.

Entry	**1a**:**2a**	Catalyst[a]	Solvent	Reaction time [h]	Yield [%][b]	
					3a	**4a**
1	1:2	$In(OTf)_3$	H_2O	2	93	trace
2	1:2	$In(OTf)_3$	CH_3CN	24	25	–
3	1:2	$In(OTf)_3$	CH_3CN/H_2O (2:1)	24	37	–
4	1:2	$In(OTf)_3$	CH_2Cl_2	24	10	–
5	1:2	$In(OTf)_3$	THF	24	7	–
6	1:2	$In(OTf)_3$	THF/H_2O (1:4)	24	Trace	–
7	1:2	HOTf	H_2O	2	86	–
8	1:2	–[c]	H_2O	2	31	–
9	1:1	$In(OTf)_3$	H_2O	24	8	79
10	1:1	$In(OTf)_3$	CH_3CN	24	10	–
11	1:1	$In(OTf)_3$	CH_2Cl_2	24	12	–
12	1:1	$In(OTf)_3$	THF	24	4	–
13	1:1	HOTf	H_2O	24	52	–

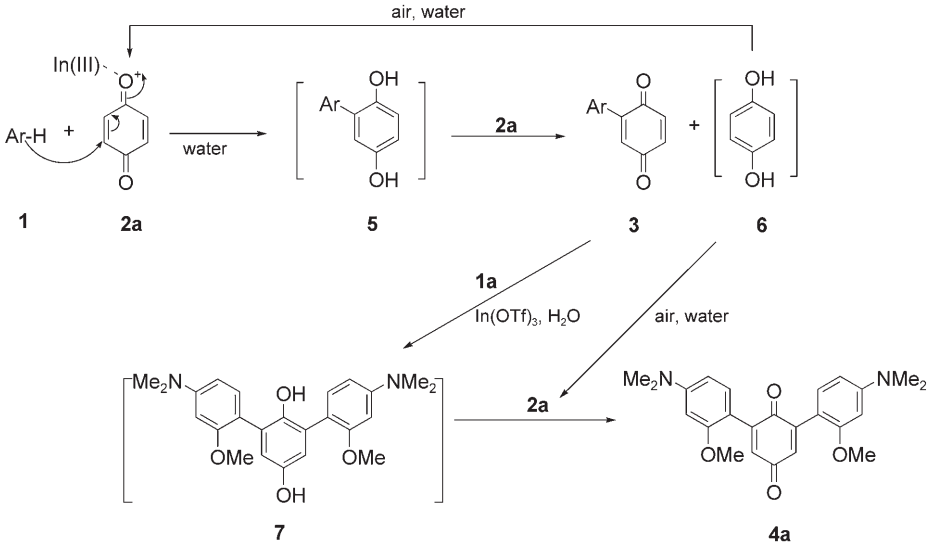
[a] Catalyst loading: 5 mol %.
[b] Isolated yield.
[c] Without using catalyst.

of the product **3a** were poor (trace – 25%) (Scheme 1, Table 1). Several reports have shown that, aside from potential environmental benefit, the use of water as a reaction medium sometimes provides special effects for chemical reactions.[17] In a mixed solvent, CH_3CN/H_2O (2:1), the reaction yield increased to 37% (entry 3); however, the use of aqueous THF as reaction media did not improve the yield at all (entry 6). Interestingly, if the reaction of **1a** with **2a** was carried out at room temperature in air and water, the reaction time was shortened from 24 h to 2 h and the yield of **3a** increased remarkably to 93% (entry 1). When the ratio of **1a**/**2a** was changed to 1:1, the solvent effect was more obvious: the aqueous reaction gave diaryl-substituted benzoquinone (**4a**) in 79% yield (yield is based on the aromatic starting material, entry 9), while the reaction in organic solvent did not produce **4a** at all (entries 10–12). Although trifluoromethanesulfonic acid (HOTf) could also catalyze the reaction (entry 7), no diaryl-substituted product **4a** was detected in the product mixture (with **1a**/**2a** = 1:1) (entry 13). [Note: similarly, the reaction between 1,3-dimethoxybenzene (**1f**) and **2a** (1:1) did not afford diaryl-substituted quinone (**4 h**) at all in the presence of HOTf; whereas by using $In(OTf)_3$ as a catalyst, **4 h** was obtained in 79% yield (Table 3, entry 8)]. In the absence of a catalyst, **3a** was obtained in 31% yield when the reaction was carried out in water (Table 1, entry 8).

Subsequently, various aniline derivatives **1a**–**d** were used in the reaction with 1,4-benzoquinone compounds **2a**–**c** in water and in the presence of catalyst $In(OTf)_3$. The reactions were carried out under the same conditions, giving the aryl-substituted benzoquinone products **3a**–**f** in good to high yields (Table 2). All the products exhibited a *para*-amino-arylbenzoquinone structure, resulting from the aromatic *C*-nucleophilic attack on the α,β-unsaturated carbonyl unit of 1,4-benzoquinone. However, when methylaniline (**1e**) was used, an *N*-nucleophilic addition product **3g** was obtained in 63% yield (Table 2, entry 8). Oxygen-containing aromatic compounds **1f** and **1g** were also effective as aromatic *C*-nucleophiles in the reaction. The reaction of 1,3-dimethoxybenzene (**1f**) produced a mixture of mono-substituted (**3h**) and di-substituted benzoquinone derivatives **4h**, while the use of 2-methylfuran (**1g**) generated product **3j** in 64% yield (Table 2, entry 9), with the 5-position of furyl group linked to the benzoquinone moiety. On the other hand, 45% of the starting material 1,4-benzoquinone (**2a**) was recovered from the reaction of **1a** with **2a** (**1a**/**2a** = 1:2) after the reaction had gone to completion. In the reactions of both **1d** with **2a** and **1a** with **2c** (Table 2, entries 4 and 6), aryl-substituted 1,4-hydroquinone compounds could be obtained. When the reaction time was prolonged to 24 h, the ratio of benzoquinone (**3f**) to hydrobenzoquinone **3f-1** increased noticeably (Table 2, entry 7). Based on these results, the mecha-



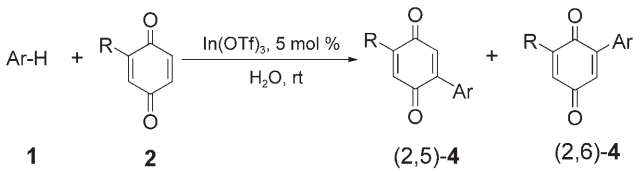
Scheme 1.



Scheme 2.

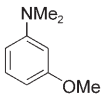
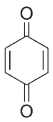
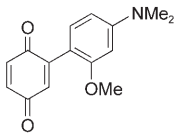
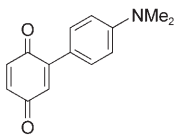
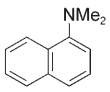
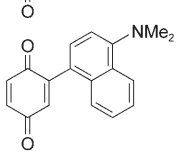
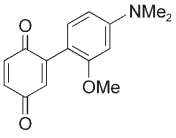
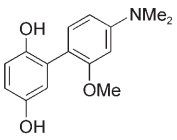
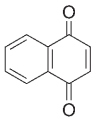
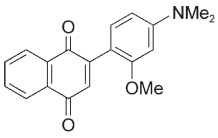
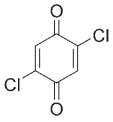
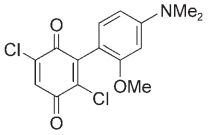
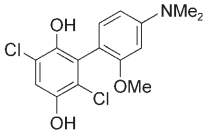
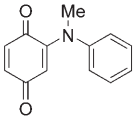
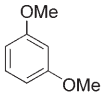
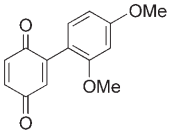
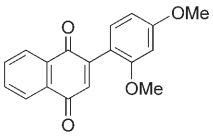
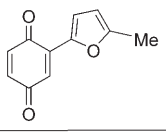
nism of the reaction can be hypothesized[18] as follows: at first, the conjugate addition of the aromatic nucleophile to 1,4-benzoquinone produced a mono-aryl-substituted hydroquinone intermediate **5**. Then one half of 1,4-benzoquinone **2a** was incorporated into the product and the other half of **2a** oxidized the 1,4-hydroquinone intermediate **5** into the mono-substituted 1,4-benzoquinone **3**. At the same time, **2a** was re-generated by the oxidation of the 1,4-hydrobenzoquinone **6** under an air atmosphere in water. In the case of **1a**, due to the high reactivity in water during the course of the reaction (**1a**/**2a** = 1:1), it could react with the mono-substituted benzoquinone **3** (generated *in situ*) to produce diaryl-substituted hydrobenzoquinone **7**, which was oxidized to give the final product, diaryl-substituted 1,4-benzoquinone (**4a**) (Scheme 2).

When mono-substituted benzoquinone was used as a substrate in this reaction, there was an issue of regioselectivity: the addition could occur at either the 5- or 6-position of 1,4-benzoquinone, leading to 2,5- or 2,6-regioisomers, respectively (Scheme 3). The regioselectivity was found to be highly dependent upon the substituent on the 1,4-benzoquinone ring. As shown in Table 3, for 2-methoxy-1,4-benzoquinone (**2d**), (2,5)-addition products **4b**–**e** were obtained exclusively in 76–89% yields, either through *C*-nucleophilic (Table 3, entries 1–3) or *N*-nucleophilic additions (entry 4). The structures of the 2,5-addition products were confirmed by X-ray analyses of the single crystals of (2,5)-**4c** and (2,5)-**4e**. For the amino-substituted 1,4-benzoquinone, the conjugate addition of 2-arylamino-1,4-quinone **3g** with *C*-nucleophile **1a** also exhibited exclusive 2,5-selectivity (entry 12). However, when 2-methyl-1,4-benzoquinone (**2e**) was used, very poor regioselectivity (2,5-/2,6- = 1:1.1) was observed by ^{1}H NMR of the product mixture (entry 5).[19] Changing the methyl group to a *t*-butyl group (**2f**) increased the 2,6-selectivity (2,6-/2.5-isomer = 7.3:1) (entry 6).[20] 2,6-Regioselectivity was observed in a one-pot reaction of aromatic compounds **1a** or **1f** with quinone (**2a**). When the ratio of **1a** or **1f** to **2a** was 1:1, (2,6)-substituted 1,4-benzoquinones (2,6)-**4a** and **4h** were obtained exclusively in 79% yield (Table 3, entries 7 and 8). The 2,6-selectivity was also confirmed by the X-ray analysis of the single crystals of (2,6)-**4a** and **4h**. In terms of the mechanism of the one-pot reaction, it can be hypothesized that the mono-substituted benzoquinone **3a** or **3h**, generated *in situ* from the initial reaction, underwent a subsequent reaction with the same aromatic *C*-nucleophile to give the homo-(2,6)-diaryl-substituted benzoquinones. This hypothesis was confirmed by stepwise experiments in which the reaction of preformed **3a** with **1a** also gave the identical homo-diaryl-substituted 1,4-quinone, (2,6)-**4a**, in 64% yield (Table 3, entry 9). In contrast, when *N*-methylaniline **1e** was reacted with **2a** (**1e**/**2a** = 1:1), (2,5)-homo-diarylamino-substituted benzoquinone (2,5)-**4i** was obtained in 65% yield (Table 3, entry 10). The stepwise reaction could be used to generate the cross-2,6-diaryl-substituted 1,4-quinone (2,6)-**4j** (Table 3, entry 11). In the case of an *N*-nucleophile, which is more reactive than aromatic *C*-nucleophiles, (2,6)-selectivity was also observed (Table 3, entry 13). By using the stepwise reactions two isomers, (2,6)-**4k**



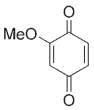
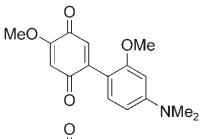
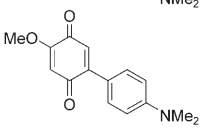
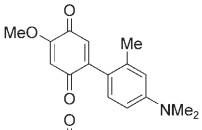
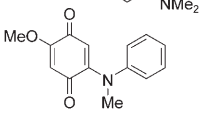
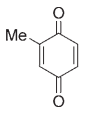
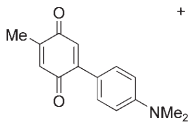
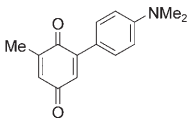
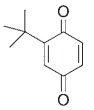
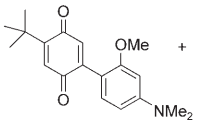
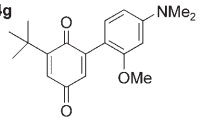
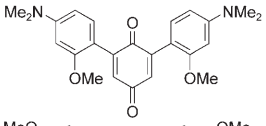
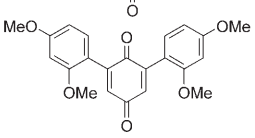
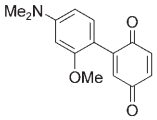
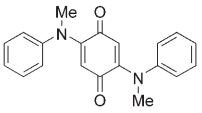
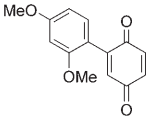
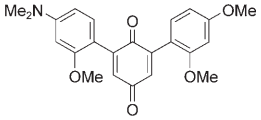
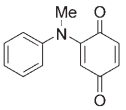
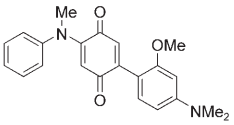
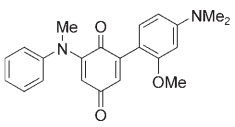
Scheme 3.

Table 2. Reactions of Ar–H with quinones catalyzed by $In(OTf)_3$[a] in water.

Entry	Ar-H[b]	Quinone[b]	Time [h]	Product	Yield[c] [%]
1	**1a** 	**2a** 	2	**3a** 	93
2	**1b** 	**2a**	24	**3b** 	84
3	**1c** 	**2a**	24	**3c** 	69
4	**1d** 	**2a**	24	**3d**  + **3d-1** 	33+56
5	**1a**	**2b** 	12	**3e** 	86
6	**1a**	**2c** 	2	**3f**  + **3f-1** 	40+55
7	**1a**	**2c**	24	**3f** + **3f-1**	65+28
8	**1e** 	**2a**	2	**3g** 	63
9	**1f** 	**2a**	24	**3h**  + (2,6)-**4h**[d]	60+17
10	**1f**	**2b**	24	**3i** 	78
11	**1g** 	**2a**	24	**3j** 	64

[a] Catalyst loading: 5 mol %.
[b] Ar-H/quinine = 1 : 2.
[c] Isolated yield.
[d] Di-substituted quinine **4h**, see Table 3, entry 8.

Table 3. Regioselectivity of the $In(OTf)_3$-catalyzed[a] reactions of Ar–H with quinones in water.

Entry	Ar-H	Quinone	ArH/Q	Time	Product	Yield (%)[b] (2,5-/2,6-)[c]
1	**1a** 	**2d** 	1 : 2	2 h	(2,5)-**4b** 	85 (1: 0)
2	**1b** 	**2d**	1 : 2	24 h	(2,5)-**4c** 	76 (1: 0)
3	**1d** 	**2d**	1 : 2	24 h	(2,5)-**4d** 	81 (1: 0)
4	**1e** 	**2d**	1 : 2	40 min	(2,5)-**4e** 	89 (1: 0)
5	**1b**	**2e** 	1 : 2	24 h	(2,5)-**4f**  + (2,6)-**4f** 	76 (1: 1.1)
6	**1a**	**2f** 	1 : 2	24 h	(2,5)-**4g**  (2,6)-**4g** 	38 (1: 7.3)
7	**1a**	**2a**	1 : 1	24 h	(2,6)-**4a** 	79 (0: 1)
8	**1f** 	**2a**	1 : 1	24 h	(2,6)-**4h** 	79[d] (0: 1)
9	**1a**	**3a** 	1 : 2	24 h	(2,6)-**4a**	64 (0: 1)
10	**1e**	**2a**	1 : 1	2 h	(2,5)-**4i** 	65 (1: 0)
11	**1a**	**3h** 	1 : 2	24 h	(2,6)-**4j** 	65 (0: 1)
12	**1a**	**3g** 	1 : 2	2 h	(2,5)-**4k** 	71 (1: 0)
13	**1e**	**3a**	1 : 2	12 h	(2,5)-**4k** + (2,6)-**4k** 	83 (1: 3.2)

[a] Catalyst loading: 5 mol %.
[b] Isolated yield.
[c] Determined by ^1H and ^{13}C NMR of the product mixture.
[d] With mono-substituted product **3h** (13% yield).

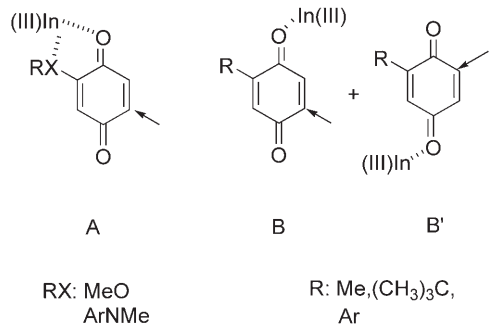


Figure 1.

and (2,5)-**4k**, could be obtained respectively (entries 12 and 13).

The regioselectivities are attributed to the different coordinating sites of benzoquinones to $In(OTf)_3$ (Figure 1). For 2-methoxy-1,4-benzoquinone, a chelation between In(III) with oxygen atoms in the methoxy and 1-carbonyl groups (A) would occur during the reaction, which resulted in the 2,5-selectivity; whereas in the case of the alkyl substituents (R = methyl and *t*-butyl), no chelation was possible and both carbonyl groups of 1,4-benzoquinone ring could coordinate with the Lewis acid, depending on the steric effect of the R group. The smaller methyl group led to the coordination of a Lewis acid to both carbonyl groups with no significant selectivity (a mixture of almost equal amounts of B and B′) of the addition reaction; however, the bulky *t*-butyl group prevented the coordination of its neighboring carbonyl and favored the B′ coordination mode, resulting in the 2,6-selectivity predominantly. In the case of heteroaromatic-substituted 1,4-benzoquinones (such as **3a** and **3b**), although nitrogen- and oxygen-containing groups were present on the phenyl ring, no chelation between $In(OTf)_3$ and the carbonyl group occurred. Thus, the B′ coordination mode was also predominant, resulting in the 2,6-regioselectivity.

Conclusion

A convenient and efficient method for the synthesis of aryl-substituted 1,4-quinones through a $In(OTf)_3$-catalyzed conjugate addition reaction followed by an *in situ* dehydrogenation was developed in water. Water not only serves as the reaction media but also promotes the reaction. (2,6)-Regioselectivity was observed for the bis-arylation reaction and the regioselectivity was confirmed in the reactions of mono-substituted 1,4-quinones without the chelating group, by using either a *C*-nucleophile or *N*-nucleophile.

Experimental Section

General Remarks

IR spectra were recorded on a Bruker Tensor 27 infra-red spectrometer. ^1H and ^{13}C NMR spectra were measured on a Bruker AV-300 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were recorded on a GCT-MS Micromass spectrometer. Elemental analyses were performed on a Carlo Flash 1112 Element Analysis instrument. Melting points were measured by a Beijing-Tike X-4 apparatus and are uncorrected. The X-ray crystal structures were measured on Rigaku R-axis RAPID IP. Common reagents and materials were purchased from commercial sources and purified before used.

Typical Experimental Procedure

A mixture of *N*,*N*-dimethyl-3-methoxyaniline (**1a**, 15.1 mg, 0.1 mmol), 1,4-benzoquinone (**2a**, 21.6 mg, 0.2 mmol), and $In(OTf)_3$ (2.8 mg, 0.005 mmol) in water (2 mL) was stirred at room temperature. The reaction was monitored by TLC. After **1a** had disappeared, the reaction mixture was extracted with dichloromethane (10 mL × 3). The combined organic layer was dried over Na_2SO_4 and evaporated to remove the solvent. The crude product was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 6:1) to give **3a** as a blue solid; yield: 24 mg (93%).

Synthesis of Diaryl-Substituted 1,4-Quinones with a One-Pot Reaction

A mixture of **1a** (30.2 mg, 0.2 mmol), **2a** (21.6 mg, 0.2 mmol) and $In(OTf)_3$ (5.6 mg, 0.01 mmol) in water (2 mL) was stirred at room temperature for 24 h. The reaction was monitored by TLC. After **1a** had disappeared, the reaction mixture was extracted by dichloromethane (6 mL × 3). The combined organic layer was dried over Na_2SO_4 and evaporated to remove the solvent. The crude product was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 6:1) to give (2,6)-**4a** as a red solid; yield: 32 mg (79%).

Characterization data for all products can be found in the Supporting Information file. Crystallographic data (excluding structure factors) for **4a**, **4c**, **4e**, and **4 h** have been deposited with the Cambridge Crystallographic Data Centre with the following supplementary publication nos.: (2,6)-**4a**: CCDC 288003, (2,5)-**4c**: CCDC 288004, (2,5)-**4e**: CCDC 288005, (2,6)-**4 h**: CCDC 288006. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax.: (internat.) +44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

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[19] The ratio of 2,5- to 2,6-isomers was determined by the ratio of the ^{1}H NMR peaks of the reaction mixture at $\delta =$ 2.12 and 2.08 ppm.

[20] The ratio of 2,5- to 2,6-isomers was determined by the ratio of the ^{1}H NMR peaks of the reaction mixture at $\delta =$ 6.57, 6.68 and 6.64, 6.71 ppm.

