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Graphene Oxide Promotes Site-Selective Allylic Alkylation of Thiophenes with Alcohols

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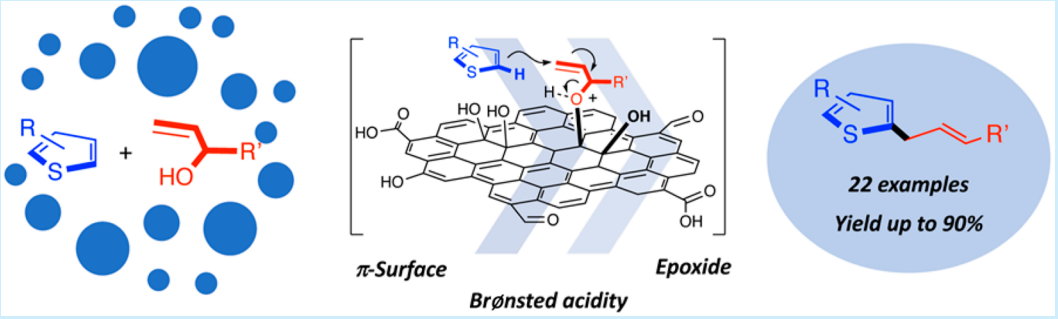
Supporting Information



ABSTRACT: The graphene oxide (GO) assisted allylic alkylation of thiophenes with alcohols is presented. Mild reaction conditions and a low GO loading enabled the isolation of a range of densely functionalized thienyl and bithienyl compounds in moderate to high yields (up to 90%). The cooperative action of the Brønsted acidity, epoxide moieties, and π-surface of the 2D-promoter is highlighted as crucial in the reaction course of the present Friedel−Crafts-type protocol.

The site-selective functionalization of the thiophene nucleus is still of undoubted importance due to their ubiquitous use in the realization of functionalized molecular materials for organic electronics and photonics.[1] Catalysis represents an ultimate synthetic tool for the chemical "decoration" of this class of heteroarenes, enabling critical aspects such as selectivity, simplicity, and sustainability to be satisfied simultaneously. In this context, the Friedel−Crafts (FC) allylic alkylation reaction is still receiving growing attention, since it makes feasible further chemical manipulations of the aromatic core due to the installation of carbon−carbon double bonds.[2] The synthetic interest for this approach can be further amplified by adopting cheap, readily available, and user-friendly π-alcohols (i.e., allylic, propargylic, and allenylic alcohols) as alkylating agents.[3] However, important synthetic challenges such as regioselectivity and mono- vs polyalkylation, with specific reference to electron-rich aromatic rings, are still not fully addressed.

Bearing all that in mind, we envisioned the emerging "carbocatalytic" approach[4] as a promising tool to overcome these difficulties. In particular, we identified graphene oxide (GO)[5] as a mediating agent for site-selective allylation of functionalized thiophenes with readily accessible alcohols. Moreover, due to its moderate Brønsted acidity, diversified surface functionalization, and possible implementation into composite materials, GO has already found elegant applications in several synthetic organic transformations such as oxidation of alcohols/amines,[6a−e] hydrogenation of alkenes,[6f] click chemistry,[6g] and aminolysis.[6h] Contrarily, and unexpectedly, the use of GO in carbon−carbon bond forming reactions is still limited.[7]

In this context, He and Szostak have recently reported an elegant GO-assisted alkylation of arenes that caught our attention. In detail, the benzylation of electron-activated aromatic compounds with styrenes was discussed by using GO (200 wt %) as the promoting agent (Figure 1a).[8]

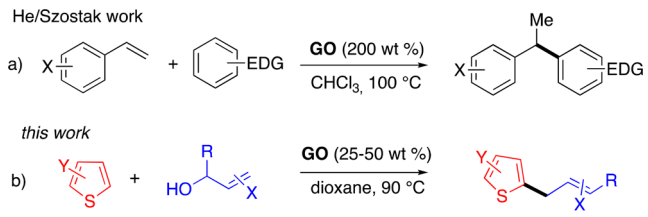


Figure 1. Previous study on GO-based Friedel−Crafts-type alkylation of alkenes (a) and the present work (b).

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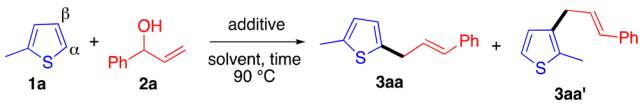
In combination with our ongoing interest in catalytic methodologies for the direct functionalization of arenes with alcohols,[9] we envisioned the possibility of implementing a metal-free GO-assisted allylating protocol on thiophenes (Figure 1b). In this letter, preliminary findings and mechanistic investigations on the topic are documented.

At the outset of our investigation, we considered the commercially available 2-methyl-thiophene **1a** and 1-phenyl-prop-2-en-1-ol **2a** as model substrates with the specific intent to assess the reliability of the protocol toward (a) polyalkylation, (b) α- vs β-regioselectivity, (c) an S_N vs S_N' mechanism (i.e., regiochemistry toward the allylic framework), and (d) the stereochemistry of the newly formed C=C. A range of carbocatalysts and reaction conditions were screened (Table 1).

Table 1. Optimization of the Reaction Conditions[a]



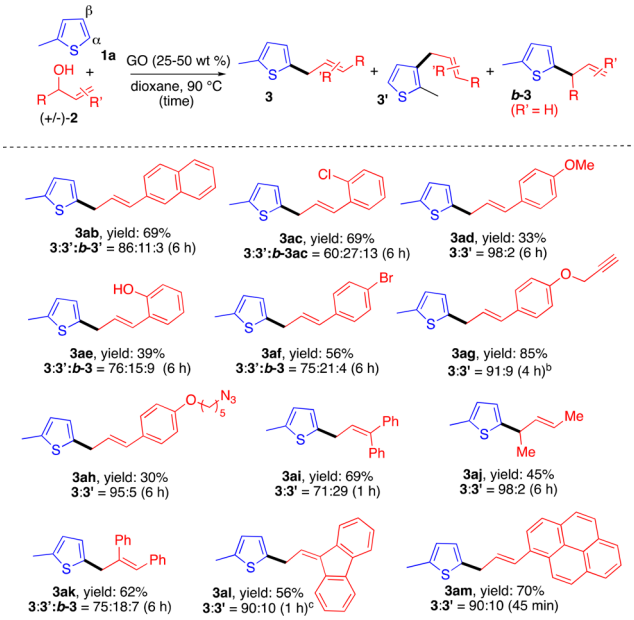
run	additive (wt %)	solvent/time (h)	yield (%)[b]	3aa:3aa'[c]
1	GO (50)	$CHCl_3$/16	36	86:14
2	GO (25)	$CHCl_3$/16	23	85:15
3	GO_{aq}[d] (25)	$CHCl_3$/16	traces	–
4	GO (25)	THF/4	34	72:28
5	GO (25)	ACN/4	51	75:25
6	GO (25)	DMF/4	NR	–
7	GO (25)	$(CH_2Cl)_2$/4	77	78:22
8	GO (25)	DCE/8	89	78:22
9	GO (25)	dioxane/4	90	86:14
10	graphene (25)	dioxane/4	NR	–
11	rGO (25)	Dioxane/4	NR	–

[a]All the reactions were carried out in reagent-grade solvents without any moisture exclusion (**1a**:**2a** = 3:1). [b]Isolated yield after flash chromatography. [c]Both **3aa** and **3aa'** were isolated as *E*-stereoisomers and resulted in being inseparable via flash chromatography. [d]Aqueous solution (5 mg/mL) of GO was employed. NR: no reaction. ACN: acetonitrile.

Interestingly, a promising isolated yield of the **3aa**/**3aa'** mixture was recorded by using only 50 wt % of catalyst in $CHCl_3$ at 90 °C (entry 1) that was subsequently reduced to 25 wt % (entry 2) with a decrease of the overall performance (23% yield). Contrarily, the use of an aqueous solution of GO failed in producing the final product. DCE and 1,4-dioxane were elected as the best solvents providing comparable outcomes (yields 89–90% and up to 86:14 **3aa**/**3aa'** ratio). However, the shorter reaction time (4 h vs 8 h) led us to choose 1,4-dioxane for the reaction scope investigation.[10] It is worth mentioning that while the blank reaction clearly emphasized the pivotal role of the GO[11] (entry 10), graphene and reduced graphene oxide (rGO) proved completely ineffective in the present protocol. Finally, only the thermodynamically more stable linear compounds **3aa** and **3aa'** were isolated ($S_{N'}$ vs S_N) along with the exclusive formation of the (*E*)-isomer. Furthermore, only in sporadic cases, traces of branched **3aa** (i.e., *b*-**3aa**) were also observed in the reaction crude.[12]

The optimized reaction conditions were applied to a range of diversely substituted allylic alcohols (**2b**–**m**; see Supporting Information) in the Friedel–Crafts alkylation of **1a** (Scheme 1). In all cases, S_N2'-type allylation compounds **3** were obtained exclusively with the (*E*)-C=C configuration in moderate to

Scheme 1. Scope of the Reaction: Alcohols[a]



[a]0.2 mmol of **2** (**1a**:**2** = 3:1) unless otherwise specified. [b]With **1a**:**2g** = 6:1 and GO loading of 50 wt %. [c]*t* = 80 °C. In some specific cases, minor amounts of branched **3** were also detected by NMR (see SI).

very good yield (30–85%). 1-Aryl-propen-1-ols carrying both electron-donating (e.g., OH, OR) and electron-withdrawing (e.g., Cl, Br) groups are proven efficient under optimal conditions. Additionally, synthetically useful alkyne (**3ag**) and azide (**3ah**) groups were effectively tolerated. It is worth noting that the unprotected phenolic group was also tolerated in the process, underlying that the FC-based C–C bond forming product **3ae** was favored with respect to the C–O bond formation under GO-assistance. The synthetic approach was also applied to the moderately site-selective functionalization of **1a** with concomitant formation of products (**3ai** and **3ak**). The reactivity of aliphatic allylic alcohols was also demonstrated by condensing **2j** with **1a** under optimal conditions. Interestingly, the corresponding C(2)-alkylated thienyl compound **3aj** was isolated in 45% yield as a single regio- and stereoisomer. Finally, the protocol also enabled the incorporation of chromophoric units (e.g., fluorenyl and 1-pyrenyl) into the model aromatic compound in moderate to good yields (56–70%) with a very short reaction time (45 min–1 h)

Therefore, we turned our attention toward the generality of the method related to thiophene derivatives. 2-*n*Hex-thiophene **1b** displayed feasibility for the present methodology furnishing the corresponding alkylated compound **3ba** in 51% yield. Analogously, differently substituted bithienyl compounds **1c**–**h** underwent the FC-allylative process in a satisfying manner (yields up to 64%) by means of 50 wt % of GO. In all cases, monosubstituted linear α-allylated compounds **3** were obtained as the predominant arene (Scheme 2). β-Functionalized linear allyl-thiophenes were also observed in a non-negligible amount in the case of **3ca**–**3ea**. Differently, α-branched isomers *b*-**3** were formed only in traces with the exception of substituted bithiophenes **1d** and **1e**.[13] Additionally, also widely employed rigid "cores" in organic electronics such as dithienothiophene **1g**[14a] and dithienopyrrole **1h**[14b] underwent allylic alkylation with alcohols **2a** and **2f** resulting in a moderate yield (32%) and very high regioselectivity (up to 95:5).

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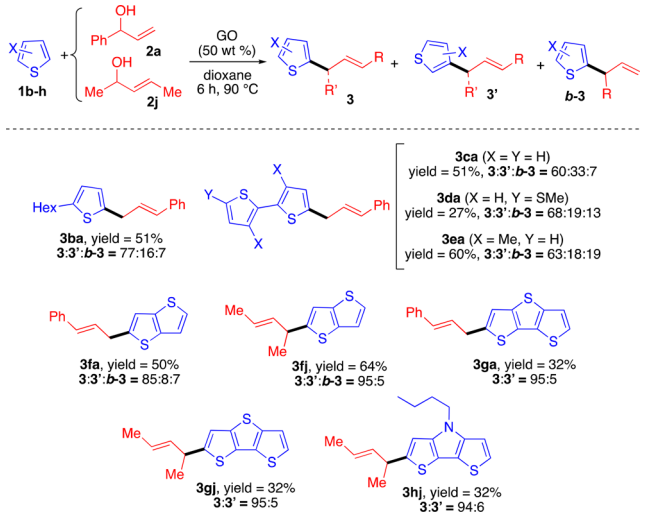
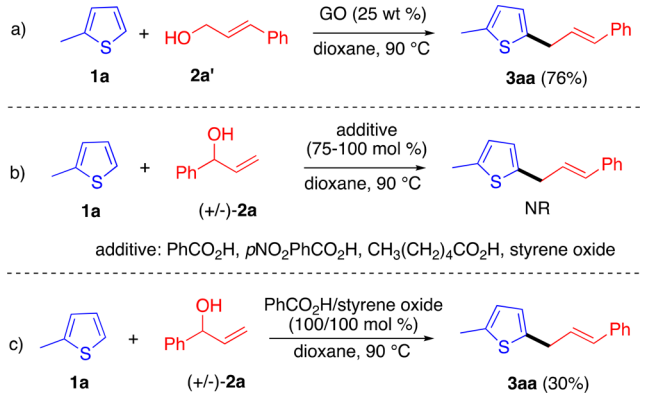
Scheme 2. Scope of the Reaction: Thiophenes[a]



[a]Isolated yields after flash chromatography. Regioselectivity was determined by GC-MS and/or ^{1}H NMR on the reaction crudes.

In order to obtain mechanistic insight, some control experiments were performed. First, when branched or linear allylic alcohols **2a** and **2a′** were utilized, comparable chemical and stereochemical outcomes in (*E*)-**3aa** were recorded (90% and 76% yields, respectively, Scheme 3a). Additionally, the

Scheme 3. Control Experiments for the Present GO-Assisted Friedel−Crafts Condensation[a]



[a]0.2 mmol of **2a**/**2a′** (**1a**:**2** = 3:1).

impact of the sole Brønsted acidity conferred by the GO solution in dioxane (~5 mg/mL → pH = 3.70) was assessed by running the model process in the presence of several organic Brønsted acids (loading = 75−100 wt %), namely, benzoic acid (pH = 5.10, 5 mg/mL), *p*NO_2-benzoic acid (pH = 3.82, 1 mg/mL), and *n*-hexenoic acid (pH = 4.22, 5 mg/mL), but no formation of **3aa** was observed. Analogously, when (±)-styryl epoxide (100 wt %) was employed the reaction did not procede at all (Scheme 3b). The control experiment carried out with stoichiometric amounts of styrene oxides was intended to verify the potential role of the oxiranes moieties present in the GO surface on the reaction mechanism. Such evidence unambiguously highlights the concerted action of the GO skeleton and the functional groups present in the 2D-material in making the C−C bond formation process effective. In contrast, when **1a** and **2a** were reacted with the simultaneous presence of benzoic acid and styryl oxide (both at 100 wt %), **3aa** was formed in 30% conversion (^{1}H NMR), providing preliminary evidence of the synergistic action of the Brønsted acidity and the oxirane units in promoting the condensation of the thiophene ring and the allylic alcohol.

To further prove the direct involvement of epoxide units in the reaction mechanism, X-ray Photoelectron Spectroscopy (XPS) analysis was carried out in samples of GO before and after the catalytic protocol (Figure 2).

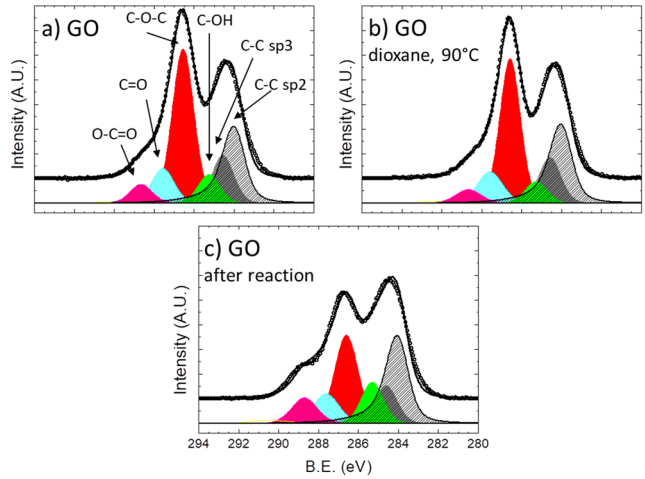


Figure 2. C 1s XPS spectra of (a) pristine GO, (b) GO after 4 h at 90 °C in dioxane, and (c) GO after the allylic alkylation of thiophenes with alcohols.

The fitting of the high-resolution C 1s peak quantified the relative amounts of aromatic carbon (C−C sp^2, 284.4 eV), aliphatic carbon (C−C sp^3, 285.0 eV), hydroxyl (C−OH, 285.7 eV), epoxy (C−O−C, 286.7 eV), carbonyl (C═O, 288.0 eV), and carboxyl (O−C═O, 290.1 eV).[15]

Figure 2 shows the C 1s spectra of (a) pristine GO, (b) GO after 4 h at 90 °C in dioxane, and (c) GO after the site-selected allylic alkylation of thiophenes with alcohols. First, it is possible to exclude any reaction between GO and dioxane at 90 °C since GO (a) and GO after 4 h at 90 °C in dioxane (b) have no remarkable differences. In contrast, after reaction (Figure 2c) the relative abundance of the epoxy groups decreased substantially from 40.3 ± 0.8% to 27.4 ± 0.6%, while the hydroxyl groups increased from 7.6 ± 0.3% to 11.9 ± 0.3% suggesting that a partial ring opening of the epoxide units of the promoting agent took place concomitantly to the reaction course. As expected, aromatic carbons are not affected by the reaction (see SI for details).

We combined all spectroscopic and experimental information with the QM/MM study to elucidate in detail the reaction mechanism.[16] We used **1a** and **2a** as model substrates. The reaction mechanism resulted in being a three-step process, as depicted in Figure 3. In step 1 the allylic alcohol grafts to the GO surface. The reaction follows an S_N1 mechanism where the protonation (proton source could rely on the intrinsic Brønsted acidity of GO) of the epoxide ring on the GO surface leads to an unstable oxonium unit that opens without overcoming any barrier (**Rx**). This gives a reactive *α*-carbocation that undergoes a nucleophilic attack by the allylic alcohol (**Ts1**). From this picture emerges the crucial role of the GO *π*-system in stabilizing the carbocation generated by the epoxide ring opening event. The concerted action of the GO *π*-system and

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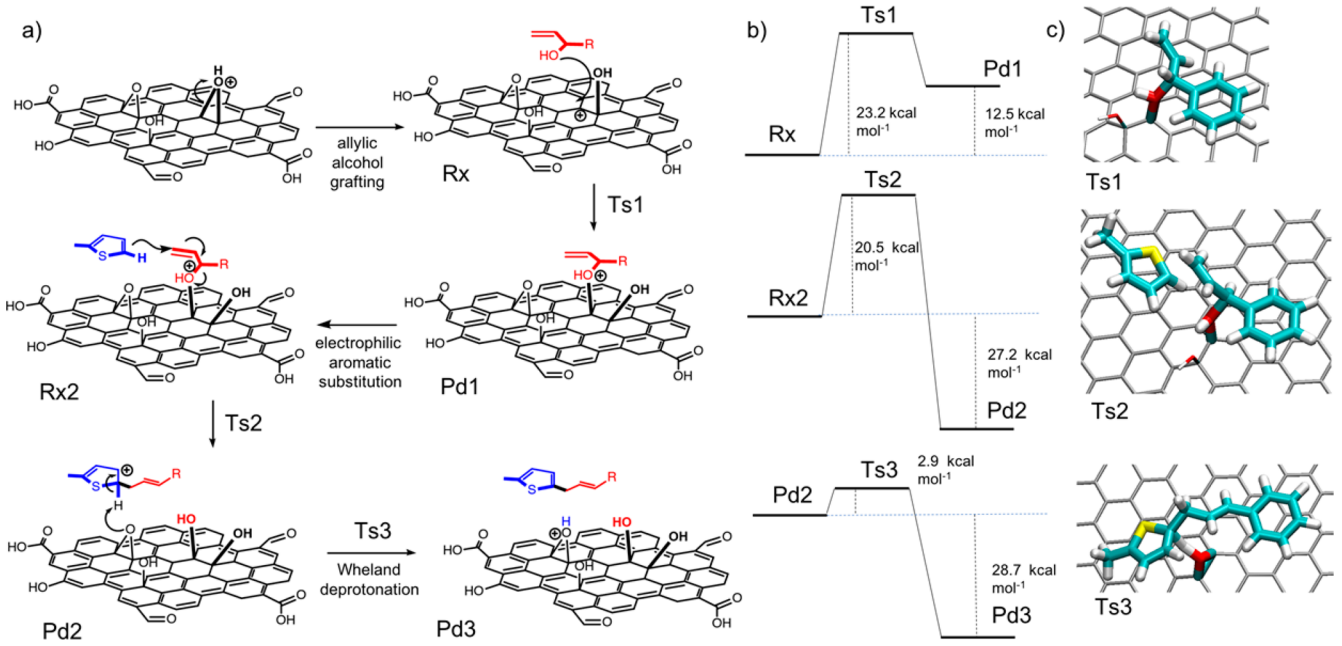

Figure 3. (a) Schematic representation of the reaction mechanism; (b) energy profiles for the three steps; (c) 3D representation of the identified transition states.

the functional groups present in the 2D-material is highlighted in agreement with experimental observations. The obtained protonated allyl ether may undergo a Friedel−Crafts-type allylic alkylation providing the observed allyl-thiophene (**Pd1**). Step 2 follows a concerted mechanism where the α-carbon of the 2-methyl-thiophene attacks the allylic position (**Ts2**), inducing a reorganization of the π-system (Figure 3c). The leaving O−H group remains grafted on the GO surface (**Pd2**). Such a mechanism justifies the overall increase of alcoholic moieties versus the oxirane ones spectroscopically observed by XPS.

The GO catalyst also played a role in the regioselectivity of the attack carried out by the α carbon of the thiophene derivatives (**3aa** vs **3aa′**). In fact, if the attack is carried out by the α carbon (major regioisomer, Figure SI1) the sulfur atom of the thiophene points toward the graphene sheet, while if the attack is carried out by the β-carbon there is no interaction between the S atom and GO. It is well-known that sulfur−π interactions are strongly stabilizing,[17] favoring the attack in α by 6.5 kcal mol^{-1} (Figure SI1). The final step, namely the deprotonation of the Wheland-like intermediate (**Ts3**), is a fast process (a barrier of only 2.9 kcal mol^{-1} was computed) carried out by other epoxide groups present on the GO surface. The recorded drop in catalytic performance (isolated yields in **3aa**) by the recovered GO (I run: 88%, II run: 66%, III run: 45%, IV run: 29%) supports the current mechanistic hypothesis. In particular, the lower the content of epoxide units is on the GO surface, the less effective the carbocatalysis is.[18]

In conclusion, the regioselective allylic alkylation of thiophenes with alcohols is documented under the assistance of readily available and chemically unmodified graphene oxide. The protocol features unique key aspects such as high functional group tolerance, mild reaction conditions, and low to moderate GO loading. The extension of the present GO-based protocol to other C−C bond forming functionalizations of π-systems is currently under investigation in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01531.

Synthetic procedures, XPS analysis and NMR spectra of unknown compounds and computational detail (PDF)

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Notes

The authors declare no competing financial interest.

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(10) The flakes of GO tended to dissolve completely during the heating and reaction time.

(11) GO was used in flakes, and it exfoliated during the reaction. In a comparative experiment, GO was exfoliated for 10 h in the reaction solvent and the suspension used as-is for the catalysis. No differences in reaction performances were recorded.

(12) Additionally, other "conventional" Lewis acids were tested in the model reaction providing unsatisfying results in terms of yields or **3aa:3aa′** regioselectivity: *p*TSA (10 mol %) → 18% yield; $FeCl_3$ (10 mol %) → NR; $In(OTf)_3$ → 84% yield (2:1).

(13) Attempts to extend the protocol to longer thiophene oligomers such as quaterthiophene failed in performing the FC-type process.

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