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Nickel-Catalysed Direct Alkylation of Thiophenes *via* Double C(*sp*³)-H/C(*sp*²)-H Bond Cleavage: The Importance of KH₂PO₄

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A Ni-catalyzed oxidative C-H/C-H cross-dehydrogenative coupling (CDC) reaction was developed for constructing various highly functionalized alkyl(aryl)-substituted thiophenes. This method employs thiophenes and aliphatic(aromatic) amides that contain an 8-aminoquinoline as a removable directing group in the presence of a sliver oxidant. The approach enables the facile one-step synthesis of substituted thiophenes with high functional group compatibility via double C-H bond cleavage without affecting C-Br and C-I bonds. DFT calculations verify the importance of KH₂PO₄ as an additive for promoting C-H bond cleavage and support the involvement of a Ni(III) species in the reaction.

Thiophenes and analogues thereof are ubiquitous in pharmaceuticals, ^1 natural products, ^{1b} and functional materials. ^2 (supporting information, SI). ^{1,2}



Conventional methods for the functionalization of thiophenes include the metal-catalyzed cross-coupling of organic halides with organometallic reagents such as Kumada coupling, Stille coupling, and Suzuki-Miyaura coupling (Scheme 1a).³ Alternatively, lithiation of thiophenes at low temperatures by *n*-BuLi followed by nucleophilic substitution with an alkyl halide enables $C(sp^2)-C(sp^3)$ linkages to be installed (Scheme 1b).⁴ However, disadvantages associated with these conventional methods include the need of tedious, multistep procedures for preparing the starting materials, expensive reagents, poor substrate availability, and low tolerance towards functional groups (especially when organometallic species such as organolithiums or organomagnesiums are involved). To tackle these problems, considerable attention has been paid to developing new methods for installing thiophenes via more meeting these requirements is oxidative C-H/C-H crossdehydrogenative coupling (CDC) ⁵ between a thiophene and a hydrocarbon as the coupling partner. Extensive studies in this vein have been reported, and remarkable successes have been achieved for C(sp²)-H/C(sp²)-H coupling using base metals (Co,^{6a} Cu,^{6b} Mn,^{6c} Ni,^{6d}) and noble metals (Pd, ⁷ Rh,⁸ Ru, ⁹ Au¹⁰) (Scheme 1c). Oxidative $C(sp^{3})$ -H/C(sp²)-H coupling has recently been recognized as a promising and straightforward method for introducing alkyl groups to arenes and olefins.⁵ However the oxidative coupling of thiophenes with either activated or non-activated alkanes has not yet been accomplished. Herein we report the first example of the oxidative alkylation of thiophenes with unactivated alkanes using an 8-aminoquinoline (8-AQ)¹¹ as the directing group. The reaction proceeds selectively via $C(sp^3)$ -H/C(sp²)-H CDC catalysed by a nickel salt¹² (Scheme 1d), which can be used even in cases where thiophenes have been incorporated with a $C(sp^2)$ -X (Cl, Br, I) bond(s). Using this approach, halothiophene products were prepared on a gram scale and subjected to further manipulation via palladium-catalyzed coupling with alkenes and alkynes. The present CDC reaction can be successfully applied to the alkylation of thiazoles and furans as well as to cross-coupling between two heteroarenes.

practical, efficient, and economical approaches. An ideal strategy to

As a model reaction, the cross-coupling between an aliphatic amide **1a** and thiophene (**2a**) was examined (Table S1 in Supporting Information). After optimization of reaction conditions, the oxidative $C(sp^3)$ -H/ $C(sp^2)$ -H coupling took place to give **3a** in 64% yield when the reaction was conducted at 160 °C using Ni(OTf)₂ as the catalyst in the presence of Ag₂CO₃, MesCOOH, TBAB (tetrabutylammonium bromide) and KH₂PO₄.

We found that this catalytic system was suitable for the alkylation of a wide range of thiophenes (Table 1, 3a-3r). In addition, not only was pivalamide tolerated, but also various *N*-quinolin-8-ylamides succumb to the CDC process. It is also noteworthy that chloro-, bromo-, and iodothiophene could

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Reaction conditions: 1 (0.2 mmol), 2 (0.6 mmol), Ni(OTf)₂ (0.04 mmol), MesCOOH (0.08 mmol), KH₂PO₄ (0.4 mmol), Ag₂CO₃ (0.6 mmol), TBAB (0.6 mmol) in DMSO (0.5 mL) at 160 °C for 24 h in a 10 mL screw-capped vial. Isolated yields.

be used in the reaction without dehalogenation (3b-d). In particular, the C-I bond in 2-iodothiophene 3d provided an opportunity for consecutive C-C bond formation by conventional cross-coupling (vide infra). Thiophenes bearing electron-donating groups reacted efficiently to give 3e and 3f. Remarkably, this method was also found to be compatible with ketone and ester groups (3g, 3h), which often require protective groups because these carbonyl functional groups are prone to enolate or carbonyl substitution processes respectively under similar conditions.¹³ However, thiophenes possessing an aminoethyl or cyanomethyl group did not afford the desired products (3i, 3j), likely because of catalyst deactivation as a result of coordination. The scope of thiophenes was not limited to such simple scaffolds, and ring-fused benzobthiophene (3k) and thieno-3,2-b-thiophene (3l) were also found to be suitable substrates. Substituents at the 3-position led to the selective cleavage at the less hindered 5-position to give 3n in good yields. Interestingly 2,3-dibromothiophene participated in the oxidative cross-coupling reaction exclusively at the 5-position, giving **3o** in a good yield without affecting either C-Br bond. Regarding the synthetic application of this method, bis- and tristhiophenes, which often appear in organic semiconductors, were functionalized with the pivalamide, giving 3p and 3q in only one step without the need to prepare heteroaryl halides and/or organometallic reagents. In addition, the 2,5-dibromothiophene didn't gave the C3-position substituted product in our conditions, it could be caused by the different electron density of thiophene.

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N-Quinolin-8-ylpropanamides bearing alkyl, and/or aryl substituents at the α -position also gave the desired products in good yields (**4a–4c**). The reaction shows a high degree of site selectivity, with methyl groups being preferred to methylene groups presumably due to steric effects (**4b**). No evidence to indicate $C(sp^2)$ -H bond functionalization of phenyl was observed in the formation of **4a**, **c**. A quaternary α -carbon is essential for efficient $C(sp^3)$ -H bond functionalization, and unsubstituted propionamide or isobutyramide did not participate in this reaction (**4f**, **4g**).^{126, 12e}

We then attempted to apply the system to the construction of bis(hetero)arene scaffolds (**5a-5f**). As expected, the reactions proceeded exclusively at the *ortho*-position, giving the target products in high yields (**5a, 5b**). Tri- and tetra-(hetero)arenes, which have interesting skeletons for organic materials, were also produced in good yields (**5c-5f**). Furthermore, the present procedure worked perfectly for the site-selective functionalization of thiazoles (**6a–6e**) and furans (**6f, 6g**). However, 1*H*-indole was unreactive and *N*-methylindole did not give the desired products.

This new CDC reaction could be easily carried out on a gram scale for the synthesis of alkyl-substituted 2-iodothiophene **3d** (1.26 g, 58% yield) as illustrated in Scheme 2. Thus, the iodinated product **3d** that was formed could be further functionalized through palladium-catalyzed Sonogashira and Mizoroki-Heck couplings to deliver the desired products (**7**, **8**) in good yields of 74% and 62%, respectively. In addition, the corresponding carboxylic acid is easy to obtain in our previous work, which means the directing group can be easily removed.¹⁴





To better understand the described reactions, several preliminary mechanistic experiments were undertaken. Kinetic isotope effects (KIE) for both coupling partners were studied. At first. an intermolecular competition reaction between benzo[b]thiophene and its deuterated derivative did not give a significant KIE value $(k_{\rm H}/k_{\rm D}$ = 1.1), indicating that the C (sp^2) -H bond cleavage could not be the rate-determining step. Additional competitive experiments indicate a primary KIE of 4.6, suggesting that the $C(sp^3)$ -H cleavage is involved in the rate-determining step (Scheme 3A). The addition of 1 equiv of a radical scavenger, such as TEMPO or 1,4-benzoquinone, BHT, had a negligible effect on the reaction (Scheme 3B), indicating that this CDC reaction does not appear to proceed via radical intermediates. Furthermore, with 2bromothiophene without a silver salt, a C-H/C-H coupling reaction did not occur and, instead, a C-H/C-Br coupling reaction took place.¹⁴ In the presence of a silver salt, the CDC reaction delivered the desired product 9 in 67% yield with the C-Br bond remaining intact (Scheme 3C). These results clearly indicate that the presence of a silver oxidant alters the course of the reaction, probably by oxidizing the nickel intermediates that are produced in the catalytic cycle. In addition, we obtained the x-ray crystal structure of product 9 to confirm that the coupling is indeed at the 2-position (see in SI).

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Although the full details are not currently known, a plausible catalytic cycle is proposed in Figure 1. First, a Ni(II)-amide species **A** is generated from NiX₂ and amide **1a** via C-H bond cleavage. Then, the Ni(III) intermediate **B** was formed through an oxidation by Ag salt. The electrophilic Ni(III) intermediate **B** reacts with thiophene **2a** to generate intermediate **C**. Reductive elimination of intermediate **C** gives the desired product **3a** and Ni(I). Finally, Ni(I) is re-oxidised to Ni(II) to complete the catalytic cycle.



Scheme 3. Mechanistic experiments ($^{\rm a}$ Isolated yields of major products; $^{\rm b}$ Using DMF as solvent).

To shed lights on the details and probability of the reaction pathways, DFT calculations (see SI for details) were carried out. The calculated energies and geometries of stationary points are shown in Scheme 4 (see SI for details). It was found that anion exchange between Ni(OTf)₂ and KH₂PO₄ is highly exergonic by 29.2 kcal/mol, suggesting the formation of $Ni(H_2PO_4)_2$ is likely and predominant in the system (Scheme 4a). Complexation of **1a** with NiX_2 (X = H_2PO_4) forms IN1 favourably, which undergoes N-H deprotonation via TS1 to generate intermediate IN2. Then $C(sp^3)$ -H bond scission at the β position proceeds by a concerted metalation deprotonation (CMD) mechanism via transition state TS2, which has much higher energy than TS1 and gives rise IN3 endergonically. Consequently, the C(sp³)-H bond cleavage requires an activation barrier of 21.4 kcal/mol as indicated by the energy gap between IN1 and TS2. Interestingly this is much lower than the activation energy of 34.5 kcal/mol that was calculated with X = OTf (see SI). This is in good agreement with the experimental fact that the addition of KH₂PO₄ is essential to achieve high yields.^[15] A possible metalation mechanism via $C(sp^2)$ -H cleavage of thiophene with NiX₂ was also considered (Scheme 4c). Because the activation energy of this process via TS1' (22.1 kcal/mol) is almost the same as the barrier of $C(sp^3)$ -H bond scission via **TS2** (21.4 kcal/mol) and because stabilizing energy of complexation of NiX $_2$ with $\mathbf{1a}$ to form IN1 is very large, metalation of thiophenes by NiX₂ seems unlikely. Metalation of thiophenes with Ni(III) complex IN4 generated by oxidation of a Ni(II) complex IN3 by Ag(I) gives IN5 via TS3, which then undergoes reductive elimination via TS4 to form arylated intermediate IN6, leading to the product. The energy barriers of

these two processes are almost the same (22.8 and 23.3 kcal/mol respectively) and are similar to the barrier of the $C(sp^3)$ -H bond scission (21.6 kcal/mol). When the ligand was changed from H₂PO₄ to OTf, the energies of transition states **TS3** and **TS4** again increased to 30.5 and 34.9 kcal/mol, respectively (see SI). It is noted that the incorporation of another KH₂PO₄ molecule in **IN4** slightly reduced the activation energy of the C(*sp*²)-H activation/reductive elimination process to 20.4 and 20.9 kcal/mol, respectively (see SI). These calculations are in accord with the proposed catalytic cycle and suggest that phosphate anion plays important roles in the processes for C-H bond breaking.





a) generaion of active catalytic species Ni(OTf)₂ + 2KH₂PO₄ <u>→</u>G=-29.2 kcal/mol Ni(H₂PO₄)₂ + 2KOTf b) C(sp³)H cleavage by Ni(II) species



c) C(sp²) -H cleavage by Ni(II) species







Scheme 4. Computational Results (relative free energies are in kcal/mol)

Conclusions

In summary, we report the efficient Ni-catalysed oxidative $C(sp^3)$ -H/C(sp^2)-H cross-coupling of thiophenes with alkylamides bearing an 8-aminoquinoline unit as a directing group. This reaction provides a general and efficient protocol for the construction of C(alkyl)-C(*heteroaryl*) bonds using readily available alkylamides. DFT calculations suggest that KH₂PO₄ represents an important additive in each step of this reaction, and supports the involvement of a Ni(III) species for efficient C(sp^2)-H cleavage and C-C coupling. The

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protocol is also applicable to oxidative $C(sp^2)$ -H/C(sp^2)-H crosscoupling reactions as well as to the alkylation of other heteroarenes, including thiazoles and furanes.

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