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# Microwave assisted cobalt(III)-catalysed C–H aminocarbonylation reactions with isocyanates for the synthesis of thiophenecarboxamides†

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A mild and efficient cobalt(III)-catalysed C–H aminocarbonylation procedure for thiophenes and benzo[*b*]thiophenes under MW assisted conditions has been developed. Site selectivity is controlled by the use of pyridine and pyrimidine directing groups. The reaction is effective with aromatic isocyanates with wide substitution patterns, although aliphatic isocyanates showed less reactivity. The introduced amide group can act as directing group in further iterative C–H functionalization reactions, allowing the diversification of the heterocyclic structures. DFT calculations have shed light on the mechanistic course and reactivity patterns.

## Introduction

Amides are ubiquitous structural motifs in natural occurring molecules, pharmaceuticals, agrochemicals[1] and polymers or materials.[2] In addition, carboxamides play a crucial role in organic synthesis as versatile building blocks[3] or directing groups for aromatic metalation[4] or transition-metal catalysed C–H functionalization reactions.[5] Although many efficient methodologies have been developed for amide synthesis,[6] one of their main drawbacks is their low atom-economy. In fact, catalytic amide bond formation[7] has been identified by the ACS Green Chemistry Institute Pharmaceutical Roundtable (ACS GCIPR) as a key initiative for green chemistry.[8] In this context, transition metal-catalysed C–H activation[9] has become an essential synthetic tool to install amide motifs in arenes and heteroarenes, reducing the number of steps and waste generation, as there is no need to use prefunctionalized substrates. The regioselectivity can be controlled by using directing groups and/or ligands or even the substrate and the method presents a high degree of functional group compatibility.[10] Thus, efficient protocols for ruthenium-,[11] rhodium- or rhenium- catalysed[12] C($sp^2$)–H aminocarbonylation reactions with isocyanates have been reported (Scheme 1A), using different directing groups to control the regioselectivity. In the case of palladium catalysis, two different approaches have been developed. On one hand, the decarboxylative *ortho*-aminocarbonylation of heteroaromatic carboxylic acids with isothiocyanates has been described, where the carboxyl acts as a traceless directing group. On the other hand, the aminocarbonylation of aryl and heteroaryl C($sp^2$)–H bonds has been achieved using CO and nitroarenes as the nitrogen source.[13]

Over the past years, cobalt has emerged as one of the most promising earth-abundant first-row metals to replace these classical transition-metals.[14] A significant breakthrough in this chemistry has been the development of air-stable high-valent Cp*Co(III) catalysts[15] for catalytic generation of nucleophilic Co(III) organometallic species in directed C–H bond functionalization reactions, mainly through electrophilic base-assisted mechanisms, such as CMD.[16] Nevertheless, only a few reports have appeared to date describing the Co(III)-catalysed C($sp^2$)–H aminocarbonylation for the synthesis of aromatic carboxamides and their application to heteroarenes (*e.g.* thiophene and benzothiophene) has been far less investigated. In 2015 Ellman[17] and Ackermann[18] independently reported the first Cp*Co(III)-catalysed C–H aminocarbonylation reactions with isocyanates as electrophiles and pyrazole as the directing group, though mainly for the synthesis of benzamides (Scheme 1B). Although Ackermann demonstrated that the isocyanate electrophiles can be generated *in situ* from the corresponding *N*-acylazides,[18] the use of *N*-acylazides can also lead to amidation reactions under similar reaction conditions, as reported by Punniyamurthy and col.[19] for the Cp*Co(III)-catalysed C–H activation of indoles with a 2-pyrimidine directing

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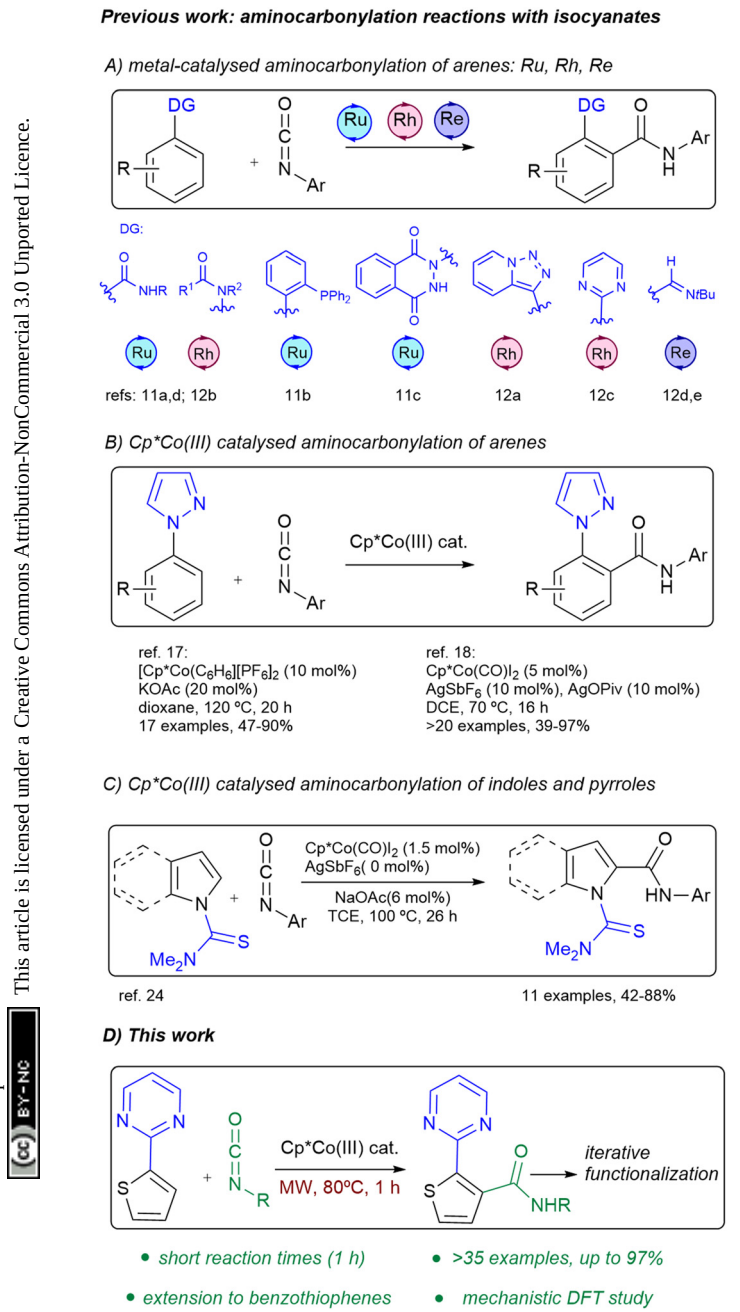
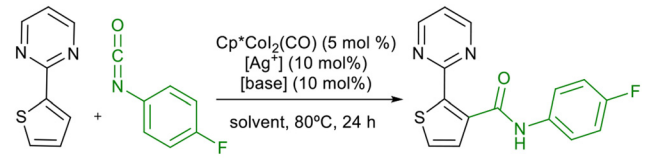
† Electronic supplementary information (ESI) available: Synthesis and characterization data for compounds **1–10**. Deuterium incorporation experiment on **1a**. Computational data. Copies of $^1$H and $^{13}$C NMR (and $^{19}$F NMR) spectra of amides **3**, **5**, **7–10**. CCDC 2463953. For ESI and crystallographic data in CIF or other electronic format see DOI: **https://doi.org/10.1039/d5ob00781j**




**Scheme 1** Metal-catalysed C–H aminocarbonylation reactions with isocyanates.

group. Related amidation reactions have been reported under Co(III) catalysis using other electrophiles (*N*-chloroacetamides,[20] dioxazolones[19,21] or α-benzoylketene dithioacetals[22]) avoiding Curtius rearrangement. Recently, Ellman[23] extended the procedure to cascade reactions between 1,3-dienes and isocyanates for synthesis of α-quaternary amides. Regarding the introduction of amides into heteroarenes, Maji[24] developed a thiocarbamate-directed Cp*Co(III)-catalysed aminocarbonylation /cascade annulation of pyrroles and indoles with isocyanates that provide access diverse pyrro-

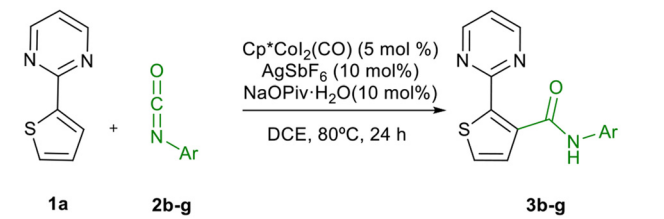
**Table 1** Aminocarbonylation of **1a** with 4-flourophenylisocyanate (**2a**)

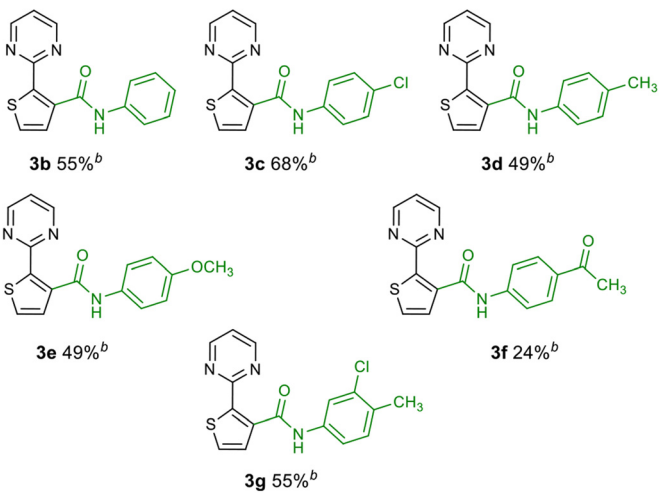



| Entry | Solvent[a] | [$Ag^+$] | [Base] | **3a**[b] (%) |
|---|---|---|---|---|
| 1 | DCE | $AgSbF_6$ | AgOAc | 27[c,d] |
| 2 | DCE | $AgSbF_6$ | AgOAc | 78[c] |
| 3 | DCE | $AgSbF_6$ | CsOAc | 84[c] |
| 4 | DCE | $AgSbF_6$ | RbOAc | 84[c] |
| 5 | DCE | $AgSbF_6$ | AgTFA | 55[c] |
| 6 | DCE | $AgSbF_6$ | CsOPiv | 57[c] |
| 7 | DCE | $AgSbF_6$ | NaOPiv·$H_2O$ | 91 |
| 8 | DCE | $AgNTf_2$ | NaOPiv·$H_2O$ | 85[c] |
| 9 | DCE | $AgPF_6$ | NaOPiv·$H_2O$ | 65[c] |
| 10 | DCE | $AgBF_4$ | NaOPiv·$H_2O$ | —[c] |
| 11 | Toluene | $AgSbF_6$ | NaOPiv·$H_2O$ | 82[c] |
| 12 | $PhCF_3$ | $AgSbF_6$ | NaOPiv·$H_2O$ | 81[c] |
| 13 | DCE | $AgSbF_6$ | — | 40 |
| 14 | DCE | — | NaOPiv·$H_2O$ | nr |
| 15[e] | DCE | $AgSbF_6$ | NaOPiv·$H_2O$ | nr |

[a] The reactions were carried out with **1a** (0.5 mmol), $Cp^*CoI_2(CO)_2$ (0.025 mmol), [$Ag^+$] (0.05 mmol), [base] (0.05 mmol) and **2a** (1 mmol) in 20 mL sealed reaction tubes inserted in a heating block. The temperature refers to the external temperature of the heating block. [b] Yield (%) of isolated pure compound. [c] Unreacted **1a** was recovered. [d] 70 °C, 16 h. [e] No $Cp^*Co(CO)I_2$ was added.

**Table 2** Aminocarbonylation of **1a** with arylisocyanates **2**[a]



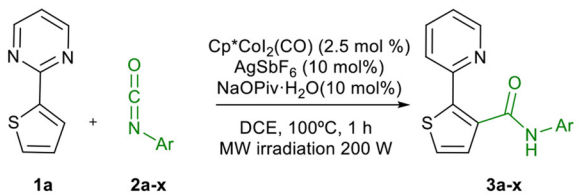




[a] Yield (%) of pure isolated product. Reactions were done in a 0.5 mmol scale for **1a** using 20 mL sealed reaction tubes inserted in a heating block. The temperature refers to the external temperature of the heating block. [b] Unreacted **1a** was recovered.

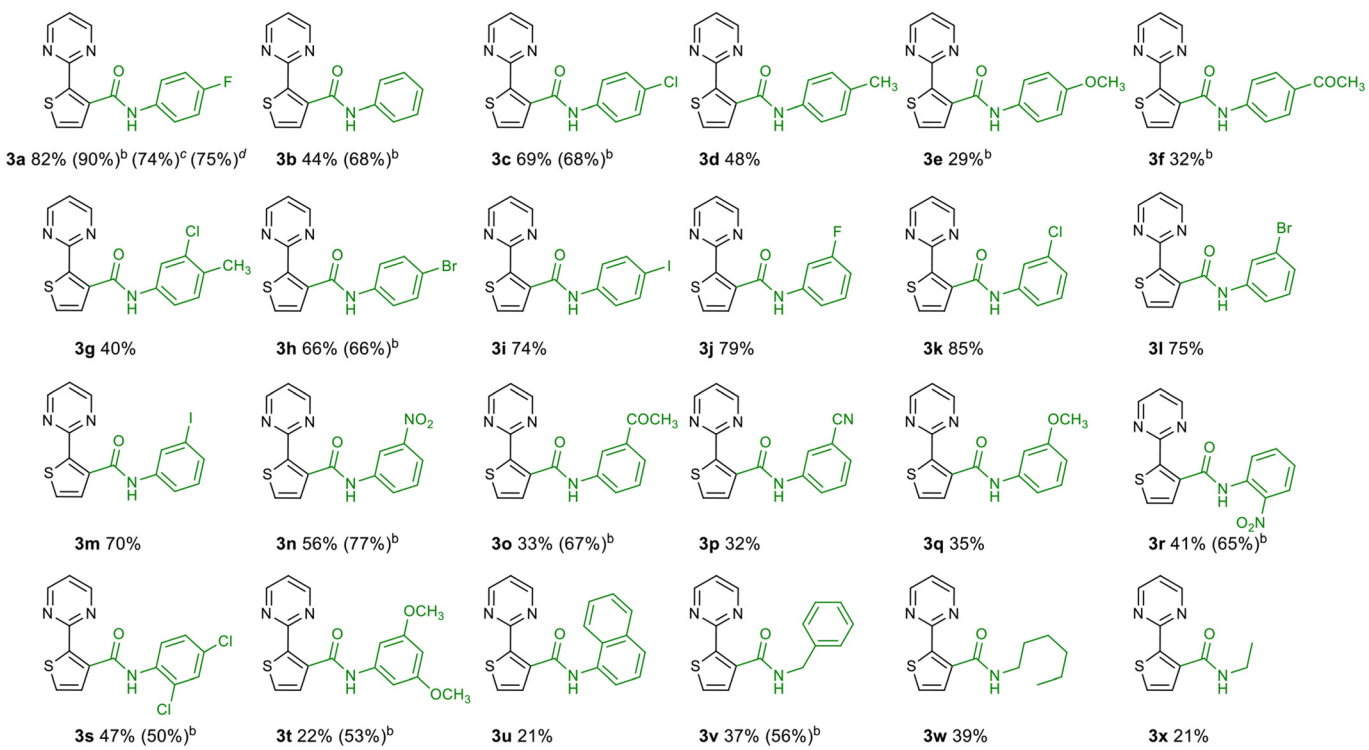
lecarboxamides (Scheme 1C). On the other hand, the aminocarbonylation of indoles can also be achieved with amines and CO using low-valent cobalt catalysis.[25]

Considering the potential and the limitations of amide functional group insertion into (hetero)arenes, we became interested in the Co(III)-catalysed C–H aminocarbonylation reaction for the synthesis of thiophene- and benzo[*b*]thiophenecarboxamides. The synthesis of *N*-arylthiophen-3-carboxamides has attracted the interest of synthetic chemists as they have been identified as human dihydroorotate dehydrogenase (DHODH) inhibitors involved in the treatment of autoimmune diseases (rheumatoid arthritis and multiple sclerosis) and cancer therapy.[26] The thiophene- and benzo[*b*]thiophene-2-carboxamide motifs are also essential to overcome cancer chemoresistance.[27] Additionally, these derivatives can be used as agrochemical fungicides.[28] Structural variations may cause important differences in the mechanism of action of this type of drugs. For example, the introduction of heteroaryl motifs on the thiophene would give heterobiaryl scaffolds as pyridyl- or pyrimidinyl-thiophenecarboxamides with applications both in medicinal chemistry[29] and material science.[30] This type of biheteroarylcarboxamides have been previously synthetized *via* palladium-catalysed C-3 arylation reactions of thiophene-2-carboxamides, though a limited number of aromatic substituents (phenyl, 2-methylthiophenyl and quinol-8-yl) have been tested at the amide nitrogen atom.[31] The palladium-catalysed C-2 arylation reaction of thiophene-3-carboxamides[32] has also allowed the introduction of a pyridyl group, though the procedure required the use of a perfluorotoluimide as directing group. In the context of our interest in Cp*Co(III) catalysed C–H functionalization reactions,[33] herein we report a microwave-assisted cobalt(III)-catalysed C–H aminocarbonylation of thiophenes and benzo[*b*]thiophenes with isocyanates using pyridine or pyrimidine as directing groups to control site selecti-

**Table 3** Microwave assisted aminocarbonylation of **1a** with arylisocyanates **2** [a]




**1a** **2a-x** **3a-x**



**3a** 82% (90%)[b] (74%)[c] (75%)[d] **3b** 44% (68%)[b] **3c** 69% (68%)[b] **3d** 48% **3e** 29%[b] **3f** 32%[b]

**3g** 40% **3h** 66% (66%)[b] **3i** 74% **3j** 79% **3k** 85% **3l** 75%

**3m** 70% **3n** 56% (77%)[b] **3o** 33% (67%)[b] **3p** 32% **3q** 35% **3r** 41% (65%)[b]

**3s** 47% (50%)[b] **3t** 22% (53%)[b] **3u** 21% **3v** 37% (56%)[b] **3w** 39% **3x** 21%

[a] Yield (%) of pure isolated product. Reactions were done in a 0.5 mmol scale using 10 mL sealed reaction tubes. The indicated temperature, obtained using a maximum power of 200 W, refers to the internal reaction temperature measured by an infrared sensor. [b] 5 mol% of catalyst was used. [c] Reaction done in 1 mmol scale. [d] Reaction done in 2 mmol scale.

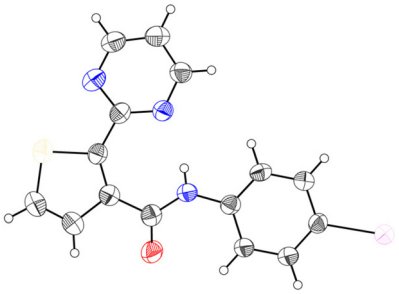


Fig. 1 ORTEP plot of compound **3i** with thermal ellipsoids at the 50% probability level (CCDC 2463953†).

vity (Scheme 1D). The use of MW irradiation significantly shortens the reaction times compared to standard thermal conditions. The introduced *N*-arylamide group can act as directing group in further iterative C–H functionalization reactions, allowing the diversification of the heterocyclic structures. Besides, DFT studies have shed light on the reaction mechanism.

## Results and discussion

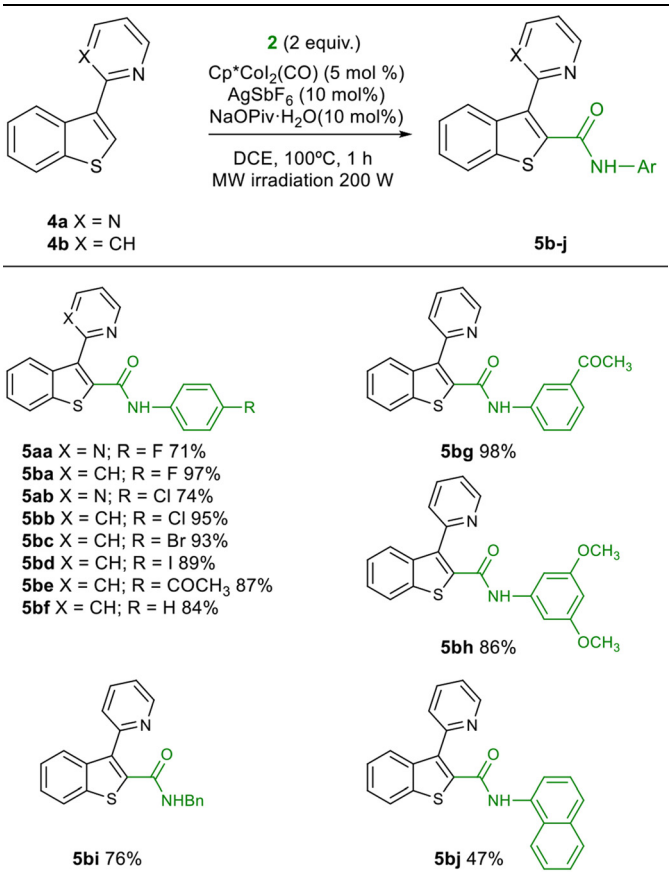
We started studying the reaction of thiophene **1a** and 4-fluorophenyl isocyanate **2a** as a model, using Cp*$CoI_2$(CO) as catalyst in DCE at 70 °C, based on the reaction conditions described by Ackerman as starting point.[18] Under these reaction conditions, the amide **3a** was obtained in low yield, recovering unreacted starting material (Table 1, entry 1.). When the temperature was increased to 80 °C and the reaction time was extended to 24 h, the yield increased to 78% (Table 1, entry 2). Next, different bases were tested. When CsOAc and RbOAc were used, amide **3a** was obtained in 84% yield (Table 1, entries 3 and 4). The yield dropped when AgTFA or CsOPiv where used, recovering unreacted **1a** (Table 1, entries 5 and 6). Full conversion was observed with sodium pivalate, obtaining **3a** in a 91% yield (Table 1, entry 7). The use of other silver salts, such as $AgNTf_2$ or $AgPF_6$ did not improve the yield (Table 1, entries 8 and 9), and the reaction did not proceed in presence of silver tetrafluoroborate (Table 1, entry 10). Regarding solvents, the use toluene and trifluorotoluene gave lower yields (Table 1, entries 11 and 12 *vs.* entry 7).

With the optimized reaction conditions in hand, we checked that the carboxylate base has a positive effect on reactivity (Table 1, entry 13), and that the cobalt complex and the silver salt are essential for the C–H activation process (Table 1, entries 14 and 15). Once the optimal reaction conditions were selected, the reaction was extended to aromatic isocyanates **2b–g** (Table 2). However, in all cases, lower reactivity was observed for these isocyanates, regardless of the electronic nature of the substituents. The amides **3b–g** were obtained in modest yields, recovering unreacted **1a** in all cases. At this point, we thought that this would be a suitable scenario to study the effect of MW irradiation on these reactions. The acceleration effect of MW on transition metal-catalysed cross-coupling reactions is well known,[34] although the application of MW in C–H activation reactions is still less extended.[35] In this context, our group reported recently the microwave-assisted palladium(II)-catalysed C-3 acylation of thiophenes with aldehydes *via* C($sp^2$)–H activation.[36] Recent examples with Rh(III) catalysts have also been described,[37] but this technique has been scarcely applied in Co(III) catalysis.[38]

After a brief optimisation of the catalyst loading and time, (see Table S1 in ESI†), amide **3a** could be obtained in a 90% yield at 100° C in a sealed reaction tube under MW irradiation with a maximum power of 200 W after only 1 hour (Table 3).

The catalyst loading could be reduced from 5 mol% to 2.5 mol% without a big erosion of the yield (82%). At this point we also checked the use of pyridine as directing group, instead of pyrimidine. 2-(Thiophen-2-yl)pyridine was used as substrate under these reaction conditions, obtaining a significantly lower yield of the corresponding amide (50%, see Scheme S1 in ESI†). The presence of a directing group is also fundamental to obtain the observed reactivity and regioselectivity. In fact, when 2-methyl- and 2-phenylthiophene

Table 4 C-2 Aminocarbonylation of benzothiophenes **4** [a]



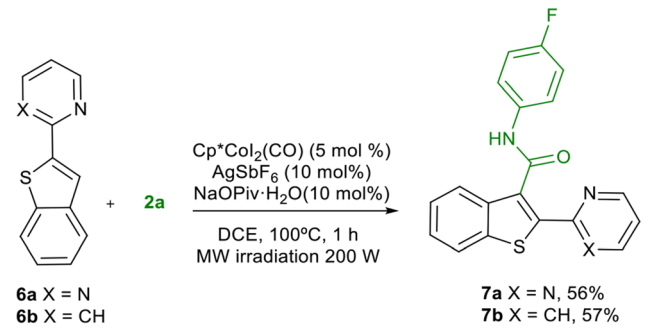

[a] Yield (%) of pure isolated product. Reactions were done in a 0.5 mmol scale using 10 mL sealed reaction tubes. The indicated temperature, obtained using a maximum power of 200 W, refers to the internal reaction temperature measured by an infrared sensor.

were tested as substrates, no reaction was observed with **2a** under the optimized conditions (see Scheme S2 in ESI†). Considering these results, **1a** was used as substrate, and the reaction was extended to a variety of aromatic isocyanates **2b–2u**. The reaction works with both electron deficient and electron rich isocyanates, although electron deficient isocyanates were more reactive (for example, **3a** *vs.* **3d** or **3e**), as has been reported previously,[18,24] although both **3e** and **3f** were obtained in low yield using 5 mol% of the catalyst. The *meta*-substituted isocyanates gave in general good results (**3j–3q**). The reaction is also compatible with *ortho*-substituted (**3r**, **3s**) and disubstituted isocyanates (**3g**, **3s**, **3t**). Alkyl isocyanates were also reactive, leading to the corresponding amides **3v–3x** in moderate yield. In some cases, the yields could be improved using 5 mol% of the catalyst. The reaction could also be scaled up to 1 and 2 mmol (Table 3, **3a**) with consistent yields.

The structure of the amides was unambiguously confirmed by X-ray analysis of one of the derivatives (**3i**, Fig. 1).[39]

We next extended the reaction for the C-2 aminocarbonylation of benzothiophenes (Table 4). Pyrimidine and pyridine were incorporated as directing groups at C-3 of benzothiophene (**4a**,**b**). Pyrimidine resulted an efficient directing group in the reaction of **4a** with isocyanates **2a**,**b**, obtaining **5aa** and **5ab** in good yields under the optimised conditions. However, in this case pyridine was a more efficient directing group, obtaining **5ba** and **5bb** in almost quantitative yields (Table 4). The reaction was then extended to a variety of isocyanates obtaining the corresponding benzo[*b*]thiophene-2-carboxamides **5bc** to **5bj** in generally high yields. The aminocarbonylation in C-3 of the benzothiophene ring was also feasible, introducing the directing group in C-2 (Scheme 2). Under the optimised reaction conditions, both pyrimidine and pyridine behaved as efficient directing groups, leading to moderate yields of amides **7a** and **7b**.

With the experimental results in hand, we decided to carry out DTF studies to elucidate the mechanism operating in the reaction. All structures were optimized using density functional theory (DFT) as implemented in Gaussian 16,[40] with B3LYP[41] as functional, 6-31G(d,p) as basis set for non-metallic atoms, and LANL2DZ[42] as basis set for cobalt. Final energies were obtained performing single-point calculations on the previously optimized structures at M06[43]/6-311++G(d,p) level of




**Scheme 2** C-3 aminocarbonylation of benzothiophenes **6**.

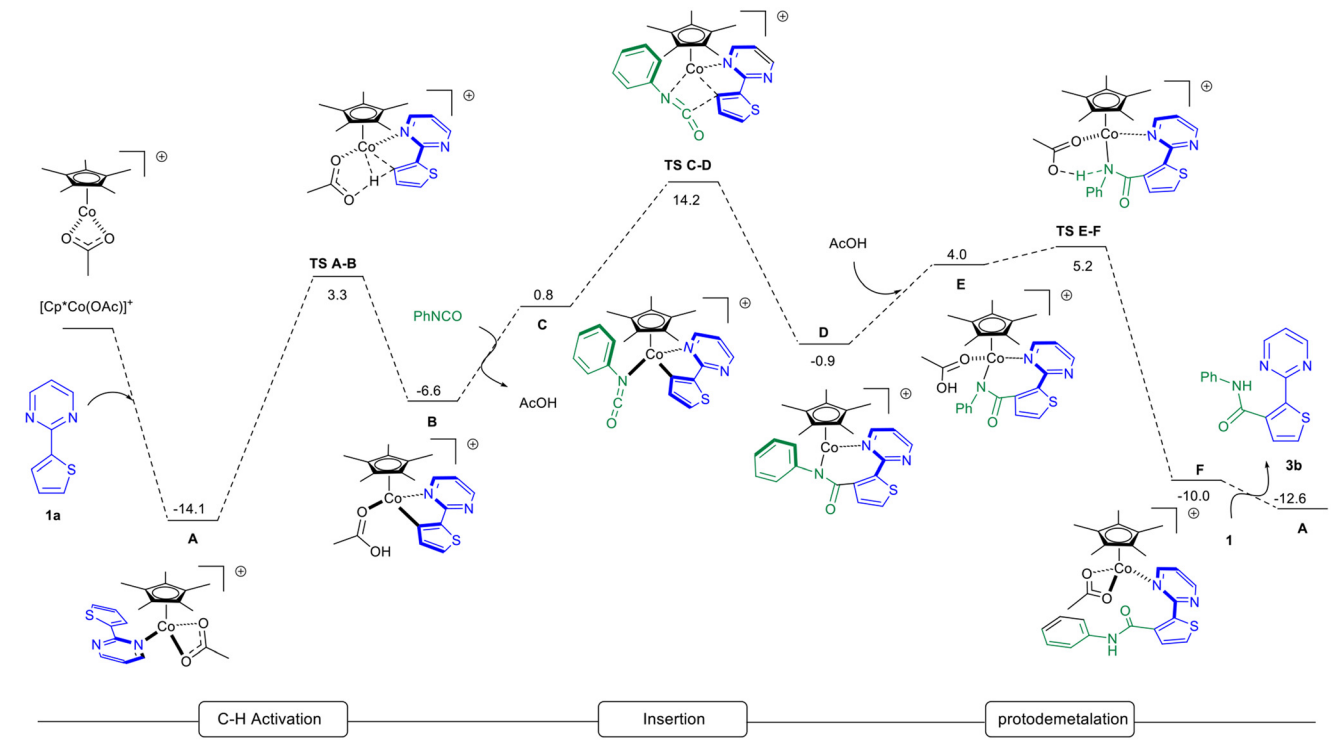
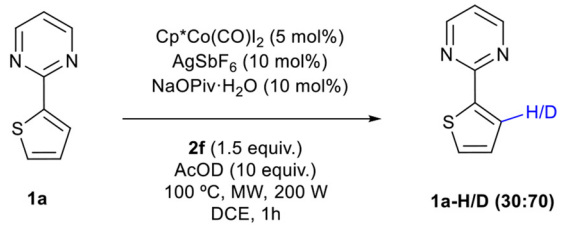


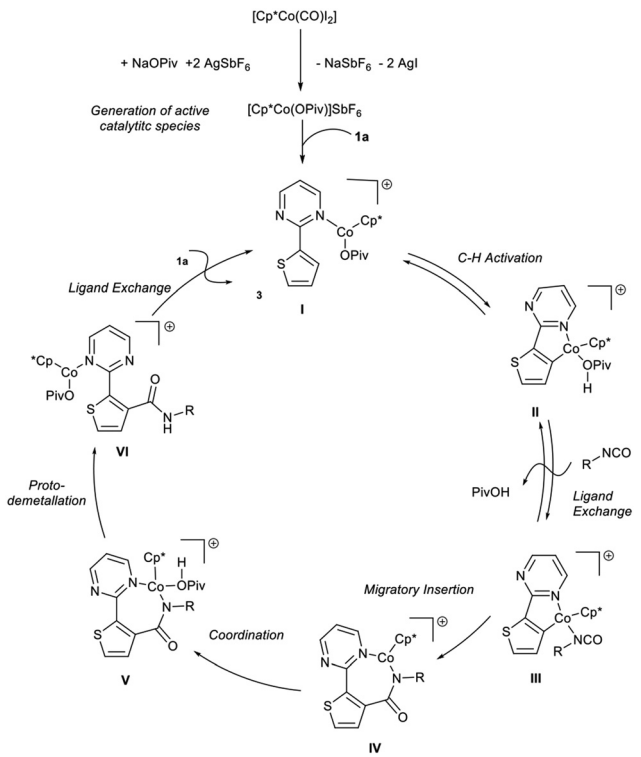

**Fig. 2** Free energy profile of $[Cp^*CoOAc]^+$ catalysed C–H aminocarbonylation of **1a** with **2b** characterised at M06/6-311++G(d,p) level of theory (energy values expressed in kcal $mol^{-1}$).

theory for non-metallic atoms and SDD basis set for cobalt,[44] introducing solvation factors with the IEF-PCM[45] method, and 1,2-dichloroethane as solvent. The stationary points were characterized by frequency calculations in order to verify that they have the right number of imaginary frequencies.

For the mechanistic calculations (Fig. 2), we used the cationic complex $[Cp^*Co(OAc)]^+$ as starting point, which has been previously proposed as the catalytic active species.[46,33b] Coordination of this species with a molecule of substrate **1a** comes with a stabilizing effect of −14.1 kcal mol$^{-1}$ to give intermediate **A**, which can undergo a non-rate-determining and reversible C–H activation step ($\Delta G^{\ddagger}$ = 17.4 kcal mol$^{-1}$), rendering **B**. To confirm the reversible character of the C–H activation step, deuteration experiments were carried out, observing a 70% deuterium incorporation when the substrate was subjected to the reaction conditions in the presence of 4-acetylphenyl isocyanate **2f** and 10 equivalents of AcOD (Scheme 3).



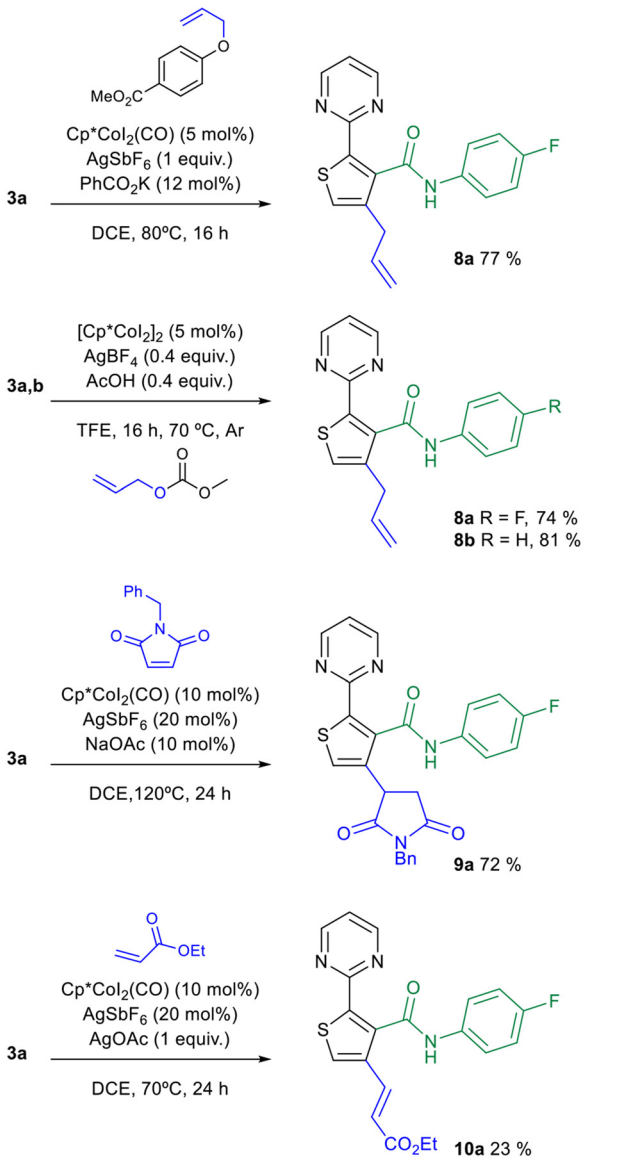

**Scheme 3** Deuterium incorporation in **1a**.




**Scheme 4** Proposed catalytic cycle.

These results are in agreement with related examples.[18,24] After this C–H activation process, ligand exchange occurs, releasing a molecule of acetic acid and incorporating phenyl isocyanate **2b** coupling partner to generate complex **C**, which undergoes a rate-determining migratory insertion to the N=C bond with an activation energy of 13.4 kcal mol$^{-1}$, forming intermediate **D**. After coordination of acetic acid to give **E**, a fast and irreversible proto-demetalation process ($\Delta G^{\ddagger}$ = 1.2 kcal mol$^{-1}$) takes place giving complex **F**. At this point, the desired product **3b** is released through a ligand exchange that also regenerates initial complex **A**.

With these computational results in hand, the catalytic cycle depicted in Scheme 4 can be proposed for the aminocarbonylation of thiophenes. First of all, $[Cp^*Co(CO)I_2]$ would undergo ligand exchange with NaOPiv and $AgSbF_6$, present in the reaction media, to form active catalytic species $[Cp^*Co(OPiv)]^+$. This




**Scheme 5** Iterative C–H functionalizations.

species would then coordinate a molecule of substrate **1a**. Generated complex **I** is then proposed to undergo C–H activation, rendering **II**, which forms **III** after release of pivalic acid and coordination of the corresponding isocyanate coupling partner. Afterwards, migratory insertion to the C=N double bond would occur, leading to intermediate **IV**. This complex can coordinate a molecule of pivalic acid to form **V**, which undergoes proto-demetalation. The corresponding amidated product **3** would be released from species **VI** after coordination of another molecule of **1a**, regenerating initial complex **I**.

Finally, we decided to study the use of the introduced *N*-arylamide group as directing group for further iterative Cp*Co(III) catalysed C–H functionalization reactions, allowing the diversification of the heterocyclic structures. To showcase this possibility, we selected reported allylation, alkylation and alkenylation reactions, using amides **3a**,**b** as substrates (Scheme 5). The *N*-arylamide group behaved indeed as an efficient directing group for allylation reactions. Using an allyl benzoate as allylating agent under the reaction conditions described by our group,[33b] or ally carbonate under the conditions described by Glorious,[47] the 4-allylated thiophenes were obtained in good yields, significantly higher than the yields obtained for the allylation of thiophenes using *N*-methyl[33b] or *N*,*N*-dimethyl amides[47] as directing groups. C-4 alkylation with *N*-benzylmaleimide was also possible in high yield, using the conditions previously described.[48] Finally, alkenylation with ethyl acrylate was also possible under Matsunaga conditions,[49] although in lower yield.

## Conclusions

In conclusion, the cobalt(III)-catalysed C–H aminocarbonylation of thiophenes and benzo[*b*]thiophenes takes place efficiently using pyridine or pyrimidine as directing groups to control site selectivity. The use of MW irradiation significantly shortens the reaction time to 1 h, obtaining generally high yields of the amides. The reaction is effective with aromatic isocyanates with a wide substitution pattern, although aliphatic isocyanates showed less reactivity. DFT mechanistic studies have shown that the reaction proceeds *via* a non-rate-determining and reversible C–H activation step, followed by coordination with the isocyanate, rate-determining migratory insertion to the N=C bond and fast protodemetalation. The introduced *N*-arylamide group can act as directing group in further iterative C–H functionalization reactions, allowing the diversification of the heterocyclic structures.

## Author contributions

A. Carral-Menoyo, N. Sotomayor and E. Lete conceptualized and supervised the project. N. Sotomayor and E. Lete wrote the original draft, reviewed, and edited the manuscript. B. Taboada-Seras and C. Santiago did the major chemical experimental part and wrote the first experimental draft of ESI.† E. Sustatxa participated in the chemical experimental work. A. Carral-Menoyo was responsible for the computational study. N. Sotomayor and E. Lete were responsible for funding acquisition. All authors have read and agreed to the published version of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

The data supporting this article have been included as part of the ESI.†

## Acknowledgements

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