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Directed C–H Allylation of Aromatic Carboxamides with Allyl Aryl Ethers under Cp*Co(III)-Catalysis

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The Cp*Co(III) C–H allylation of (hetero)arenes with allyl aryl ethers has been developed using an amide as directing group (24 examples). DFT calculations have shed light on the mechanistic course and reactivity pattern, showing that strong electron releasing groups favour the reaction by reducing the activation barrier of the rate-determining C–H activation step. However, the steric strain can increase the energy of the migratory insertion step to the point of completely preventing the reaction, as in the case of the 3,5-dimethylbenzamide. The obtained allylated compounds have been transformed into a variety of interesting heterocyclic and carbocyclic structures, such as isoquinolones and isochromanones.

Introduction

Allyl arenes, common motifs in natural products and bioactive compounds,[1] have attracted much attention due to their importance in the flavor and fragrance industry.[2] In addition, the allyl moiety is a versatile functional group that offers an excellent platform for obtaining valuable complex molecules.[3]

Friedel-Crafts[4] and cross-coupling[5] reactions are classical approaches for the synthesis of allyl arenes, though these methods may have significant drawbacks, such as regioselectivity problems or the need to use prefunctionalized coupling partners. The transition-metal catalyzed C(sp^2) –H allylation reaction of aromatic substrates offers an attractive and challenging route to allylated arenes in terms of atom/step-economy, functional group compatibility, and control of regioselectivity (directing groups and/or ligands).[6] Therefore, numerous examples of the aromatic and olefinic C–H allylation using second and third row transition metals (Pd, Rh, Ru and Ir) as catalysts, have been reported.[7] After the publication of Matsunaga and Kanai's pillar work,[8] the use of high-valent Cp*Co(III)[9] has started to gain center stage as earth-abundant and less toxic metal catalysts for C–H activation of arenes.[10] The reduced electronegativity of cobalt as compared to rhodium or palladium results in more nucleophilic organometallic cobalt complexes, allowing new reactivities and improved selectivities. In this context, Glorius[11] and Ackermann[12] independently reported the Cp*Co(III)-catalyzed C–H allylation of indoles, pyrroles, and benzene derivatives with allyl carbonates or acetates using different directing groups (pyrimidine, pyridine and amides). Since those seminal works, allyl acetate[13] and carbonates,[14] including cyclic carbonates,[15] have been many times the coupling partners of choice for the achievement of Cp*Co(III)-promoted C–H allylation of different aromatic scaffolds using various directing groups (Scheme 1).

Matsunaga and Kanai demonstrated that unactivated allyl alcohols can also be used in the allylation reaction of *N*-(pyrimidin-2-yl)-1*H*-indoles.[16] Later, the scope was expanded to allylation of benzamides and 6-arylpurines,[17] as well as indole- and pyrrolecarbothioamides.[18] Related examples of allylation of arenes with tertiary allyl amines[19] and with fluorinated alkenes[20] have been also described. In these cases, the mechanism would proceed *via* C–H metalation, alkene insertion, and β-heteroatom-elimination, which would be detrimental to the atom economy of the reactions. The use of vinylcyclopropanes,[21] or even just cyclopropenes[22] as allylating agents overcomes this limitation by exploiting the ring-opening of strained cycle strategy. In a similar strategy, vinyloxyranes[23] and vinylazidirines[24] were utilized to access the corresponding allylic alcohols or amines (Scheme 1). On the other hand, unactivated alkenes can also be employed for C–H allylation of aromatics in Co(III)-catalyzed oxidative Heck-type reactions.[25]

However, allyl phenyl ethers have not yet been reported to act as coupling partners in these kind of transformations promoted by high-valent-cobalt complexes, despite they have been previously employed in the ruthenium- and iron-catalyzed C–H allylation of arenes.[26] Therefore, within our program on

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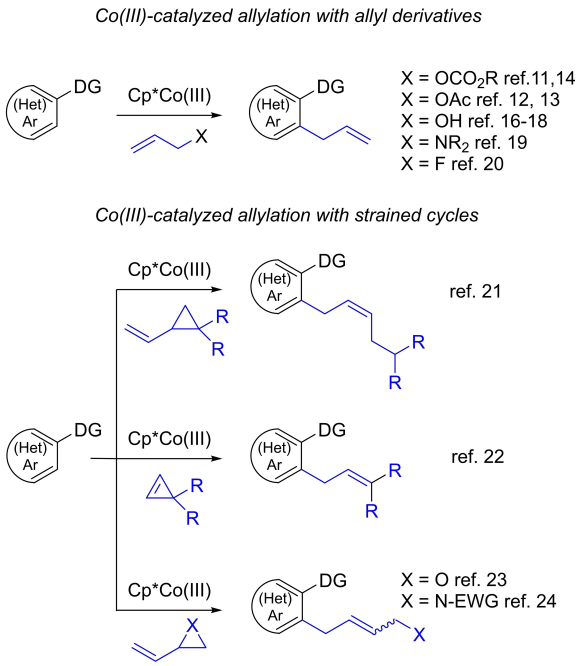
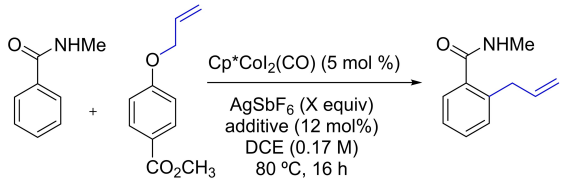


Scheme 1. Cp*Co(III)-catalyzed C–H allylation reactions.

transition-metal catalyzed C–H activation reactions,[27] we have now developed the first direct C–H allylation of (hetero)arenes **1**, using an amide as directing group, with allyl aryl ethers **2**, using earth-abundant cobalt catalysis (Scheme 2). Furthermore, a density functional theory (DFT) study has been carried out to shed light on the mechanistic course and reactivity pattern of this Co(III)-catalyzed C–H allylation reaction.

Table 1. Optimization of reaction conditions.



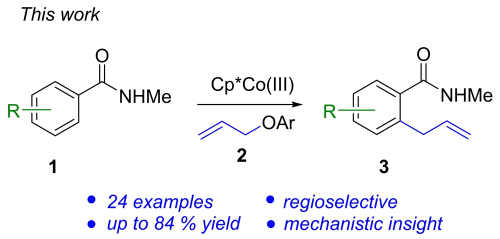
1a **2a** (1.5 equiv) **3a**

entry	$AgSbF_6$ (equiv)	additive	**3a**(%)[a]
1	0.12	KOAc	23
2	0.5	KOAc	55
3	1	KOAc	66
4	1.5	KOAc	40
5[b]	1	KOAc	43
6[c]	1	KOAc	60
7[d]	1	KOAc	66
8[e]	1	KOAc	60
9	1	–	nr
10	1	NaOAc	39
11	1	CsOAc	60
12	1	$Cu(OAc)_2$	48
13	1	CsOPiv	25
14	1	$(1\text{-Ad})CO_2K$	51
15	1	$PhCO_2K$	68
16[f]	1	$PhCO_2K$	46

[a] Yield (%) of isolated pure compound. Reactions were carried out in a 0.2 to 0.3 mmol scale in a 20 mL sealed vial. [b] The reaction temperature was 60 °C. [c] 1 equiv. of **2a** was used. [d] 2 equiv. of **2a** were used. [e] 2.5 equiv. of **2a** were used. [f] 0.5 equiv. of $PhCO_2K$ were used. nr: no reaction; starting material recovered.

Results and Discussion

We commenced the study using *N*-methyl benzamide **1a** as a substrate, and we selected methyl 4-(allyoxy)benzoate (**2a**, 1.5 equivalents) as allylating agent. The reaction conditions were related to those used in the Cp*Co(III) intramolecular hydroarylation of alkenes recently reported by our group,[28] using $AgSbF_6$ (12 mol%) as the silver source and KOAc (12 mol%) as the base additive in DCE at 80 °C. Under these conditions, the allylation reaction took place, but with a low conversion obtaining **3a** in a 23% yield (Table 1, entry 1). We then tested the effect of an increasing amount of the silver salt ($AgSbF_6$), obtaining the best result when 1 equivalent was used (Table 1, entries 2, 3), while a larger quantity proved to be detrimental (Table 1, entry 4).



Scheme 2. Cp*Co(III)-catalyzed arylation with allyl aryl ethers.

Other silver sources were also tested, but were less efficient (see Supporting Information, Table S1 for additional experiments). Lowering the reaction temperature (Table 1, entry 5) led to lower conversion, recovering unreacted **1a**. The use of fluorinated solvents, such as TFE or HFIP, that had given the best results in related allylation reactions[11b,13,14c,17] did not improve the results obtained in DCE (see Supporting Information, Table S1 for additional experiments). Next, the effect of the concentration of the allylating agent was studied, using 1, 2 or 2.5 equiv. of **2a**, but no improvement with respect to the use of 1.5 equivalents was observed (Table 1, entries 6, 7, 8 *vs.* entry 3). The additive is required, as the reaction does not take place in its absence (Table 1, entry 9). A brief screening of carboxylates was carried out, obtaining a slight improvement when potassium benzoate was used (Table 1, entries 10–15). An increase of the concentration of the base was not beneficial (Table 1, entry 16). With these optimized conditions, we next tested different allyl aryl ethers as allylating agents (Scheme 3). Simple allyl phenyl ether (**2b**) showed to be less reactive,

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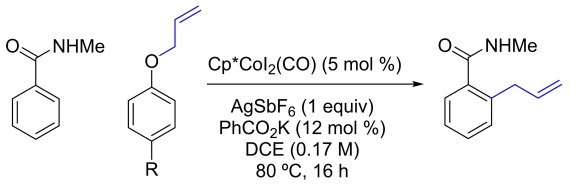


2b R = H	51%
2c R = OCH_3	nr
2d R = CO_2Et	65%
2e R = $COCH_3$	48%
2f R = NO_2	42%

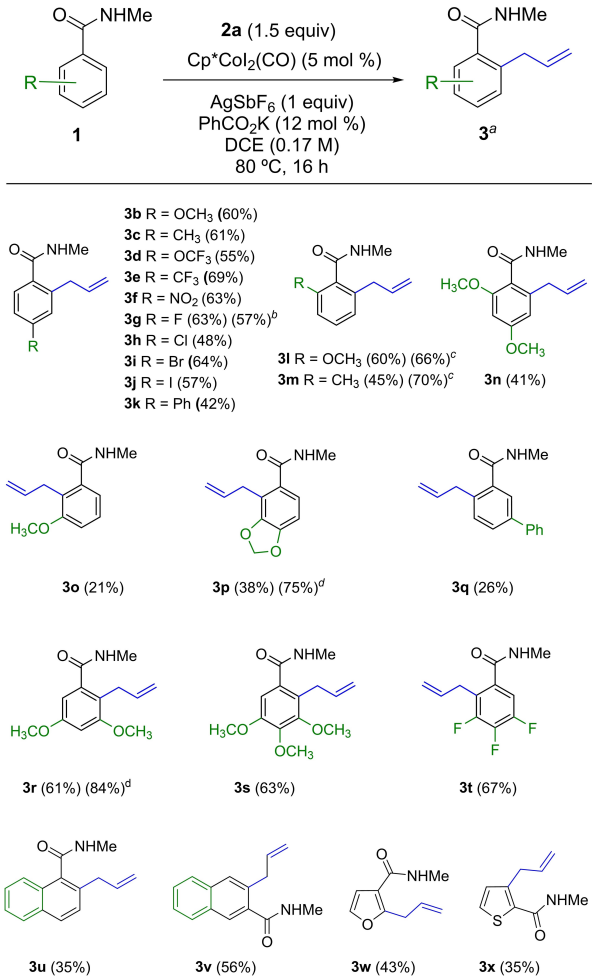
Scheme 3. Substitution on the aryl ring of the allylating agent.

obtaining **3a** with a lower yield (51%), and recovering unreacted amide. Significantly, the introduction of an electron releasing group on C-4 (**2c**) completely shut down the reactivity. As expected, **2d** gave almost the same result as **2a**, while the introduction of other electron withdrawing substituents (**2e**, **2f**) led also to lower conversions. The reactivity as allylating agents of these allyl aryl ethers seems to be related to some extent with the leaving group ability of the corresponding phenoxide. Unfortunately, the substitution on the alkene shuts down the reactivity (see Supporting Information, Scheme S1).

We next extended these reaction conditions to a series of carboxamides **1** with different substitution patterns on the aromatic ring (Table 2). The presence of electron donating or electron withdrawing groups in the C-4 position of the aromatic ring, as well as halides, is well tolerated obtaining **3b**–**3k** with moderate to good isolated yields. The corresponding 2,6-diallylated products were not isolated nor detected by NMR, as has been observed in related examples using allyl carbonates.[14b] For comparison, the allylation of 4-fluorocarboxamide **1g** was also carried out using allyl methyl carbonate as allylating agent. Under these reaction conditions, the yield obtained of **3g** was similar but lower to that obtained with **2a** (57% *vs.* 63%, Table 2). These Cp*Co(III) catalyzed reactions are generally sensitive to steric effects in the reactants. The presence of *ortho*-substituents has been reported to decrease the reactivity, probably by steric repulsion of the amide with the *ortho*-substituent during the C–H cobaltation step, lowering the yields of the allylated product[11b] or completely precluding the allylation.[14d,19] In our case, the reaction was possible in moderate yields with *ortho*-methyl and methoxy substituents (Table 2, **3l**–**3n**).

In the case of **3l** and **3m**, the conversion and the isolated yield could be improved using a higher catalyst loading. However, no conversion was obtained with other groups in the *ortho*-position (nitro, trifluoromethyl, halides. See Supporting information Scheme S2 for non-productive substrates tested). When a substituent is introduced in the *meta*-position, the regioselectivity of the allylations seems to be more influenced by electronic factors than by steric interaction. In the case of **3o** and **3p**, the allylation took place in low yield in the more sterically hindered C-2 position. This low isolated yield was due

Table 2. Allylation of amides **1**.



[a] Yield (%) of isolated pure product. Reactions were carried out in a 0.2 to 0.3 mmol scale in a 20 mL sealed reaction tube. [b] Reaction carried out with allyl methyl carbonate (instead of **2a**). [c] 10 mol% of the catalyst. [d] 1.25 mol% of the catalyst.

to low conversion (recovering unreacted **1**), but no formation of the C-6 regioisomer could be observed. On the contrary, the opposite regioselectivity, in favour of the less hindered C-6 position was observed with **1q**, although **3q** was also obtained with low yield. Similar effects have been reported for related substrates.[14,17] The allylation reaction was successfully extended to the obtention of **3r**–**t** (Table 2). However, a balance between electronic and steric effects would be affecting the reactivity, as although 3,5-dimethoxy amide **1r** was an efficient substrate, no conversion was observed with other 3,5-disubstituted amides (dimethyl, dinitro, ditrifluoromethyl. See Supporting information Scheme S2 for non-productive substrates tested). The isolated yield of **3p** and **3r** was improved using a lower catalyst loading (1.25 mol%). However, this effect of the catalyst loading could not be observed with other substrates. The reaction could also be extended to naphthalene derived amides **1u** and **1v**, obtaining regioselectively the C2 and C3 allylated compounds **3u** and **3v** in moderate yields. This same regioselectivity has

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been observed in allylation reactions using a ketone as directing group,[14c] and also in related cobalt-catalyzed reactions using amides as directing groups.[29] Finally, heteroarenes, such as furane **1w** and thiophene **1x**, could also be allylated in moderate yields (Table 2).

At this point, we decided to study this reactivity pattern by Density Functional Theory (DFT) means, to get insights on the mechanistic course of the allylation reaction in the presence of allylphenoxide All structures were optimized using density functional theory (DFT) as implemented in Gaussian 16,[30] with B3LYP[31] as functional, 6–31G(d,p) as basis set for non-metallic atoms, and LANL2DZ[32] as basis set for Cobalt. Final energies were obtained performing single-point calculations on the previously optimized structures at M06[33]/6-311++G(d,p) level of theory for non-metallic atoms and SDD basis set for Cobalt,[34] introducing solvation factors with the IEF-PCM[35] 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.

Our first mechanistic model was the reaction between benzamide **1a** and unsubstituted allyl phenyl ether **2b**. In this case, $[Cp^*CoOAc]^+$ was taken as the active Co(III) catalyst for the ease of the calculation. As shown in Table 1, although the procedure has been optimized with $PhCO_2K$, the reaction proceeded also with KOAc. Upon coordination with the benzamide substrate, complex **A** is formed (Figure 1), which logically evolves through rate limiting C–H activation step (**TS A–B**), with an affordable activation energy of 20.5 kcal/mol. This would be in accordance with the KIE obtained experimentally by Glorious using this benzamide using allyl carbonates as allylating agents under related conditions.[11b] The ligand exchange between neutral acetic acid and allyl ether **2b** occurs next to form **C**, containing the aryl and alkene unities in a *cis* disposition, favoring the consecutive insertion (**TS C–D**) and beta-phenoxide elimination steps (**TS D–E**). A final exergonic ligand exchange takes place, where acetic acid displaces the *ortho*-allylated product **3a**. The insertion (9.5 kcal/mol) and elimination (14.6 kcal/mol) steps are spontaneous and quite low in energy. Thus, the critical point during the reaction is the rate determining C–H activation, which must also determine the striking differences in reactivity observed between different substrates. Nonetheless, it must be noted that an energy barrier of 20.5 kcal/mol is perfectly affordable at the reaction conditions or even at lower temperatures, explaining the observed formation of allylated products like **3a**. The need of temperatures of 80 °C for the reaction, could be related to the need of an extra amount of energy for the efficient formation of the active catalyst $[Cp^*CoOAc]^+$ from its precursors, like $Cp^*CoI_2(CO)$.

Next, we wondered about the effect of the substituents in the aryl ring. According to our observations, electron releasing groups favor the reaction by reducing the activation barrier of the C–H activation, at such an extent that is even able to overcome the negative effect of steric hindrance. Indeed, **3l**, **3m**, **3r** are good to optimal substrates (Table 2), while 3,5-dinitro **1ae**, 3,5-dimethyl **1af** and even 2-nitrobenzamide **1z**

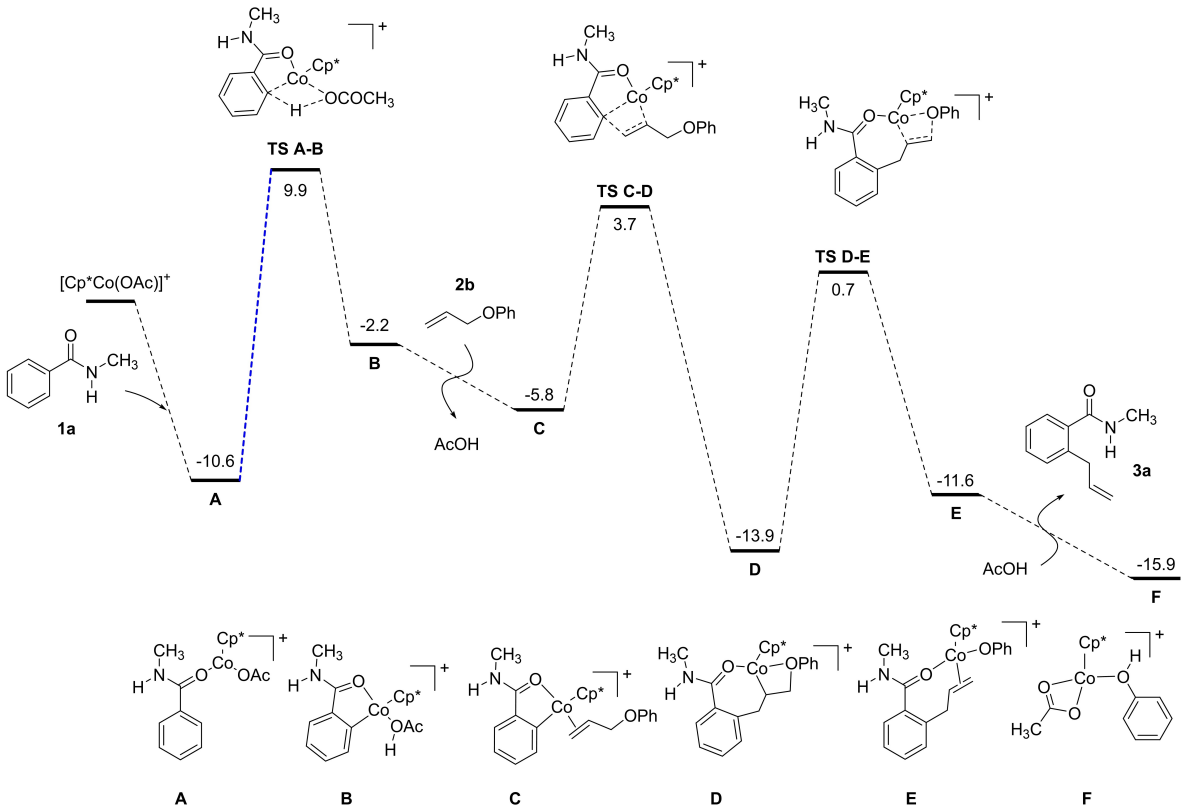

Figure 1. Free Energy profile of $[Cp^*CoOAc]^+$ catalyzed C–H allylation of **1a** with **2b** characterized at M06/6-311++G(d,p) level of theory (energy values expressed in Kcal/mol).

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derivatives do not react at all (See Supporting information Scheme S2 for non-productive substrates tested). Indeed, the study of the C–H activation in these cases was very informative (Figure 2), and a clear trend in energy values was noted, from methoxy substitution (**1 r-A**, 15.9 kcal/mol) to unsubstituted (**1 a-A**, 20.5 kcal/mol) and to nitro group (**1 ae-A**, 23.4 kcal/mol). Also, the computed preference for the methyl over the nitro group at the *ortho* position is clear (**1 m-A** *vs* **1 z-A**). These numbers suggest the participation of an electrophilic C–H activation, like the BIES type, and explain the lack of reactivity of substrates containing nitro groups, **1 ae-A** and **1 z-A**. Thus, a good correlation between the experimental yield and the activation energy was found. This reactivity trend was also confirmed experimentally by performing intermolecular competition experiments between differently substituted amides **1** (Scheme 4). The experiments were performed using an equimolar amount of each substrate [a) **1 r** *vs.* **1 a**; b) **1 r** *vs.* **1 f**] and reducing the reaction time to 5 h. The crude reaction mixtures were analyzed by GC/MS (see Supporting information). These experiments showed a clear preference in the C–H allylation for the more electron rich substrate, in good agreement with the computational data.

As mentioned before, steric effects seem to play a much less significant role than electronic effects, as reflected by the striking preference of the congested substrates **1 r-A** over the unsubstituted **1 a-A**, and the low negative effect of the *ortho* methyl group (**1 a-A** *vs* **1 m-A**).

Attending to this reasoning, substrate **1 af-A** should have shown in theory some reactivity, at least to some extent, since the presence of methyl groups should be sterically tolerated and also helpful for the electronic richness of the aryl group. Indeed, the computed activation barrier for **1 af-A** is affordable and even slightly lower than the reactive **1 a-A**, for example. Surprisingly, as mentioned before, the related 3,5-dimethyl benzamide **1 af** did not react at all (See Supporting information).

The answer to this puzzling disagreement became evident when calculating the next step, namely the migratory insertion, which in this specific case becomes rate-limiting (G = 21.1 kcal/mol, **TS C–D**, Figure 3) due to the strain introduced by the methyl groups in the *meta* positions. As a consequence of the larger steric hindrance, not only the migratory insertion, but also intermediates **B** and **C** become high in energy and very unstable, making the C–H activation easily reversible. These data can explain the lack of formation of the final product with this substrate.

Taken all these data into account, we propose the following mechanism (Figure 4), a catalytic cycle starting with the coordination of the substrate to the active Co(III) species, $(Cp^*Co(PhCO_2))^+$. As mentioned before, although, the calculations have been made using $(Cp^*Co(OAc))^+$, the catalytic cycle is proposed for the use of $PhCO_2K$ as the base additive in the optimized conditions.

This catalyst should be formed from the precatalyst $Cp^*Co(CO)I_2$, by exchange of the anionic and neutral ligands. This

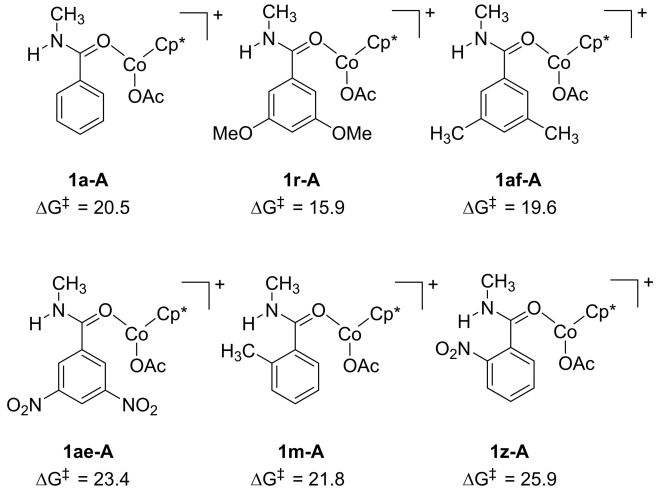
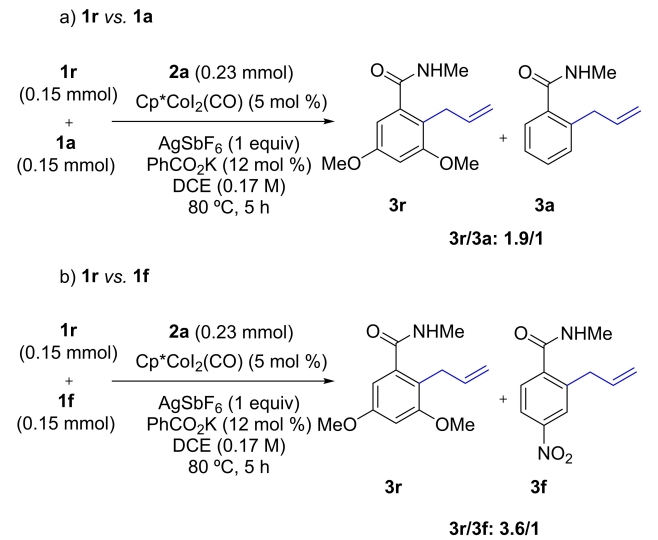


Figure 2. Comparison of the Free Energies between differently substituted arenes (energy values expressed in Kcal/mol).



Scheme 4. Competition experiments.

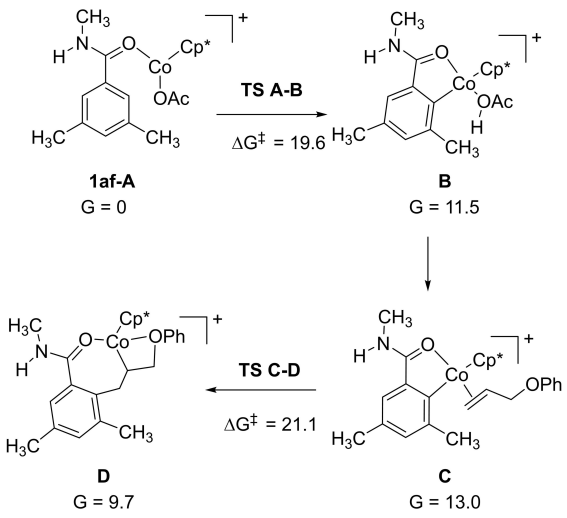


Figure 3. Activation energies for the C–H activation and migratory insertion steps for the dimethylated substrate (energy values expressed in Kcal/mol).

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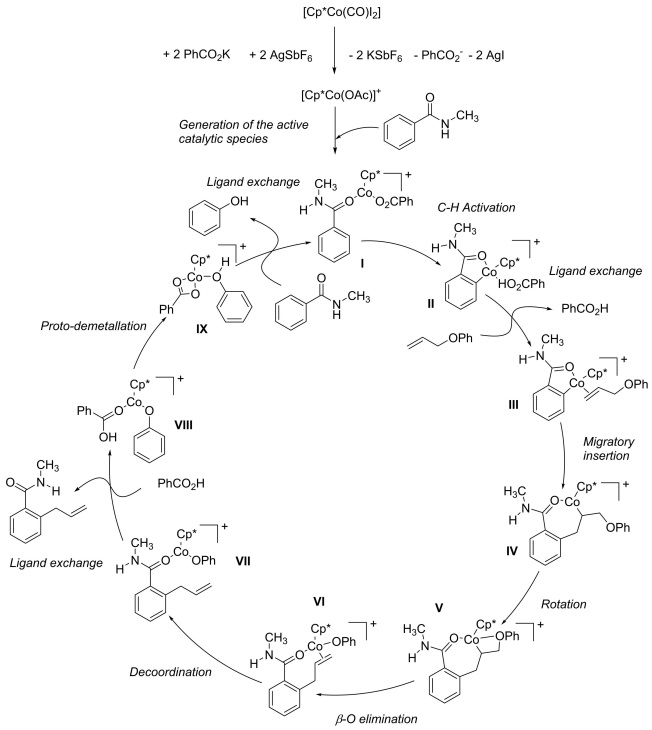
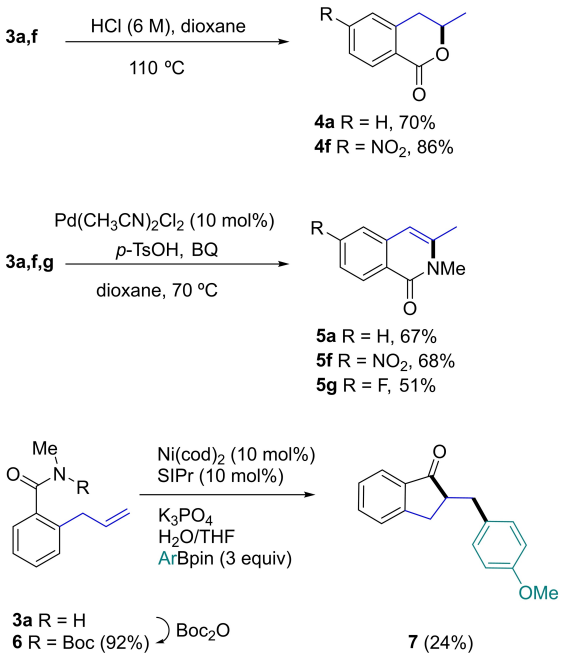


Figure 4. Catalytic cycle proposed for the Co-catalyzed allylation reaction.



Scheme 5. Derivatization of selected allylated compounds.

could explain the role of the different coadditives used experimentally in the reaction. Starting from **I**, the key C–H activation takes place, which is rate-limiting for most of the substrates. The allyl ether coordinates to the cobalt center by a simple ligand exchange, and next, the C–C bond forming migratory insertion occurs to form intermediate **IV**.

Although this step is, in general, energetically more accessible than C–H activation, we have identified at least one example (Figure 3) where the steric strain can be very detrimental for its reactivity, increasing the energy to the point of completely preventing the reaction. After **IV**, the remaining intermediates in the catalytic cycle are downhill in energy through a series of easy steps, the most prominent being a β-O-elimination and the final protodemetalation.

As mentioned, the presence of the allyl moiety offers an excellent platform for further derivatization for the access to more complex structures. To showcase some possibilities, selected allylated compounds could be easily transformed in a variety of interesting heterocyclic and carbocyclic structures, incorporating also the directing group into the final compounds. For instance, isochromanones **4a,f** were easily obtained by treatment of **3a,f** with aqueous HCl in dioxane.[36] On the other hand, an aza-Wacker reaction on **3a,f,g** led to the selective formation of isoquinoline-1-ones **5** (Scheme 5). Besides, this type of *ortho*-allyl amides have recently been shown to be efficient substrates to perform Ni-catalyzed formal carboacylation reactions with arylboronic acid pinacol esters via C–N bond activation.[37] This procedure could be applied to **3a**, through prior derivatization to protected **6**. Under the reported reaction conditions, indenone **7** could be obtained in modest yield after reaction with 4-methoxyphenylboronic acid pinacol ester.

Conclusions

In conclusion, we have shown that allyl ethers can be successfully used for C(sp^2)–H allylation under Cp*Co(III) catalysis, efficiently competing with other allylating agents. The reaction can be applied to a variety of substituted aromatics and also heteroaromatics. DFT calculations have shown that in most cases steric effects seem to play a much less significant role than electronic effects in the reactivity of the substituted aromatics. Electron releasing groups favor the reaction by reducing the activation barrier of the rate-determining C–H activation, in good accordance with the experimental results. However, the steric strain can increase the energy of the migratory insertion step to the point of completely preventing the reaction, as in the case of the 3,5-dimethylbenzamide. The obtained allylated compounds could be easily transformed in a variety of interesting heterocyclic and carbocyclic structures.

Experimental Section

Allylation reaction. General procedure: *N*-methylbenzamide **1** (0.3 mmol), methyl 4-(allyloxy)benzoate **2a** (0.45 mmol), $AgSbF_6$ (0.3 mmol), potassium benzoate (0.036 mmol, 12 mol%) and Cp*Co(CO)I_2 (5 mol%, 1.25 mol% or 10 mol%) were successively weighed in a 20 mL glass reaction tube (16×150 mm). 1,2-DCE (1.8 mL, 0.17 M) was added, the reaction tube was capped and the mixture was stirred at room temperature for 3 minutes before placing the reaction tube in a heating block preheated at 80 °C. The reaction mixture was heated at this temperature for 16 h and, afterwards, it

was diluted with AcOEt (10 mL). The volatiles were evaporated *in vacuo* and the residue was purified by flash column chromatography (silica gel, petroleum ether/AcOEt) to afford the corresponding allylated product **3.**

Supporting Information

The following information is provided in the on-line Supporting Information: typical procedure for the preparation of substrates **1**; additional allylation assays, competition experiments, experimental details and full characterization of compounds **3**–**7**; computational data; copies of ^{1}H and ^{13}C NMR (and ^{19}F NMR) spectra of compounds **3**–**7**. Additional references are cited within the Supporting Information.[38–47]

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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