Cp*Co(III)-Catalyzed coupling of benzamides with α,β-unsaturated carbonyl compounds: Preparation of aliphatic ketones and azepinones

CHIRILA, Paula G., ADAMS, Joshua, DIRJAL, Amir, HAMILTON, Alexander and WHITEOAK, Christopher <http://orcid.org/0000-0003-1501-5582>

Published version

CHIRILA, Paula G., ADAMS, Joshua, DIRJAL, Amir, HAMILTON, Alexander and WHITEOAK, Christopher (2018). Cp*Co(III)-Catalyzed coupling of benzamides with α,β-unsaturated carbonyl compounds: Preparation of aliphatic ketones and azepinones. Chemistry : A European Journal, 24 (14), 3584-3589.

Cp*Co(III)-Catalyzed Coupling of Benzamides with α,β-unsaturated Carbonyl Compounds: Preparation of Aliphatic Ketones and Azepinones

Paula G. Chirila,[a] Joshua Adams,[a] Amir Dirjal,[a] Alex Hamilton*[a] and Christopher J. Whiteoak*[a]

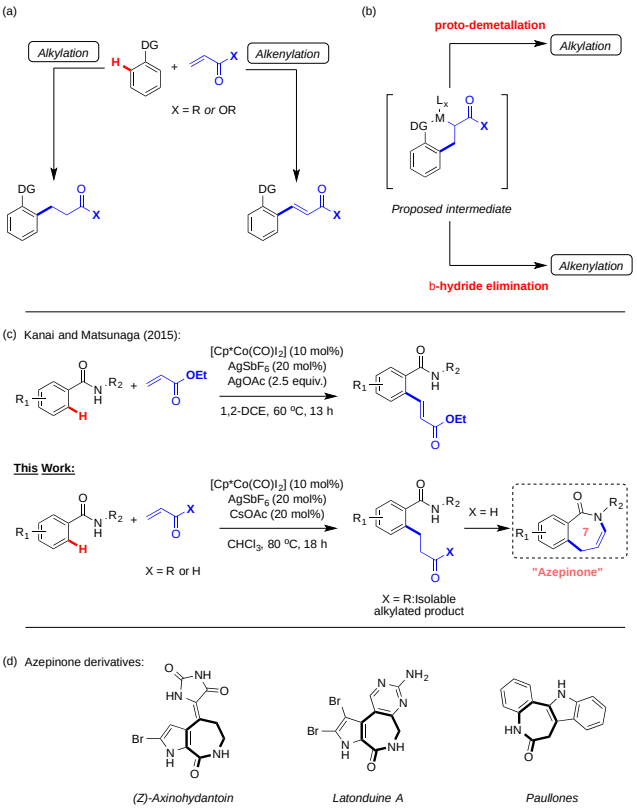
Abstract: A Cp*Co(III)-catalyzed C-H functionalization of benzamide substrates with α,β-unsaturated ketones has been optimized, providing a facile route towards aliphatic ketone products. When employing α,β-unsaturated aldehydes as coupling partners, under the optimized protocol, a cascade reaction forming azepinones has also been developed. Finally, DFT studies have demonstrated how stabilization of a metallo-enol intermediate when employing α,β-unsaturated ketones is the driving force leading to the observed aliphatic ketone product rather than olefinic products reported using α,β-unsaturated esters as coupling partners.

Introduction

The development of catalytic processes for the preparation of new carbon-carbon bonds has revolutionized synthetic chemistry over the past few decades. Whilst traditional cross-coupling protocols based on palladium have arguably provided most impact in this field, receiving the Nobel prize in 2010,[1] direct C-H functionalization presents a new challenge and an exciting future direction for this field.[2] In addition to developing C-H functionalization protocols, significant attention, with much success, has focused on the replacement of palladium with cheaper and more abundant first-row transition metals.[3] In particular, one example is cobalt, where Cp*Co(III) catalysis has shown a lot of promise and has to date provided a wide range of new carbon-carbon bond forming protocols.[4]

The formation of new carbon-carbon bonds through the coupling of α,β-unsaturated carbonyl compounds (eg. α,β-unsaturated ketones/aldehydes/esters) is an intriguing reaction as either the aliphatic or olefinic product can be accessed (Scheme 1a). This product diversity arises from the final step of the mechanism, whereby the intermediate can either undergo a proto-demetallation or a β-hydride elimination step furnishing the aliphatic and olefinic products, respectively (Scheme 1b).

In a number of reports, α,β-unsaturated ketones tend to favor the proto-demetallation of the intermediate, giving rise to the aforementioned aliphatic ketone product.[5] Meanwhile, α,β-unsaturated esters appear to favor a β-hydride elimination, furnishing the olefinic products.[6] There are however notable exceptions to this which demonstrate scope for control, for example, Chang described that the selectivity could be influenced by the nature of the directing group,[7] whilst Loh demonstrated that through the use of strong electron withdrawing substituents, olefinic products could be obtained from α,β-unsaturated ketones[8] and Ramana highlighted that



Scheme 1. (a) Alkylation and alkenylation of C(sp^2)-H bonds with α,β-unsaturated carbonyl compounds (DG = Directing Group). (b) Mechanistic rationale for differential product outcome. (c) Previous Cp*Co(III)-catalyzed coupling of benzamides with ethyl acrylate and the coupling of benzamides with α,β-unsaturated ketones/aldehydes reported in this work. (d) Natural and pharmaceutically active compounds based on the azepinone motif.

absence/presence of a base could be the controlling factor.[9]

Most recently, and in the field of Cp*Co(III) catalysis, Sundararaju has demonstrated that the aliphatic product can be obtained from the α,β-unsaturated ester through addition of pivalic acid, through favoring of the proto-demetallation pathway.[10]

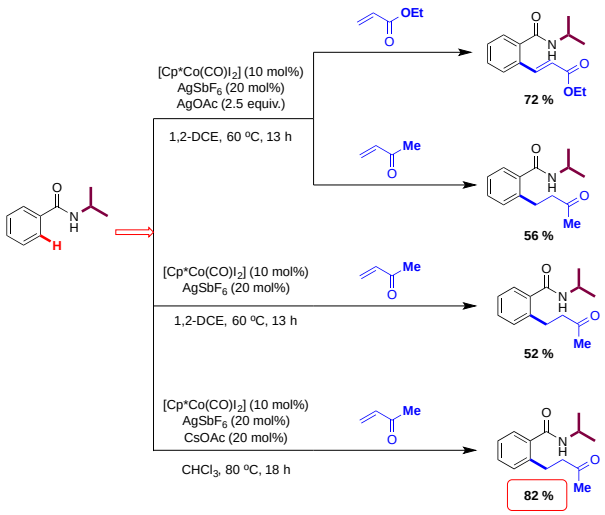
In 2015, and inspiring the work described in this contribution, Matsunaga and Kanai reported the Cp*Co(III) catalyzed coupling of benzamides and acetanilides with ethyl acrylate, providing olefinic products (Scheme 1c).[6b] Whilst ruthenium catalyzed couplings of α,β-unsaturated ketones to benzamides, furnishing the aliphatic products, have been reported by Chatani[5a] and Ackermann,[5c] no analogous Cp*Co(III) catalyzed protocol has been described to the best of our knowledge.

Herein, we report the Cp*Co(III) catalyzed coupling of benzamides with α,β-unsaturated ketones, providing the aliphatic ketone products and in the case of α,β-unsaturated aldehydes, providing azepinone products through a cascade reaction. Azepinones are important structural motifs in various natural and pharmaceutical products (Scheme 1d).[11] Previously, Cp*Rh(III)-catalyzed C-H functionalization of benzamides with diazomalonates[12]/ α,β-unsaturated aldehydes[13] or biarylamines with diazomalonates[14] have provided successful protocols for their preparation. In addition to the experimental results, the possible olefin and aliphatic

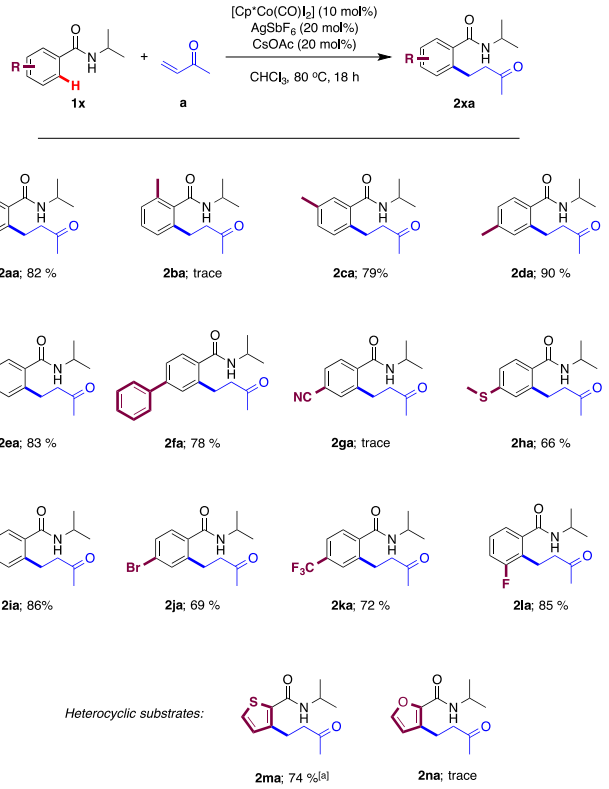
outcomes have been studied by DFT, providing insights into the reason why α,β-unsaturated ketones favor proto-demetallation and α,β-unsaturated esters a β-hydride elimination pathway.

Results and Discussion

We initiated our studies by taking the optimized reaction conditions for the Cp*Co(III)-catalyzed coupling of ethyl acrylate with benzamides reported by Matsunaga and Kanai.[6b] Under these conditions, using Methyl Vinyl Ketone (MVK) as coupling partner, we observed a 56% yield of the aliphatic product and no olefin product (Scheme 2, top). As the aliphatic product is proposed to arise from a redox-neutral mechanism involving a key proto-demetallation step, further optimization was performed in the absence of oxidant (silver acetate). In the absence of silver salt a slightly reduced yield of the aliphatic product was observed (52%) indicating that silver acetate, as expected, is not required for the alkylation protocol (Scheme 2, middle). Further optimization led to the use of $CHCl_3$ as solvent and additionally indicated the beneficial role of the addition of a catalytic amount of cesium acetate (Scheme 2, bottom; see supporting information for full details of optimization).

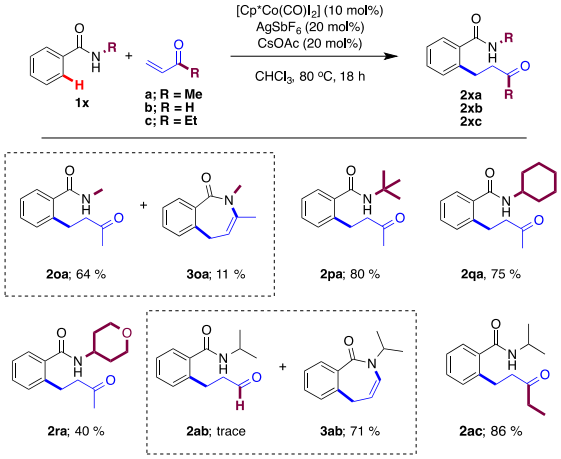


Scheme 2. Overview of optimization for Cp*Co(III)-catalyzed alkylation of benzamides using MVK as coupling partner, starting from the conditions reported by Matsunaga and Kanai for the corresponding alkenylation protocol.[6b] 1.5 equiv. α,β-unsaturated ester/ketone used in the optimization results shown in this scheme. NB. No olefinic products are observed using MVK (Methyl Vinyl Ketone).



Scheme 3. Scope of substitution on the benzamide (**1x**) using MVK (**a**) as coupling partner.[16] Conditions: **1x** (0.8 mmol), [Cp*Co(CO)I$_2$] (10 mol%, 0.08 mmol), $AgSbF_6$ (20 mol%, 0.16 mmol), CsOAc (20 mol%, 0.16 mmol), MVK (1.5 equiv., 1.2 mmol) and $CHCl_3$. [a]Traces of alkenylated product are present in the sample after column chromatography.

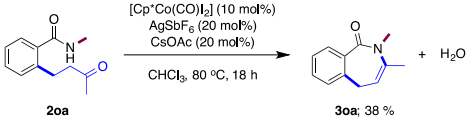
With the optimized reaction conditions in hand, the substrate scope was investigated. Firstly, the effect of changing the substituent of the aromatic moiety of the benzamide was studied (Scheme 3). Employing the *ortho*/*meta*/*para*-methyl substituted benzamides (**1b**-**d**) as substrates provided some interesting insights into the overall reactivity patterns. The *ortho*-methylated substrate (**1b**) could not be converted under the optimized reaction conditions, which is ascribed to unfavorable steric effects of substituents in this position on the aromatic ring. On the other hand, substrate **1c** was readily alkylated, furnishing **2ca**, which was found as the exclusive product. This selectivity is proposed to again arise from steric effects during the C-H activation step and this selectivity has been observed before using Cp*Co(III) C-H functionalization catalysis.[15] The para-substituted substrate, **1d**, was smoothly converted to the corresponding alkylated product (**2da**) in 90% yield. Likewise, most of the *para*-substituted substrates were readily converted in good to excellent yields with only one notable exception. Under the optimized conditions the cyano substrate, **1g**, could not be successfully converted which is proposed to be as a result of competitive coordination of this functionality to the Cp*Co(III) catalyst with the substrate. When the *meta*-fluoro substrate was employed, alkylated product **2la** was selectively obtained with no observation of the other regioisomer. The smaller size and different electronic properties of the fluorine atom compared with the aforementioned *meta*-methyl example (**2ca**) are clearly sufficient to change the regioselective outcome of the reaction.



Scheme 4. Coupling of differently substituted amides (**1x**) with MVK and coupling of acrolein (**b**) and ethyl vinyl ketone (EVK, **c**) with benzamide **1a**.[16] Conditions: **1x** (0.8 mmol), [Cp*Co(CO)I_2] (10 mol%, 0.08 mmol), $AgSbF_6$ (20 mol%, 0.16 mmol), CsOAc (20 mol%, 0.16 mmol), α,β-unsaturated ketone/aldehyde (1.5 equiv., 1.2 mmol) and $CHCl_3$.

Finally, attempts were made to extend the substrate scope to include heterocyclic compounds (**1m** and **1n**). Whilst, the thiophene product (**2ma**) was obtained in good yield, only traces of the furyl product (**2na**) were observed. It should be noted that after purification of the thiophene product, traces of the olefinic product were present which could not be further removed.

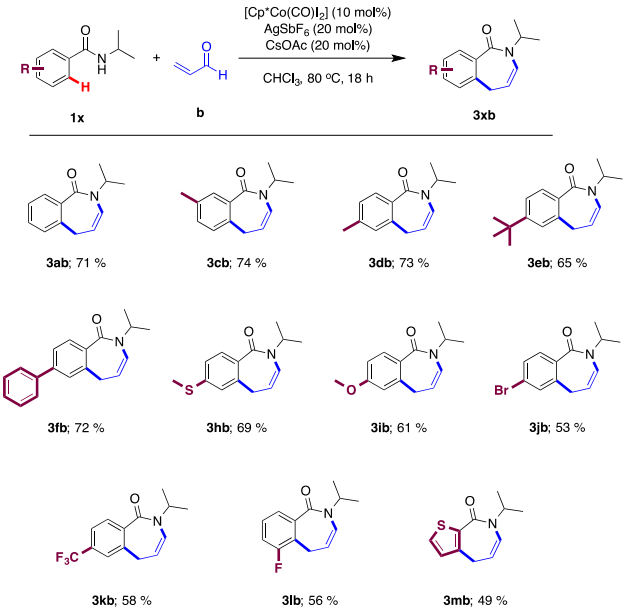
Next, effect of changing the substituent of the nitrogen atom of the amide was studied (Scheme 4). When the size of the substituent was reduced from isopropyl (**1a**) to methyl (**1o**) the expected alkylation product (**2oa**) was observed, but in addition an azepinone product (**3oa**) was also observed in low yield. It is proposed that this product arises from a Cp*Co(III) mediated dehydrative cyclization in a cascade reaction. In order to check this, isolated linear product **2oa** was subjected to the optimized reaction conditions and 38 % conversion was observed (Scheme 5). When the amide substituent was replaced with either *tert*-butyl or cyclohexanyl, good yields of the alkylated products **2pa** and **2qa** were observed. Attempts to convert a phenyl substrate were unsuccessful and a reduced yield was observed with the tetrahydropyranyl substrate (**1r**) compared with the similar cyclohexanyl substrate, which is again ascribed to result from competitive coordination of the Cp*Co(III) catalyst.



Scheme 5. Conversion of alkenylated product **2oa** to corresponding azepinone, **3oa**, under the standard reaction conditions in the absence of coupling partner. Conditions: **2oa** (0.1 mmol), [Cp*Co(CO)I_2] (10 mol%, 0.01 mmol), $AgSbF_6$ (20 mol%, 0.02 mmol), CsOAc (20 mol%, 0.02 mmol) and $CHCl_3$.

Finally, effect of changing the ketone substituent, including using the corresponding aldehyde (acrolein), was attempted (Scheme 4). When acrolein (**b**) was employed as coupling partner with substrate **1a**, the 7-membered cyclic product (**3ab**) was obtained in good yield along with only traces of the linear aliphatic product (**2ab**). Lengthening of the alkyl group of the α,β-unsaturated ketone from methyl (**a**) to ethyl (**c**) provided little difference in product yield. In order to check that the proposed selectivity towards alkylation was observed using α,β-unsaturated esters under the optimized conditions, ethyl acrylate was trialed and provided only stoichiometric alkenylation products with respect to the amount of Cp*Co(III) catalyst used. Internal α,β-unsaturated ketones were also used as coupling partners (including pent-3-en-2-one), although they only provided traces of product under the optimized conditions.

Intrigued by the selective formation of the 7-membered cyclic product (azepinone), a full scope was performed using the substrates which were successfully converted in the initially developed alkylation procedure and acrolein (Scheme 6). To our delight all of the azepinone products could be obtained in moderate to good yields. This procedure therefore provides a general and facile route towards the formation of azepinones from readily available benzamides and acrolein, producing only water as waste. It should be noted that in all cases traces of the alkylated product were observed, which would be expected as the cyclic product arises from a two-step cascade reaction with the linear aliphatic product as an intermediate species.[17]



Scheme 6. Scope of substitution on the benzamide (**1x**) using acrolein (**b**) as coupling partner for synthesis of azepinones.[18] Conditions: **1x** (0.8 mmol), [Cp*Co(CO)I_2] (10 mol%, 0.08 mmol), $AgSbF_6$ (20 mol%, 0.16 mmol), CsOAc (20 mol%, 0.16 mmol), acrolein (1.5 equiv., 1.2 mmol) and $CHCl_3$.

With the developed catalytic alkylation and cascade protocols in hand, DFT-based methods were employed in an attempt to understand the key steps involved in the Cp*Co(III)-catalyzed alkylation of benzamides with α,β-unsaturated ketones and explain why alkenylation is unfavorable with these coupling partners. The first step to be studied in the mechanistic cycle involves the coordination of the Cp*Co(III) catalyst to the benzamide substrate. Previously, Zhu has described the synthesis and characterization of cobaltacycles through C-H

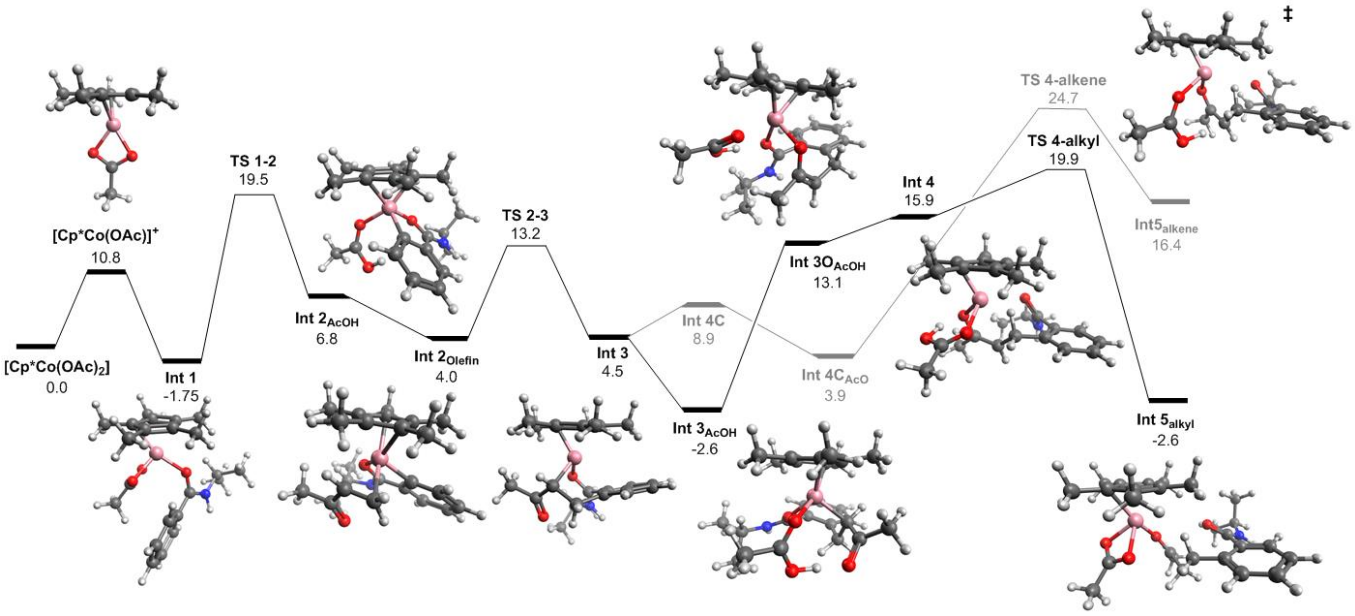


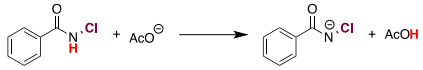
Figure 1. Solvent corrected Free Energy Surface (ΔG_{298} kcal mol^{-1}) for mechanistic divergence with α,β-unsaturated ketone. Black colored free energy surface leading to the observed alkylated product and grey colored surface leading to the unobserved alkenylation product. Free energies taken relative to the [Cp*Co(III)$(AcO)_2$] pre-catalyst and associated reagents.

activation of benzamides, clearly showing a Co(III)-N binding mode.[19] This is clearly in disagreement with the mechanistic proposal of Kanai and Matsunaga for the Cp*Co(III)-catalyzed alkenylation of benzamides with ethyl acrylate,[6b] whereby based on their previous observations,[20] Co(III)-O chelation is proposed. The key difference between these two examples is the nature of the benzamide substituent; The Co(III)-N bound example contains a chloro substituent, whereas the proposed Co(III)-O example contains methy/*tert*-butyl. Calculation of the acid:base equilibrium in the presence of an acetate anion for the chloro example and the isopropyl used in this work, showed a significantly higher energy barrier for isopropyl (18.6 kcal mol^{-1}) compared with chloro (2.9 kcal mol^{-1}), which could indeed result in different binding modes (Table 1 and Supporting Information for full details). This is not unexpected given the electron donating properties of the isopropyl group reducing the acidity of the amide proton. This observation also highlights the potential for functional group controlled mechanistic divergence as reductive elimination steps from Co(III)-N coordinated intermediates are likely to result in annulated products.[21] It is therefore proposed that in the protocol presented in this work, the initial step involves the coordination of a cationic cobalt species to the oxygen atom of the amide.

With an understanding of the potential substrate binding mode, we there then able to turn our attention to elucidating the multi-step reaction mechanism (Figure 1). The [Cp*Co(III)(OAc)$_2$] pre-catalyst can undergo loss of an acetate anion forming the cationic [Cp*Co(III)(OAc)]$^+$ species. This ligand dissociation is endergonic by 10.8 kcal mol^{-1}, but is followed by stabilization from association with the oxygen of the benzamide substrate. Notably, the equivalent nitrogen bound intermediate is approximately 20 kcal mol^{-1} less stable than the proposed cationic Co(III)-O coordinated intermediate, **Int 1**.

Thereafter, subsequent C-H activation at the *ortho* phenyl position forms the 5-membered cobaltocycle with a barrier of 21.3 kcal mol^{-1}. Ligand exchange of the acetic acid for the olefin, followed by migratory insertion into the Co(III)-C bond leads to the 7-membered cobaltocyclic intermediate, **Int 3**. This intermediate is the key to the mechanistic divergent reaction. To form the observed alkylated product **Int 3** binds an acetic acid molecule (7.0 kcal mol^{-1} exergonic) and thereafter undergoes a keto/enol like isomerization followed by a "*de-chelation isomerisation*" to form the linear **Int 4** structure. Protonation of the carbon at the γ-position, by the associated acetic acid forms the observed alkylation product and regenerates the cationic [Cp*Co(III)(OAc)]$^+$ species. Scheme 7 summarizes the proposed catalytic cycle for the formation of both aliphatic and cyclic products using the experimental and DFT results obtained in this study.

Table 1. DFT calculated acid:base equilibrium of differently substituted benzamide susbtrates.

	ΔG_{298} [kcal mol^{-1}]
	18.6
	2.9

At the divergent point in the mechanism, **Int 3**, initial "*de-chelation isomerization*" followed by the addition of an acetate anion instead of the acetic acid leads to the possibility of forming the unsaturated alkene product via β-hydride elimination (Figure 2). In the case of α,β-unsaturated ketones, the barrier for β-hydride elimination is approximately 5 kcal mol^{-1} higher in energy compared to the previously discussed γ-protonation mechanism. Interestingly, the α,β-unsaturated ester reverses the relative energies of the competing barriers, favoring the formation of the olefinic product. This change in reaction profile is due to a combination of steric and electronic parameters destabilizing the isomerization intermediates prior to proton transfer.

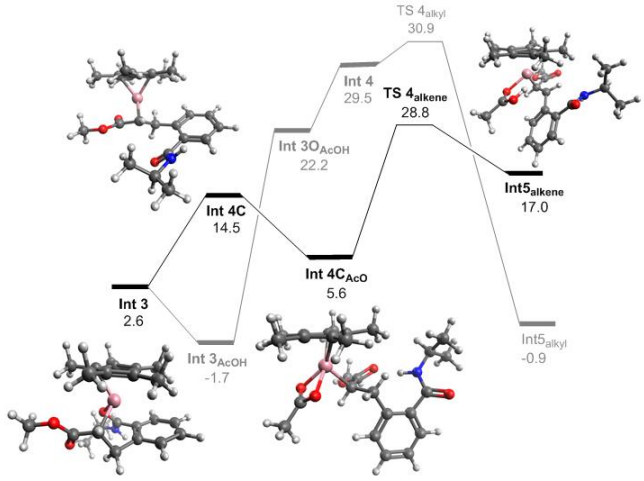
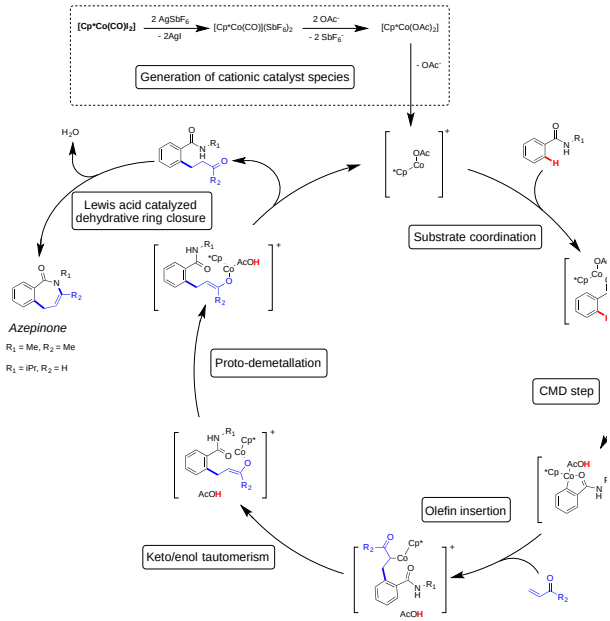


Figure 2. Solvent corrected Free Energy Surface (ΔG_{298} kcal mol^{-1}) for mechanistic divergence with α,β-unsaturated ester. Black colored free energy surface leading to the observed alkenylation product and grey colored surface leading to the unobserved alkylation product. Free energies taken relative to the [Cp*Co(III)(AcO)$_2$] pre-catalyst and associated reagents.

Conclusions

In conclusion, we have developed a facile route for the preparation of azepinones from readily available benzamides and acrolein through a cascade reaction with an initial key Cp*Co(III)-catalyzed C-H alkylation step, producing only water as waste. When α,β-unsaturated ketones were employed it was possible to

isolate the aliphatic ketone products. We have also studied the product selectivity of the reported alkylation protocol using DFT-based methods in order to explain why α,β-unsaturated ketones provide the aliphatic product. These DFT studies suggest a metallo-keto/enol isomerization being a key step in the mechanism, leading to the aliphatic ketone product when employing α,β-unsaturated ketones as coupling partner. This isomerization is significantly destabilized when employing an α,β-unsaturated ester, driving the reaction towards olefinic products.



Scheme 7. Proposed catalytic cycle for Cp*Co(III)-catalyzed coupling of α,β-unsaturated ketones/aldehydes and benzamides for the preparation of linear aliphatic products and azepinones.

Experimental Section

Typical reaction protocol for alkylation and cyclization: A scew top vial, under air, was charged with benzamide substrate (1.0 equiv.), [Cp*Co(CO)I_2] (10 mol%), $AgSbF_6$ (20 mol%), CsOAc (20 mol%), α,β-unsaturated ketone/aldehyde (1.5 equiv.) and $CHCl_3$. The vial was sealed and the reaction mixture heated to 80 °C with stirring for 18 hours. After this period the solvent was removed under reduced pressure and the crude product purified by column chromatography (Hexane:EtOAc; alkylation 60:40 and cyclization 80:20). For full characterization data of all products obtained, see supporting information.

Computational Details: All DFT calculations undertaken using the ORCA 3.03 computational software. Optimisations were performed at the BP86-D3BJ/def2-TZVP level of theory and final single point energies and solvation corrections calculated at M06/def2-TZVP. Frequencies calculations approximated the ZPE correction and entropic contributions to the free energy term as well as confirming all intermediate were true with no imaginary modes and all transition states had the correct critical frequency of decomposition (imaginary mode). Solvation correction was implemented with the COSMO model for CH_2Cl_2. Graphical visualisation using Gabedit 2.4.8 and Avogadro 1.2.0 programs. For full computational details see the Supporting Information.

Acknowledgements

The authors would like to thank the Department of Biosciences and Chemistry and the Biomolecular Sciences Research Centre (BMRC) at Sheffield Hallam University for funding.

Keywords: Cobalt • C-H functionalization • Cascade reaction • Homogeneous catalysis • Cyclization

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[15] See for examples: (a) T. Gensch, S. Vásquez-Céspedes, D.-G. Yu, F. Glorius, *Org. Lett*., **2015**, *17*, 3714. (b) J. Li, L. Ackermann, *Chem. Eur. J*., **2015**, *21*, 5718. (c) Y. Bunno, N. Murakami, Y. Suzuki, M. Kanai, T. Yoshino, S. Matsunaga, *Org. Lett*., **2016**, *18*, 2216. (d) B. Sun, T. Yoshino, M. Kanai, S. Matsunaga, *Angew. Chem. Int. Ed*., **2015**, *54*, 12968.

[16] Note: We did not observe any alkenylation product in the crude of any reaction unless noted.

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[21] For examples of Cp*Co(III)-catalyzed annulations arising from proposed or isolated Co(III)-N bound benzamide intermediates, see: (a) M. Sen R. Mandal, A. Das, D. Kalsi, B. Sundararaju, *Chem. Eur. J*., 10.1002/chem.201704155. (b) ref. 19.