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Directed carbonylative (3+1+2) cycloadditions of amino-substituted cyclopropanes and alkynes: reaction development and increased efficiencies using a cationic rhodium system

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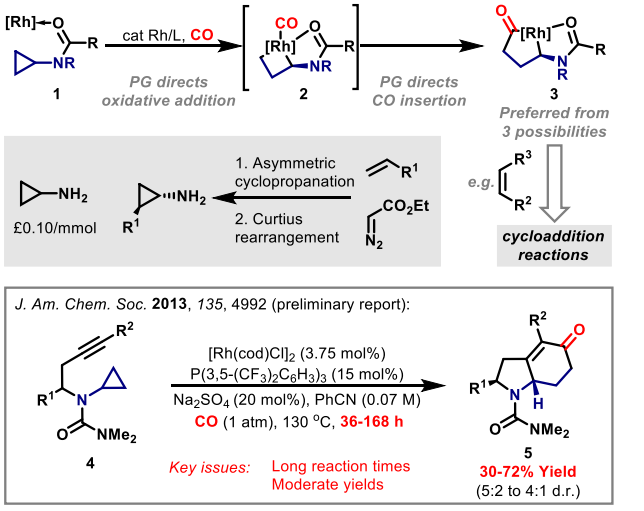
ABSTRACT

Urea-directed carbonylative insertion of Rh(I)-catalysts into one of the two proximal C–C bonds of aminocyclopropanes generates rhodacyclopentanone intermediates. These are trapped by N-tethered alkynes to provide a (3+1+2) cycloaddition protocol that accesses N-heterobicyclic enones. Stoichiometric studies on a series of model rhodacyclopentanone complexes outline key structural features and provide a rationale for the efficacy of urea directing groups. A comprehensive evaluation of cycloaddition scope and a 'second generation' cationic Rh(I)-system, which provides enhanced yields and reaction rates for challenging substrates, are presented.

1. Introduction

Synthetically flexible and modular entries to stereochemically rich N-heterocyclic scaffolds are of topical interest to the pharmaceutical sector.[1] Recently, we reported a strategy to access selectively amino-rhodacyclopentanones **3** by the carbonylative insertion of Rh(I)-catalysts into the more hindered C–C bond of amino-substituted cyclopropanes **1** (Scheme 1).[2] Specifically, we established that carbonyl-based N-protecting groups can direct oxidative addition (to **2**) and CO-insertion to generate regioisomer **3** in a selective manner. Trapping of **3** with N-tethered alkynes provided a (3+1+2) cycloaddition strategy to generate N-heterobicyclic enones (**4**→**5**).[3] These investigations provided proof-of-principle for an approach that has the potential to enable a wide range of carbonylative cycloadditions for accessing directly 'sp^3-rich' chiral scaffolds.[1,4] Indeed, to date, the catalysis platform outlined in Scheme 1 has served as the basis for related (3+1+2) cycloadditions involving alkenes,[5] and a (7+1) cycloaddition-fragmentation approach to substituted azocanes.[6] In this article we disclose our full studies on the development of urea-directed (3+1+2) cycloadditions involving alkynes. In addition to key mechanistic considerations, detailed studies on the generation of the amino-rhodacyclopentanones intermediates are outlined, and a simple modification to our original (3+1+2) cycloaddition protocol is disclosed, which provides enhanced yields and reaction rates for challenging substrates.



Scheme 1. Directed generation of amino-rhodacyclopentanones (catalysis platform).

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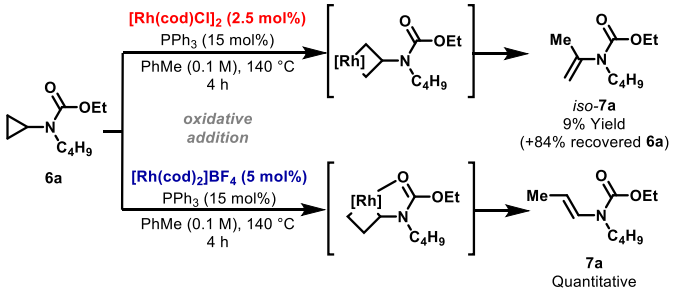
2. Results and discussion

At the outset of our studies, catalytic protocols reliant on the intermediacy of rhodacyclopentanones were scarce and processes involving amino-substituted variants had not been developed. Pioneering studies by Wilkinson demonstrated Rh/CO insertion into cyclopropane to generate a dimeric rhodacyclopentanone.[7a] Subsequent work by McQuillin examined the regioselectivity of this process for substituted variants.[7b] An alternative approach was reported by Murakami and Ito, where rhodacyclopentanones were accessed by the insertion of Rh(I)-systems into the acyl-carbon bond of cyclobutanones.[8] This process has served as the basis for a series of methodologies,[9–11] however, carbonylative rhodacyclopentanone formation has not been as widely exploited in synthesis.[3a,12] Notable processes that harness this approach include carbonylative rearrangements of spiropentanes, as reported by Murakami,[12b] and (3+1+2) cycloadditions involving alkynes to generate carbocyclic systems, as reported by Narasaka.[3a] In this latter process, the alkyne is invoked as a directing group. For the strategy outlined in Scheme 1, the most pertinent work is that of Chirik, who demonstrated efficient phosphinite-directed insertion of neutral Rh(I)-systems into alkyl-substituted cyclopropanes, albeit under non-carbonylative conditions.[13,14] With this report in mind, our initial goal was to establish the viability of using N-directing groups to control Rh/CO insertion.

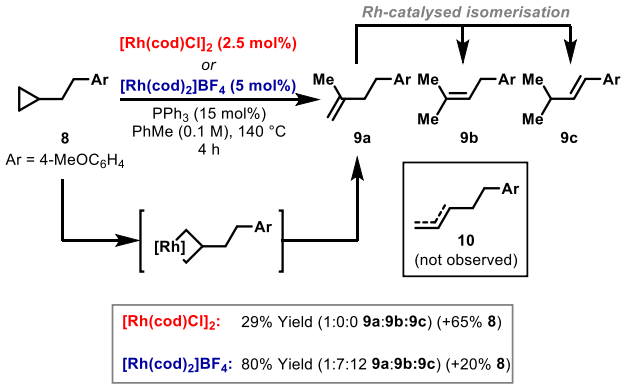
2.1. Regioselective generation and key structural features of amino-rhodacyclopentanones

Preliminary studies examined the regioselectivity of Rh(I)-insertion into carbamate-protected aminocyclopropane **6a** (Scheme 2). A neutral Rh(I)-system, derived from $[Rh(cod)Cl]_2$ and PPh_3, delivered branched vinyl carbamate *iso*-**7a** via insertion into the *less* hindered C–C bond. In contrast, employment of $[Rh(cod)_2]BF_4$ as the pre-catalyst resulted in rapid and quantitative formation of linear vinyl carbamate **7a** via Rh-insertion into the *more* hindered C–C bond. For $[Rh(cod)_2]BF_4$, significant conversion to **7a** was observed even at 60 °C; this indicates that oxidative addition is reasonably facile. The faster rate of vinyl carbamate formation versus $[Rh(cod)Cl]_2$ may be due to an additional vacant coordination site facilitating β-hydride elimination. These results suggest that relatively Lewis acidic metal complexes (i.e., cationic vs neutral) are required to ensure coordination to the carbamate directing group and contrast Chirik's studies where neutral Rh(I)-systems were effective with strongly directing phosphinites.[13]



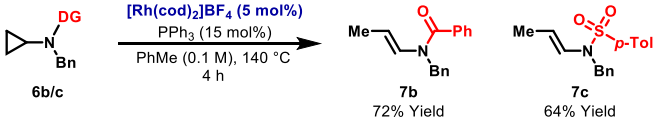
Scheme 2. Catalyst and directing group controlled regioselective vinyl carbamate formation.

To confirm the role of the directing group in the conversion of **6a** to **7a**, analogous regioselectivity studies on alkyl-substituted cyclopropane **8** were conducted (Scheme 3). Both neutral and cationic Rh(I)-systems delivered *only* branched products, resulting from Rh-insertion into the less hindered C–C bond; no detectable levels of linear product **10** were observed. Using $[Rh(cod)Cl]_2$, alkene **9a** was observed as the sole product, whereas $[Rh(cod)_2]BF_4$ delivered a mixture of branched adducts **9a**–**c**. **9b**–**c** presumably arise from Rh-catalysed isomerisation of alkene **9a**. The sole formation of branched alkenes **9a**–**c** from alkyl-substituted cyclopropane **8** confirms the importance of the N-directing group for the conversion of **6a** to **7a** in Scheme 2.



Scheme 3. Non-directed insertions of neutral and cationic Rh(I)-systems into an alkyl-substituted cyclopropane.

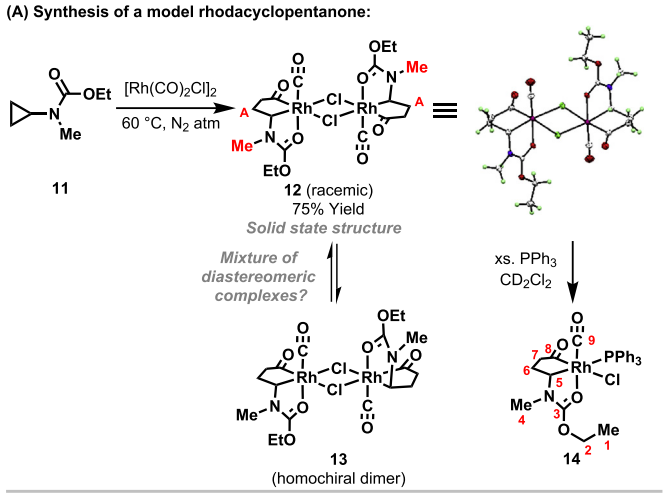
Further studies were conducted to assess the capability of other N-protecting groups for directing Rh-insertion (Scheme 4). Accordingly, amide **6b** and sulfonamide **6c** were exposed to $[Rh(cod)_2]BF_4/PPh_3$ under non-carbonylative conditions. The exclusive formation of linear products **7b**/**c** was observed in both cases, thereby supporting a directed oxidative addition pathway.



Scheme 4. Amide and sulfonamide directed Rh-insertions.

The studies described above show that, under non-carbonylative conditions, only Lewis acidic cationic Rh(I)-catalysts can be utilised for protecting group directed oxidative addition. It was anticipated that, under carbonylative conditions, CO-ligated neutral catalysts may be sufficiently Lewis acidic because CO is a strong π-acceptor ligand, and this, in turn, should increase the electron deficiency of the Rh-centre. However, when carbamate-protected cyclopropane **6a** was exposed to a neutral Rh-catalyst ($[Rh(cod)Cl]_2$, PPh_3) under a CO atmosphere, formation of linear or branched vinyl carbamates **7a** and *iso*-**7a** did not occur. The absence of **7a** or *iso*-**7a** is suggestive of fast migratory insertion of CO at the stage of the incipient rhodacyclobutane to generate small quantities of the corresponding rhodacyclopentanone. Consequently, stoichiometric reactions were conducted with the aim of isolating and characterising neutral amino-substituted rhodacyclopentanones and thereby determining the regioselectivity of Rh/CO insertion. Wilkinson reported the synthesis of a dimeric rhodacyclopentanone from cyclopropane and $[Rh(CO)_2Cl]_2$; addition of triphenylphosphine generated the corresponding monomeric complex.[7a] Accordingly, exposure of carbamate-protected cyclopropane **11** to stoichiometric $[Rh(CO)_2Cl]_2$[7b] delivered dimeric rhodacyclopentanone **12** in 75% yield (Scheme 5A). The solid state structure of **12** was confirmed by single crystal X-ray diffraction, which revealed: (a) a heterochiral dimeric complex, (b) the desired regioselectivity for oxidative addition, (c) the desired regioselectivity for migratory insertion of CO and (d) axial coordination of the carbamate directing group to the Rh-centre. This demonstrates that carbonyl-ligated *neutral* Rh(I)-

catalysts are effective for directed insertion into aminocyclopropanes. Cowie and co-workers have reported an X-ray crystal structure of a bimetallic rhodacyclopentanone derived from allene insertion into a methylene-bridging CO-ligated Rh–Ru complex.[15] However, the structure shown in Scheme 5A is the first X-ray crystal structure of a rhodacyclopentanone derived from carbonylative cyclopropane ring expansion.

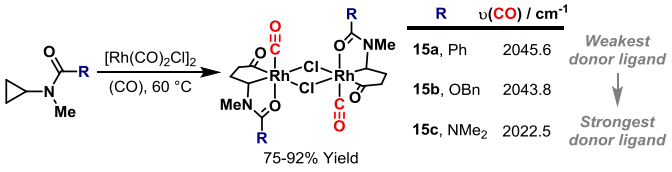


Scheme 5.

At 27 °C, the ^{1}H and ^{13}C NMR spectra (CD_2Cl_2) of rhodacyclopentanone **12** were broad and suggestive of the presence of two different species (Scheme 5B). Low temperature NMR data (−13 °C) revealed a divergence and sharpening of the two sets of signals, indicating the presence of two components in dynamic equilibrium. The precise structure of the two components has not been determined, however, rhodacycle **12** may be in equilibrium with a monomeric species or, alternatively, two diastereomeric complexes, such as **12** and **13**, may be interconverting. Addition of one equivalent of PPh_3 resulted in sharpening of the signals in the ^{1}H NMR spectrum to a single, new, rhodacyclopentanone complex **14** (Scheme 5A). The ^{31}P NMR spectrum showed a doublet at 16.2 ppm ($J_{Rh\text{-}P}$=80 Hz) confirming coordination of PPh_3 to the Rh-centre. Addition of a second equivalent of PPh_3 resulted in no change in the aliphatic region of the ^{1}H NMR spectrum, whereas the ^{31}P NMR spectrum showed a doublet at 16.2 ppm and an additional singlet at −5.56 ppm (corresponding to unbound PPh_3) in a 1:1 ratio, thereby demonstrating that only one phosphine ligand is coordinated in the new rhodacyclopentanone complex. Wilkinson and co-workers reported that addition of excess PPh_3 to dimeric rhodacyclopentanone complexes (derived from cyclopropane) delivered monomeric complexes with two phosphine ligands bound to the Rh-centre.[7a] In the present case, both the directing group carbonyl and a CO ligand remain bound to the Rh-centre, consequently only one phosphine ligand can be accommodated. The ^{13}C NMR spectrum of complex **14** (see the Supplementary data) confirmed the presence of the CO and PPh_3 ligands, and also showed that the carbamate directing group remains bound to the Rh-centre because (a) ^{3}J-coupling of C3 to phosphorus was observed (J=10 Hz) and (b) there was little change in the chemical shift of C3 between the dimeric and monomeric complexes (dimer **12**: 164.6 ppm vs monomer **14**: 165.3 ppm vs starting material **11**: 157.8 ppm).

^{13}C NMR coupling constants were used to assign the geometry of complex **14**. An alkyl/acyl C–Rh coupling constant of ~20 Hz was observed for C5 and C8 and a carbonyl-Rh coupling of 77 Hz was observed for C9; these coupling constants are consistent with related structures in the literature.[16] The C–P coupling constants for C5, C8 and C9 are 86.0, 3.0 and 11.5 Hz respectively, indicating that C5 has a *trans* relationship to PPh_3 (large coupling constants are reported for *trans* C–Rh–P relationships).[16] C8 and C9 have small C–P coupling constants which suggests a *cis* relationship to PPh_3. The structure of **14** was supported further by the relatively small $J_{Rh\text{-}P}$, indicative of a complex with a coordination number of five or six and containing an alkyl group *trans* to the phosphine.[17] We have recently reported an X-ray crystal structure of a related phosphine-bound rhodacyclopentanone complex, the NMR data of which are consistent with those of **14**.[5]

For the strategy outlined in Scheme 1, a key factor is the coordinating strength of the N-directing group. Studies in the literature have compared the binding strength of various carbonyl groups with Lewis or Brønsted acids,[18] but these results are not directly transferable to transition metal complexes. Consequently, we synthesised a series of rhodacyclopentanone complexes (**15a–c**), which were characterised by X-ray diffraction, and evaluated the relative donor strength of each directing group by comparing the stretching frequencies of the *trans* CO ligand in each case (Scheme 6).[19] From these studies the following ranking of directing group strength emerges: urea>>carbamate>amide. Attempted synthesis of an analogous complex containing a sulfonamide directing group was not successful (cf. Scheme 4) and so, at the present time, we have been unable to quantify the donor strength of this class of directing group.

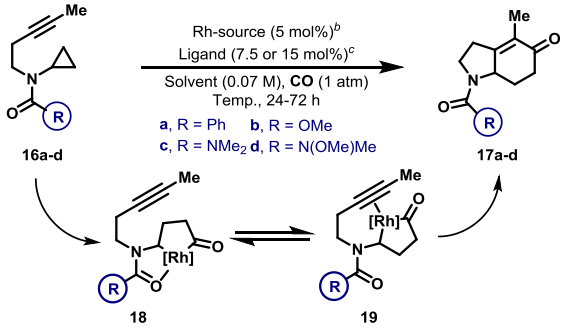


Scheme 6. Relative donor strengths of potential directing groups.

2.2. Development of a neutral Rh(I)-system for (3+1+2) carbonylative cycloadditions of aminocyclopropanes and alkynes

The regioselectivity studies outlined above demonstrate that amino-substituted rhodacyclopentanones can be accessed in a selective manner utilising the directing group strategy outlined in Scheme 1. Our initial synthetic studies sought to incorporate this activation mode into (3+1+2) cycloadditions involving N-tethered alkynes (Table 1). Narasaka and Koga have reported (3+1+2) carbonylative cycloadditions of alkyl-substituted cyclopropanes, possessing tethered alkynes, to afford carbocyclic enones.[3a] In this process, the alkyne was proposed to direct oxidative addition of the Rh(I)-catalyst into the more hindered C–C bond and relatively harsh reaction conditions were required (20 mol% [Rh], 160 °C). It

Table 1
Development of a neutral Rh(I)-system[a]



Entry		Rh-source	Ligand	Solvent	T/°C	Yield (%)
1	**16a**	$[Rh(cod)Cl]_2$	BINAP	DCB	160	26
2	**16b**	$[Rh(cod)Cl]_2$	BINAP	DCB	160	33
3	**16c**	$[Rh(cod)Cl]_2$	BINAP	DCB	160	42
4	**16d**	$[Rh(cod)Cl]_2$	BINAP	DCB	160	<5
5[d,e]	**16c**	$[Rh(cod)Cl]_2$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$	DCB	130	53
6[d,e]	**16c**	$[Rh(cod)_2]BF_4$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$	DCB	130	29
7[d,e]	**16c**	$[Rh(cod)_2]BARF$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$	DCB	130	<10
8[d,e]	**16c**	$[Rh(cod)Cl]_2$	$P(3,5\text{-}(CF_3)_2C_6H_3)_3$	PhCN	130	72

[a] Isolated yields are quoted; DCB=1,2-dichlorobenzene.
[b] 2.5 mol % for dimeric complexes and 5 mol % for monomeric complexes.
[c] 7.5 mol % for bidentate ligands and 15 mol % for monodentate ligands.
[d] Na_2SO_4 (20 mol %) was employed as desiccant.
[e] [Rh] (7.5 mol %) and $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (15 mol %) were used.

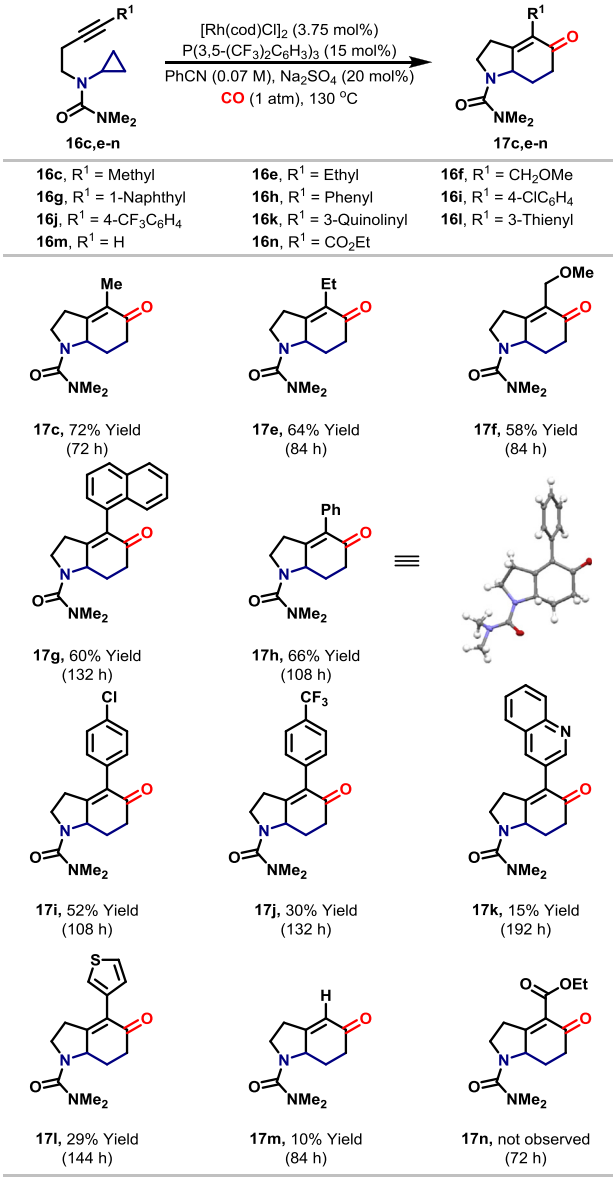
was anticipated that our carbonyl directed approach may allow related ring expansions of substituted aminocyclopropanes to proceed under milder reaction conditions. It is important to note that, for processes described here, a key aspect is the requirement that the directing group dissociates from the metal centre after rhodacyclopentanone formation to allow C–N rotation and coordination of the alkyne. Consequently, a range of directing groups were evaluated in the hope of fine-tuning the equilibrium between **18** and **19** (Table 1).

Early studies identified that, at 160 °C in DCB, a BINAP-ligated neutral Rh(I)-system effected cycloaddition of amide **16a** to **17a** in 26% yield under an atmospheric pressure of CO (Entry 1). At this stage, the influence of the directing group was investigated, and it was found that cycloaddition efficiency increased progressively as the donor strength was increased to carbamate **16b** and then urea **16c** (Entries 2 and 3; cf. Scheme 6). Notably, complete consumption of **16c** was observed within 24 h, whereas cycloaddition of **16b** to **17b** took 72 h. The structure of N-heterobicyclic enone **17b** was confirmed by single crystal X-ray diffraction. To enhance reaction efficiency further, methoxy-urea **16d** was prepared, however, cyclisation of this substrate was not effective and only trace quantities of target **17d** were observed (Entry 4). N-Boc and N-tosyl directing groups were also completely ineffective. The urea directing group of **16c** allowed the reaction temperature to be lowered to 130 °C and further optimisation led to the conditions outlined in Entry 5, which use 7.5 mol % [Rh] and $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ as ligand to deliver **17c** in 53% yield. Under these conditions, cationic Rh-sources were considerably less effective (Entries 6 and 7, vide infra). Final optimisation involved switching the solvent from DCB to PhCN and, under these conditions, **17c** was generated in 72% yield after 72 h (Entry 8).

The results of the cycloadditions of **16a–c** (Entries 1–3) merit further comment because they suggest that equilibration to **19** is not a key issue (because stronger directing groups are more effective). It is likely that the dimethylurea directing group is especially efficient because it is able to outcompete the alkyne moiety for coordination of the Rh(I)-catalyst, and thereby enhance the rate of oxidative addition. Indeed, for related processes involving alkenes, we have established that carbamate directing groups are preferred over ureas.[5] In these cases, the less strongly coordinating alkene component does not inhibit directed oxidative addition and so a strongly coordinating urea directing group is not required. Additionally, equilibration to the intermediate π-complex (cf. **19**) is more challenging, such that a less strongly coordinating directing group leads to faster rates.

The scope of the reaction with respect to the alkyne component has been assessed by exposing aminocyclopropanes **16e–n** to the optimised neutral Rh(I)-system (Table 2). Both alkyl- and aryl-substituted alkynes can be utilised, and a range of electron-rich and -neutral derivatives (**16e–i**) cyclised to the target enones **17e–i** in moderate to good yield. The structure of cyclohexenone **17h** was confirmed by X-ray crystallography. However, electron-deficient alkynes (e.g., **16j**) and heteroaromatic variants (e.g., **16k** and **16l**) cyclised less efficiently and the target enones were isolated in low yield. The inefficiency observed for quinoline derivative **17k** may be due, in part, to competitive coordination of the Rh-catalyst

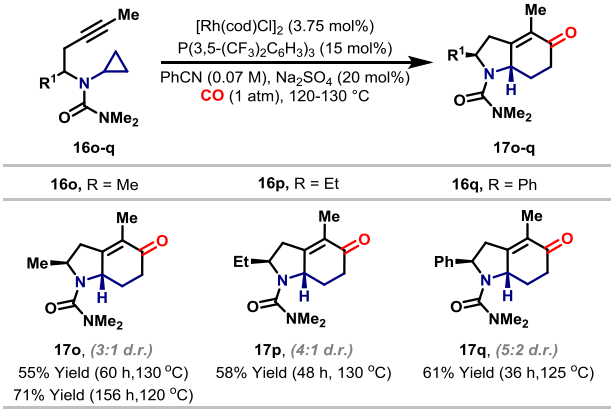
Table 2
Scope of the alkyne component



to the Lewis basic nitrogen. Terminal alkynes (**16m**) are not tolerated and this limitation is tentatively attributed to competitive formation of Rh-alkylidene complexes.[20] In all cases, reaction times are long and, ultimately, this stimulated the development of a 'second generation' protocol, which is discussed later.

Heterocyclic products of greater stereochemical complexity can be accessed by employing substrates with substitution on the alkyne tether (Table 3). Carbonylative cycloadditions of substrates **16o**–**q** delivered cyclohexenones **17o**–**q** in good yields and with moderate diastereoselectivity; the relative stereochemistry of the major diastereomers was determined by NOE experiments. Substitution on the alkyne tether resulted in increased rates of cycloaddition relative to unsubstituted substrate **16c**, and, in certain cases, this enabled the employment of marginally lower temperatures (120 °C for **16o** vs 130 °C for **16c**). The increased rate of reaction for **16o**–**q** may reflect a greater propensity for the incipient rhodacycle to adopt a conformation that allows alkyne insertion. The observed levels of diastereoselectivity for **16o**–**q** are constant over the timeframe of the reaction. Additionally, no equilibration was observed when the diastereomers of **17q** were separated and resubmitted to the reaction conditions. These observations suggest that diastereoselection occurs during cycloaddition rather than by equilibration (via epimerisation) of the products. The modest diastereoselectivities are unsurprising given that high diastereoselection likely requires the R^1 group to bias Rh-insertion into one of the two diastereotopic cyclopropane C–C bonds of **16o**–**q**. In related (3+1+2) cycloadditions involving alkenes, a solution to this issue was developed which relies upon reversible rhodacyclopentanone formation.[5] Unfortunately, this strategy is not applicable to the current scenario, perhaps due to more rapid insertion of the alkyne (vs the alkene), which diminishes reversibility.

Table 3
Substitution on the alkyne tether



2.3. Development of a cationic Rh(I)-system for (3+1+2) carbonylative cycloadditions of aminocyclopropanes and alkynes

Preliminary mechanistic studies indicated that cationic Rh(I)-systems are especially effective for directed oxidative addition (see Section 2.1), presumably because the more Lewis acidic Rh(I)-centre (vs neutral Rh(I)-systems) enhances coordination to the Lewis basic directing group. Accordingly, we decided to re-examine cationic Rh(I)-systems in more detail and ^{1}H NMR profiling of the reactions outlined in Entries 5 and 6 in Table 1 was undertaken (Fig. 1). This revealed that the use of $[Rh(cod)Cl]_2$ effects slow but steady formation of product **17c**. On the other hand, employment of $[Rh(cod)_2]BF_4$ promotes faster product formation over the initial

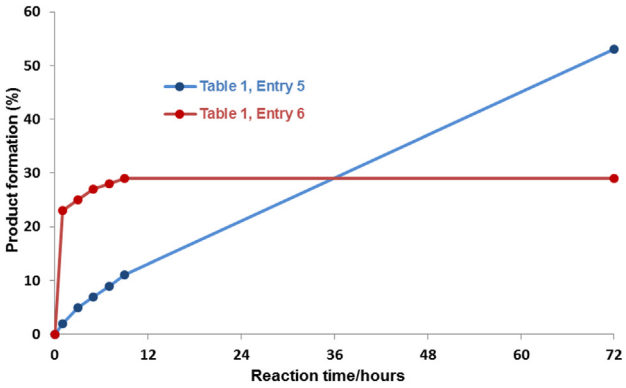
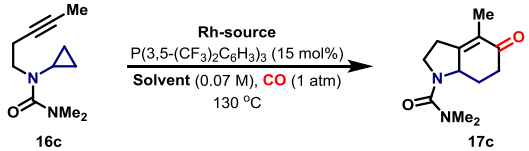


Fig. 1. Reaction profiles for Table 1, Entries 5 and 6.

stages of the reaction, but after this only gradual degradation of the starting material occurs. These data establish that cationic Rh(I)-sources provide higher initial turnover frequencies but less stable catalysts (i.e., lower turnover numbers) than neutral systems.

To improve the performance of cationic Rh(I)-derived systems we assayed a range of ligands and coordinating solvents that might stabilise the catalyst further (Table 4). In the event, simply changing the reaction solvent from DCB to PhCN provided conditions that generated **17c** in 72% yield after 9.5 h (Entry 1). Other coordinating solvents (e.g., valeronitrile and DMF) were less effective (Entries 2 and 3).[21] The difference in performance between PhCN and the more strongly coordinating valeronitrile is particularly striking and indicates that reversible binding of the solvent to the metal centre is a key factor.[22] Using PhCN as solvent, a range of cationic Rh(I)-sources were efficient and no strong dependency on the counterion was observed (Entries 4–6). The key benefits of the conditions outlined in Entries 1 and 4–6 are the significantly shorter reaction times (7.5–9.5 h vs 72 h for Table 1, Entry 8) and better substrate scope (vide infra) compared to the neutral Rh(I)-system. These 'second generation' conditions also tolerate decreased catalyst loading, but this comes at the expense of longer reaction times (Entry 7).[23] The reaction scope has been explored using the conditions outlined in Table 4, Entry 6. We have focussed on substrates that were problematic using the 'first generation' protocol and a comparison of the original and improved catalysis conditions is presented in Table 5 ($[Rh(cod)_2]OTf$ versus $[Rh(cod)Cl]_2$). In all cases, reaction times are reduced significantly by replacing $[Rh(cod)Cl]_2$ with $[Rh(cod)_2]OTf$. For example, cyclisation of **16f** was complete after 16 h to give a 73% isolated yield of **17f**, compared to a 58% yield in 84 h using $[Rh(cod)Cl]_2$.

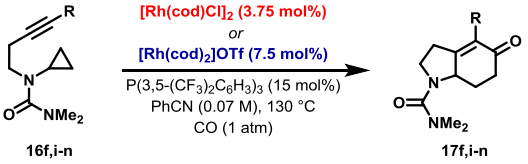
Table 4
Optimisation of a cationic Rh(I)-system

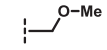
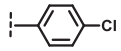
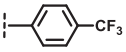
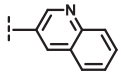


Entry	Rh-source		Solvent	Time/h	Yield (%)[a]
1	$[Rh(cod)_2]BF_4$	(7.5 mol %)	PhCN	9.5	72
2	$[Rh(cod)_2]BF_4$	(7.5 mol %)	BuCN	72	42
3	$[Rh(cod)_2]BF_4$	(7.5 mol %)	DMF	72	22
4	$[Rh(cod)_2]SbF_6$	(7.5 mol %)	PhCN	7.5	73
5	$[Rh(cod)_2]BARF$	(7.5 mol %)	PhCN	8	77
6	$[Rh(cod)_2]OTf$	(7.5 mol %)	PhCN	9	76
7[b]	$[Rh(cod)_2]OTf$	(5 mol %)	PhCN	14	67

[a] Isolated yield.
[b] $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (10 mol %) was used.

Table 5
Comparison of neutral and cationic Rh(I)-systems for (3+1+2) cycloadditions involving functionalised alkynes



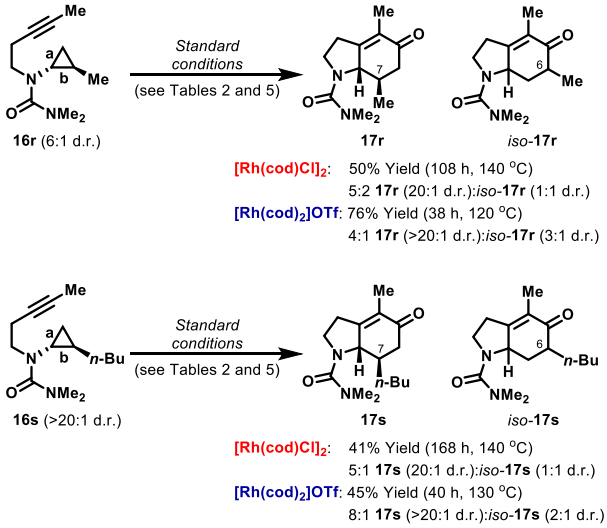
Substrate	R	Neutral System[a]		Cationic system	
		Time/h	Yield (%)	Time/h	Yield (%)
16f		84	58	16	73
16i		108	52	32	88
16j		132	30	32	82
16k		192	15	48	63[b]
16l		144	29	18	87
16m		84	10	3	23
16n		72	—	24	—

[a] Na_2SO_4 (20 mol %) was used as an additive.
[b] $[Rh(cod)_2]OTf$ (10 mol %) and $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20 mol %) were used.

Pronounced improvements were also seen with substrates **16i**–**l** and higher yields (63–88%) of the targets **17i**–**l** could be achieved in considerably shorter reaction times (18–48 h vs 108–192 h using $[Rh(cod)Cl]_2$). Quinoline **16k** required a higher catalyst loading (10 mol % $[Rh(cod)_2]OTf$) for efficient conversion, presumably due to the aforementioned issues associated with the Lewis basic quinoline nitrogen.[24] Terminal alkyne **16m**, which provided only a 10% yield of **17m** under the 'first generation' conditions, cyclised in 23% yield using the cationic Rh(I)-system. Evidently, in this case, further optimisation is still required and this will be a focus of future studies. However, even under these modified conditions, electron deficient alkyne **16n** does not participate and target **17n** was not observed. Intriguingly, for **16o** and **16q** (see Table 3), where additional substitution is present on the alkyne tether, reaction rates were improved using $[Rh(cod)_2]OTf$, but the isolated yields and diastereoselectivities associated with **17o** and **17q** were lower than when $[Rh(cod)Cl]_2$ was employed (using $[Rh(cod)_2]OTf$, **17o**: 57% yield, 4:3 d.r., 39 h; **17q**: 45% yield, 1:1 d.r., 24 h). In these particular cases, the neutral Rh(I)-system is therefore preferred.

2.4. (3+1+2) cycloadditions of substituted aminocyclopropanes

Carbonylative (3+1+2) cycloadditions involving *trans*-1,2-disubstituted aminocyclopropanes can potentially deliver two different regioisomeric products depending on the selectivity of oxidative addition. Carbonylative cycloaddition of methyl-substituted cyclopropane **16r** using the neutral Rh(I)-system, yielded a 5:2 mixture of regioisomers **17r** and *iso*-**17r**, resulting from competing oxidative addition of the Rh(I)-catalyst into either of the proximal cyclopropane C–C bonds (Scheme 7). For the major regioisomer **17r**, which is derived from oxidative addition of the Rh(I)-catalyst into less hindered proximal cyclopropane C–C bond **a**, complete transfer of the cyclopropane stereochemistry of the major diastereomer of **16r** was observed. The regiochemistry of **17r** was determined by HMBC analysis, and the relative stereochemistry was corroborated by NOE experiments. Minor regioisomer *iso*-**17r** was obtained as a 1:1 mixture of diastereomers, perhaps due to epimerisation of the C6 stereocentre of the product under the reaction conditions. Using $[Rh(cod)_2]OTf$, a 76% yield of **17r**/*iso*-**17r** was achieved, and because the reaction temperature could be lowered to 120 °C (from 140 °C), selectivity for **17r** also increased (4:1 **17r**:*iso*-**17r** vs 5:2 **17r**:*iso*-**17r** at 140 °C using $[Rh(cod)Cl]_2$).[25] Notably, the cationic conditions resulted in a decrease in the reaction time from 108 to 38 h. For **16s**, where the steric bulk of the cyclopropane substituent is increased, selectivity for oxidative addition of the Rh(I)-catalyst into the less hindered proximal C–C bond **a** was increased and a 5:1 ratio of **17s**:*iso*-**17s** was obtained using the neutral system. Again, complete transfer of the cyclopropane stereochemistry to the major regioisomer **17s** was achieved. In this case, the cationic Rh-system increased both the reaction rate and regioselectivity, but only provided a modest improvement to the yield.

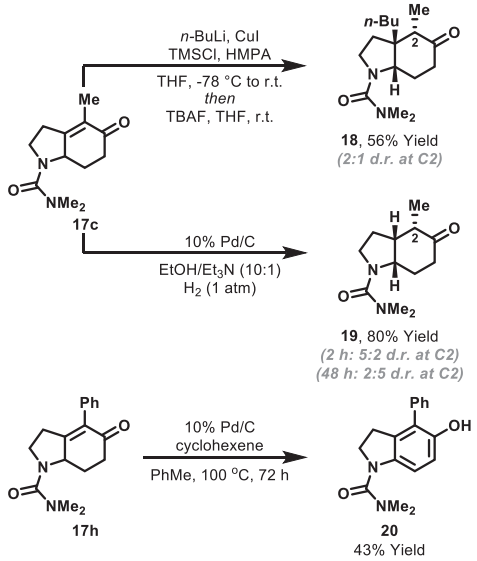


Scheme 7. Cycloadditions involving *trans*-1,2-disubstituted aminocyclopropanes.

2.5. Derivatisations of the cycloaddition products

The utility of the N-heterobicyclic enone products described here is outlined in Scheme 8. Addition of the Gilman-cuprate derived from *n*-BuLi to enone **17c** proceeded with excellent facial selectivity, in favour of the *cis*-ring junction, to deliver **18** in 56% yield.[26] The C2 stereocentre of **18** was not readily controlled and attempted epimerisation of this position under a variety of basic or acidic conditions did not enhance diastereopurity. Hydrogenation of **17c** (Pd/C, H_2) proceeded smoothly under mildly basic conditions (Et_3N) to deliver **19** in 80% yield. Again, the stereochemistry of the ring junction was readily controlled, presumably due to *syn*-addition of hydrogen to the less hindered face of **17c**, which delivers initially the depicted diastereomer of **19**. The C2 stereocentre of **19** was labile under the reaction conditions, such that prolonged reaction times (48 h vs 2 h) afforded predominantly the alternate (and presumably thermodynamically favoured) diastereomer (not depicted). Oxidative transformations are also feasible. For example, under transfer hydrogenative conditions (Pd/C, cyclohexene),[27] the

cyclohexenone moiety of **17h** underwent oxidation to provide phenol **20**, albeit in moderate yield.



Scheme 8. Synthetic manipulations of **17c** and **17h**.

3. Conclusions

In summary, we outline studies on the selective generation and trapping of amino-substituted rhodacyclopentanones. A range of N-directing groups are effective at directing oxidative addition of Lewis acidic Rh(I)-systems. This underpins an efficient and controlled approach to the key metallacyclic intermediates. For prototypical cycloaddition processes involving N-tethered alkynes, efficient oxidative addition requires a strongly donating urea directing group to outcompete the alkyne for coordination of the Rh(I)-catalyst. Subsequent dissociation of the urea at the stage of the rhodacyclopentanone is relatively facile and allows alkyne insertion to provide the heterocyclic target. A 'first generation' neutral Rh(I)-system is effective at promoting (3+1+2) cycloadditions, but suffers from low yields and long reaction times in cases where the alkyne component is electron deficient or bears a heterocyclic substituent. A 'second generation' cationic Rh(I)-system provides increased efficiencies in these cases and the success of this protocol is strongly dependent upon the use of PhCN as solvent. Current studies are focussed on the development of catalyst systems that tolerate synthetically versatile directing groups (e.g., carbamates) and allow expansion of the approach to asymmetric processes and 6-ring cyclisations.

4. Experimental section

4.1. General experimental

Starting materials sourced from commercial suppliers were used as received unless otherwise stated. Dry solvents, where necessary, were obtained by distillation using standard procedures or by passage through a column of anhydrous alumina using equipment from Anhydrous Engineering based on the Grubbs' design.[28] Melting points were determined using a Reichert melting point table and temperature controller and are uncorrected. Infrared spectra were recorded in the range 4000–600 cm^{-1} on a Perkin Elmer Spectrum either as neat films or solids compressed onto a diamond window. NMR spectra were recorded using either a Varian 400 MHz or JOEL ECS 400 MHz spectrometer. Chemical shifts are quoted in parts per million (ppm), coupling constants (J) are given in Hz to the nearest 0.5 Hz. Other abbreviations used are s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). ^1H and ^{13}C NMR spectra were referenced to the appropriate residual solvent peak. Mass spectra were determined by the University of Bristol mass spectrometry service by either electron impact (EI^+) or chemical ionization (CI^+) using a Fisons VG Analytical Autospec spectrometer, or by electrospray ionization (ESI^+) using a Brüker Daltonics Apex IV spectrometer. Experimental procedures and data for compounds that were reported in our earlier work are not included here.[2] X-ray crystallographic data for compounds **12**, **15b**, **15c**, **17b** and **17h** have been reported previously.[2,5]

4.2. General procedure for (3+1+2) carbonylative cycloadditions of aminocyclopropanes and alkynes using a neutral Rh(I)-catalyst system

An oven-dried reaction tube, fitted with a magnetic stirrer, was charged with $[Rh(cod)Cl]_2$ (3.75 mol %), $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (15 mol %) and Na_2SO_4 (20 mol %). The tube was fitted with a rubber septum and purged with argon. Aminocyclopropane substrate (100 mol %) in argon sparged anhydrous PhCN (0.07 M) was added via syringe. The reaction mixture was sparged with CO for ca. 2 min, then heated at the specified temperature (120–140 °C as noted) under a CO atmosphere (1 atm) until complete consumption of starting material was observed by thin layer chromatography (36–192 h as noted). The mixture was cooled to rt and purified directly by flash column chromatography, under the conditions noted, to afford the target cyclohexenone.

4.3. General procedure for (3+1+2) carbonylative cycloadditions of aminocyclopropanes and alkynes using a cationic Rh(I)-catalyst system

An oven-dried reaction tube, fitted with a magnetic stirrer, was charged with $[Rh(cod)_2]OTf$ (7.5 mol %) and $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (15 mol %). The tube was fitted with a rubber septum and purged with argon. Aminocyclopropane substrate (100 mol %) in argon sparged anhydrous PhCN (0.07 M) was added via syringe. The reaction mixture was sparged with CO for ca. 2 min, then heated at the specified temperature (120–130 °C as noted) under a CO atmosphere (1 atm) until complete consumption of starting material was observed by thin layer chromatography (3–48 h as noted). The mixture was cooled to rt, concentrated in vacuo and purified by flash column chromatography, under the conditions noted, to afford the target cyclohexenone.

4.4. Experimental procedures and data for new compounds

*4.4.1. N-Benzyl-N-cyclopropylbenzamide (**6b**).* To a solution of *N*-cyclopropylbenzamide[29] (1.00 g, 6.20 mmol) in anhydrous THF (12.4 mL) was added NaH (1.24 g, 31.0 mmol). The suspension was stirred at rt for 1 h and then benzyl bromide (3.7 mL, 31.0 mmol) was added dropwise over 5 min. The reaction mixture was stirred at rt for 16 h. The solution was cooled to 0 °C and then water (20 mL) and Et_2O (20 mL) were added. The layers were separated and the aqueous portion was further extracted with Et_2O (3×20 mL). The organic extracts were combined, washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (20% EtOAc/hexane) to afford the title compound **6b** (1.31 g, 84%) as a colourless oil; IR (neat): 1630, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.60–7.18 (m, 10H), 4.75 (s, 2H), 2.59 (tt, J=7.0, 4.0 Hz, 1H), 0.75–0.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz):

δ 172.5, 137.9, 137.3, 129.6, 128.6, 128.0, 127.3, 127.2, 50.7, 31.6, 9.9; HRMS: (ESI$^+$) calcd for $C_{17}H_{17}NONa$: 274.1208. Found $[M+Na]^+$: 274.1205.

*4.4.2. (E)-N-Benzyl-N-(prop-1-en-1-yl)benzamide (**7b**).* An oven-dried reaction tube, fitted with a magnetic stirrer, was charged with $[Rh(cod)_2]BF_4$ (11.0 mg, 0.0271 mmol) and PPh_3 (21.3 mg, 0.0811 mmol). The tube was fitted with a rubber septum and purged with argon. Amide **6b** (136 mg, 0.541 mmol) in argon sparged anhydrous toluene (5.4 mL) was added via syringe. The tube was sealed and the reaction mixture was heated at 140 °C for 4 h. The mixture was cooled to rt and concentrated in vacuo. The residue was purified by flash column chromatography (20% Et_2O/hexane) to afford the title compound **7b** (98 mg, 72%) as a colourless oil; IR (neat): 1636, 1397, 1372, 1318, 1284, 1148 cm^{-1}; ^{1}H NMR (CD_3CN, 400 MHz): δ 7.49–7.27 (m, 10H), 6.45 (br m, 1H), 5.06–4.98 (m, 3H), 1.66–1.35 (br m, 3H); ^{13}C NMR (CD_3CN, 100 MHz): δ 170.9, 137.0, 131.0, 130.7, 129.6, 129.4, 128.7, 127.9, 127.6, 108.1, 47.6, 15.4; *m/z* (CI$^+$) 105 (100%), 252 ($[M+H]^+$, 80%); HRMS: (CI$^+$) calcd for $C_{17}H_{18}NO$: 252.1388. Found $[M+H]^+$: 252.1380.

*4.4.3. (E)-N-Benzyl-4-methyl-N-(prop-1-en-1-yl)benzenesulfonamide (**7c**).* An oven-dried reaction tube, fitted with a magnetic stirrer, was charged with $[Rh(cod)_2]BF_4$ (11.0 mg, 0.0271 mmol) and PPh_3 (21.3 mg, 0.0811 mmol). The tube was fitted with a rubber septum and purged with argon. Sulfonamide **6c**[30] (163 mg, 0.541 mmol) in argon sparged anhydrous toluene (5.4 mL) was added via syringe. The tube was sealed and the reaction mixture was heated at 140 °C for 4 h. The reaction was cooled to rt and concentrated in vacuo. The residue was purified by flash column chromatography (10% Et_2O/hexane) to afford the title compound **7c** (104 mg, 64%) as a colourless oil; ^{1}H NMR (CD_3CN, 400 MHz): δ 7.71–7.67 (m, 2H), 7.37–7.35 (m, 2H), 7.32–7.21 (m, 5H), 6.55 (dq, *J*=13.5, 1.5 Hz, 1H), 4.75 (dq, *J*=13.5, 6.5 Hz, 1H), 4.45 (s, 2H), 2.39 (s, 3H), 1.48 (dd, *J*=6.5, 1.5 Hz, 3H); ^{13}C NMR (CD_3CN, 100 MHz): δ 145.3, 137.5, 136.9, 130.9, 129.5, 128.3, 128.0, 127.8, 127.3, 109.4, 50.2, 21.6, 15.3. The spectroscopic properties of this compound were consistent with the data available in the literature.[31]

*4.4.4. Monomeric rhodacyclopentanone complex (**14**).* To a solution of dimer **12** (11.0 mg, 0.0163 mmol) in CD_2Cl_2 (1 mL) in an NMR tube was added PPh_3 (8.5 mg, 0.0326 mmol). NMR analysis showed formation of the PPh_3 bound monomer **14**; ^{1}H NMR (CD_2Cl_2, 400 MHz): δ 7.69–7.64 (m, 6H), 7.44–7.35 (m, 9H), 5.28 (m, 1H), 3.96–3.86 (m, 2H), 2.96 (d, *J*=1.0 Hz, 3H), 2.46 (ddd, *J*=16.0, 14.0, 6.5 Hz, 1H), 2.38 (m, 1H), 2.12 (m, 1H), 1.86 (m, 1H), 1.08 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (CD_2Cl_2, 100 MHz): δ 231.9 (dd, *J*=27.5, 3.0 Hz, C**8**), 187.5 (dd, *J*=77.0, 11.5 Hz, C**9**), 165.3 (d, *J*=10.0 Hz, C**3**), 74.6 (dd, *J*=86.0, 20.0 Hz, C**5**), 65.4 (C**2**), 52.0 (d, *J*=6.0 Hz, C**7**), 35.1 (d, *J*=4.5 Hz, C**4**), 33.5 (C**6**), 14.9 (C**1**). Aromatic signals are excluded as characterisation by ^{13}C NMR was conducted after the addition of a second equivalent of PPh_3.

*4.4.5. Amide rhodacyclopentanone complex (**15a**).* *Di-μ*-chloro-tetracarbonyldirhodium (20.0 mg, 0.0514 mmol) and *N*-cyclopropyl-*N*-methylbenzamide[32] (0.4 mL) were stirred at 60 °C for 24 h under an atmosphere of N_2 and then cooled to rt. Hexane (1 mL) was added to complete precipitation of the metal complex and then the solvent was removed upon sedimentation of the metallacycle. The precipitate was washed with Et_2O (5×1 mL) and then dried in vacuo to afford metallacycle **15a** (28.4 mg, 75%) as a pale yellow solid; IR (neat): 2046, 2029, 1701, 1589, 1567, 1502, 1452, 1443, 1411 cm^{-1}; Metallacycle **15a** was poorly soluble in CD_2Cl_2, attempts to characterise the metallacycle by NMR produced extremely weak spectra. The metallacycle was recrystallised from CH_2Cl_2 to afford yellow crystals for characterisation by single crystal X-ray crystallography.[19]

*4.4.6. 1-Cyclopropyl-3,3-dimethyl-1-(4-(quinolin-3-yl)but-3-yn-1-yl)urea (**16k**).* An oven-dried reaction tube, fitted with a magnetic stirrer, was charged with $Pd(PPh_3)_4$ (38.6 mg, 0.0334 mmol) and CuI (12.7 mg, 0.0668 mmol). The tube was fitted with a rubber septum and purged with argon. A solution of **16m**[2] (300 mg, 1.67 mmol), 3-bromoquinoline (0.34 mL, 2.51 mmol) and Et_3N (0.70 mL, 5.01 mmol) in anhydrous DMF (3.3 mL) was sparged with argon and added to the reaction tube. The reaction was stirred at 60 °C for 16 h and then the mixture was cooled to rt and concentrated in vacuo. The residue was purified by flash column chromatography (5% MeOH/EtOAc) to afford the title compound **16k** (427 mg, 83%) as a pale yellow solid; mp 95–98 °C (CH_2Cl_2-hexane); IR (neat): 1619, 1488, 1441, 1400, 1361, 1339, 1249, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.86 (d, *J*=2.0 Hz, 1H), 8.17 (d, *J*=2.0 Hz, 1H), 8.08 (br d, *J*=8.5 Hz, 1H), 7.77 (dd, *J*=8.5, 1.0 Hz, 1H), 7.71 (ddd, *J*=8.5, 7.0, 1.0 Hz, 1H), 7.56 (ddd, *J*=8.5, 7.0, 1.0 Hz, 1H), 3.56 (t, *J*=7.0 Hz, 2H), 2.93 (s, 6H), 2.81–2.76 (m, 3H), 0.83–0.78 (m, 2H), 0.68–0.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.5, 152.3, 146.6, 138.1, 129.8, 129.3, 127.5, 127.3, 127.2, 117.8, 91.6, 79.0, 47.9, 37.9, 31.1, 19.4, 8.9; *m/z* (CI$^+$) 308 ($[M+H]^+$, 90%); HRMS: (CI$^+$) calcd for $C_{19}H_{22}N_3O$: 308.1763. Found $[M+H]^+$: 308.1760.

*4.4.7. 1-Cyclopropyl-3,3-dimethyl-1-(4-(thiophen-3-yl)but-3-yn-1-yl)urea (**16l**).* An oven-dried reaction tube, fitted with a magnetic stirrer, was charged with $Pd(PPh_3)_4$ (38.6 mg, 0.0334 mmol) and CuI (12.7 mg, 0.0668 mmol). The tube was fitted with a rubber septum and purged with argon. A solution of **16m**[2] (300 mg, 1.67 mmol), 3-bromothiophene (0.23 mL, 2.51 mmol) and Et_3N (0.70 mL, 5.01 mmol) in anhydrous DMF (3.3 mL) was sparged with argon and added to the reaction tube. The reaction was stirred at 60 °C for 18 h and then the mixture was cooled to rt and concentrated in vacuo. The residue was purified by flash column chromatography (50% EtOAc/hexane) to afford the title compound **16l** (310 mg, 71%) as a pale yellow oil; IR (neat): 2927, 1626, 1490, 1452, 1398, 1355, 1253, 1171, 1063 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 (dd, *J*=3.0, 1.0 Hz, 1H), 7.24 (dd, *J*=5.0, 3.0 Hz, 1H), 7.06 (dd, *J*=5.0, 1.0 Hz, 1H), 3.49 (t, *J*=7.0 Hz, 2H), 2.90 (s, 6H), 2.74 (tt, *J*=6.5, 4.0 Hz, 1H), 2.67 (t, *J*=7.0 Hz, 2H), 0.80–0.75 (m, 2H), 0.65–0.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.6, 129.9, 127.8, 125.1, 122.6, 87.4, 77.2, 48.0, 37.9, 30.9, 19.1, 8.9; *m/z* (CI$^+$) 263 ($[M+H]^+$, 100%); HRMS: (CI$^+$) calcd for $C_{14}H_{19}N_2OS$: 263.1218. Found $[M+H]^+$: 263.1212.

*4.4.8. Ethyl 5-(1-cyclopropyl-3,3-dimethylureido)pent-2-ynoate (**16n**).* To a solution of **16m**[2] (300 mg, 1.67 mmol) in THF (17 mL) at −78 °C was added *n*-BuLi (1.09 mL, 1.67 mmol, 1.54 M in hexanes) and the solution was stirred for 1 h under nitrogen. Ethyl chloroformate (0.32 mL, 3.34 mmol) was added and the reaction was slowly warmed to rt and stirred for 16 h. Satd aq NH_4Cl (30 mL) was added and the solution was extracted with EtOAc (3×30 mL). The organic extracts were combined, washed with brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (5% acetone/Et_2O) to afford the title compound **16n** (327 mg, 78%) as a yellow oil; IR (neat): 2235, 1706, 1630, 1492, 1399, 1364, 1247, 1067 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.21 (q, *J*=7.0 Hz, 2H), 3.47 (t, *J*=7.0 Hz, 2H), 2.91 (s, 6H), 2.73 (m, 1H), 2.61 (t, *J*=7.0 Hz, 2H), 1.30 (t, *J*=7.0 Hz, 3H), 0.80–0.75 (m, 2H), 0.64–0.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.1, 153.6, 87.1, 74.1, 61.8, 47.0, 37.8, 31.5, 18.6, 14.0, 9.0; HRMS: (ESI$^+$) calcd for $C_{13}H_{20}N_2O_3Na$: 275.1363. Found $[M+Na]^+$: 275.1366.

*4.4.9. 4-(Methoxymethyl)-N,N-dimethyl-5-oxo-2,3,5,6,7,7a-hexahydro-1H-indole-1-carboxamide (**17f**).* *General procedure A*: Aminocyclopropane **16f**[2] (40 mg, 0.18 mmol) was employed and the

reaction was stirred for 84 h at 130 °C. Flash column chromatography (100% EtOAc) afforded the title compound **17f** (26 mg, 58%) as an off white solid. *General procedure B*: Aminocyclopropane **16f** (40 mg, 0.18 mmol) was employed and the reaction was stirred for 16 h at 130 °C. Flash column chromatography (100% EtOAc) afforded the title compound **17f** (33 mg, 73%) as an off white solid. The spectroscopic data for **17f** was consistent with that reported in our previous publication.[2]

*4.4.10. 4-(4-Chlorophenyl)-N,N-dimethyl-5-oxo-2,3,5,6,7,7a-hexahydro-1H-indole-1-carboxamide (**17i**). General procedure A*: Aminocyclopropane **16i**[2] (52 mg, 0.18 mmol) was employed and the reaction was stirred for 108 h at 130 °C. Flash column chromatography (100% EtOAc) afforded the title compound **17i** (29 mg, 52%) as a pale yellow oil. *General procedure B*: Aminocyclopropane **16i** (52 mg, 0.18 mmol) was employed and the reaction was stirred for 32 h at 130 °C. Flash column chromatography (100% EtOAc) afforded the title compound **17i** (50 mg, 88%) as a pale yellow oil. The spectroscopic data for **17i** was consistent with that reported in our previous publication.[2]

*4.4.11. N,N-Dimethyl-5-oxo-4-(4-(trifluoromethyl)phenyl)-2,3,5,6,7,7a-hexahydro-1H-indole-1-carboxamide (**17j**). General procedure A*: Aminocyclopropane **16j**[2] (58 mg, 0.18 mmol) was employed and the reaction was stirred for 132 h at 130 °C. Flash column chromatography (100% EtOAc) afforded the title compound **17j** (19 mg, 30%) as a yellow oil. *General procedure B*: Aminocyclopropane **16j** (58 mg, 0.18 mmol) was employed and the reaction was stirred for 32 h at 130 °C. Flash column chromatography (100% EtOAc) afforded the title compound **17j** (52 mg, 82%) as a yellow oil. The spectroscopic data for **17j** was consistent with that reported in our previous publication.[2]

*4.4.12. N,N-Dimethyl-5-oxo-4-(quinolin-3-yl)-2,3,5,6,7,7a-hexahydro-1H-indole-1-carboxamide (**17k**). General procedure A*: Aminocyclopropane **16k** (55 mg, 0.18 mmol) was employed and the reaction was stirred for 192 h at 130 °C. Flash column chromatography (5% MeOH/EtOAc) afforded the title compound **17k** (9 mg, 15%) as a yellow oil. *General procedure B*: In a modification to the general procedure, 10 mol% $[Rh(cod)_2]OTf$ and 20 mol% $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ were used. Aminocyclopropane **16k** (55 mg, 0.18 mmol) was employed and the reaction was stirred for 48 h at 130 °C. Flash column chromatography (5% MeOH/EtOAc) afforded the title compound **17k** (38 mg, 63%) as a yellow oil; IR (neat): 2943, 1670, 1620, 1493, 1456, 1392, 1360, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.69 (d, J=2.0 Hz, 1H), 8.09 (br d, J=8.5 Hz, 1H), 7.98 (d, J=2.0 Hz, 1H), 7.81 (m, 1H), 7.71 (ddd, J=8.5, 7.0, 1.5 Hz, 1H), 7.55 (ddd, J=8.5, 7.0, 1.5 Hz, 1H), 4.95 (m, 1H), 3.54–3.50 (m, 2H), 2.97–2.88 (m, 7H), 2.78–2.57 (m, 4H), 1.83 (dddd, J=14.0, 12.5, 11.5, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.7, 163.5, 163.0, 151.3, 147.2, 137.2, 131.0, 130.0, 129.2, 128.1, 127.6, 127.4, 127.0, 58.8, 48.7, 38.1, 36.3, 31.3, 30.0; *m/z* (CI^+) 336 ($[M+H]^+$, 60%); HRMS: (CI^+) calcd for $C_{20}H_{22}N_3O_2$: 336.1712. Found $[M+H]^+$: 336.1701.

*4.4.13. N,N-Dimethyl-5-oxo-4-(thiophen-3-yl)-2,3,5,6,7,7a-hexahydro-1H-indole-1-carboxamide (**17l**). General procedure A*: Aminocyclopropane **16l** (47 mg, 0.18 mmol) was employed and the reaction was stirred for 144 h at 130 °C. Flash column chromatography (100% EtOAc) afforded the title compound **17l** (15 mg, 29%) as a pale yellow oil. *General procedure B*: Aminocyclopropane **16l** (47 mg, 0.18 mmol) was employed and the reaction was stirred for 18 h at 130 °C. Flash column chromatography (100% EtOAc) afforded the title compound **17l** (45 mg, 87%) as a pale yellow oil; IR (neat): 2932, 2880, 1668, 1624, 1496, 1388, 1356, 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32 (dd, J=5.0, 3.0 Hz, 1H), 7.22 (dd, J=3.0, 1.0 Hz, 1H), 7.05 (dd, J=5.0, 1.0 Hz, 1H), 4.87 (m, 1H), 3.54–3.50 (m, 2H), 2.89 (s, 6H), 2.85–2.52 (m, 5H), 1.76 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.6, 162.9, 161.0, 134.0, 129.0, 125.2, 124.5, 58.6, 48.6, 38.0, 36.3, 31.4, 29.7; *m/z* (CI^+) 291 ($[M+H]^+$, 100%), 319 (10%); HRMS: (CI^+) calcd for $C_{15}H_{19}N_2O_2S$: 291.1167. Found $[M+H]^+$: 291.1170.

*4.4.14. N,N-Dimethyl-5-oxo-2,3,5,6,7,7a-hexahydro-1H-indole-1-carboxamide (**17m**). General procedure A*: Aminocyclopropane **16m**[2] (32 mg, 0.18 mmol) was employed and the reaction was stirred for 84 h at 130 °C. Flash column chromatography (100% EtOAc) afforded the title compound **17m** (4 mg, 10%) as a yellow oil. *General procedure B*: Aminocyclopropane **16m** (32 mg, 0.18 mmol) was employed and the reaction was stirred for 3 h at 130 °C. Flash column chromatography (100% EtOAc) afforded the title compound **17m** (8.5 mg, 23%) as a yellow oil; IR (neat): 1667, 1630, 1496, 1390, 1265, 1188 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.95 (br dd, J=2.5, 2.5 Hz, 1H), 4.70 (m, 1H), 3.59 (ddd, J=10.0, 10.0, 6.5 Hz, 1H), 3.51 (ddd, J=10.0, 10.0, 2.5 Hz, 1H), 2.89 (s, 6H), 2.81 (m, 1H), 2.64 (m, 1H), 2.56–2.38 (m, 3H), 1.64 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.8, 166.1, 163.0, 122.5, 57.8, 48.5, 37.9, 35.8, 31.7, 30.3; *m/z* (CI^+) 209 ($[M+H]^+$, 100%), 237 (10%); HRMS: (CI^+) calcd for $C_{11}H_{17}N_2O_2$: 209.1290. Found $[M+H]^+$: 209.1294.

4.4.15. (2S,7aS*)- and (2R*,7aS*)-N,N,2,4-Tetramethyl-5-oxo-2,3,5,6,7,7a-hexahydro-1H-indole-1-carboxamide (**17o**). General procedure A*: Aminocyclopropane **16o**[2] (37 mg, 0.18 mmol) was employed and the reaction was stirred for 156 h at 120 °C. Flash column chromatography (100% EtOAc) afforded the title compound **17o** (30 mg, 71%) as a yellow oil. Cyclohexanone **17o** was obtained as a mixture of diastereomers (3:1 d.r.). Under standard reaction conditions at 130 °C, no starting material remained after 60 h (55% yield). *General procedure B*: Aminocyclopropane **16o** (37 mg, 0.18 mmol) was employed and the reaction was stirred for 39 h at 130 °C. Flash column chromatography (100% EtOAc) afforded the title compound **17o** (24 mg, 57%) as a yellow oil. Cyclohexanone **17o** was obtained as a mixture of diastereomers (4:3 d.r.). The spectroscopic data for **17o** was consistent with that reported in our previous publication.[2]

4.4.16. (2R,7aS*)- and (2S*,7aS*)-N,N,4-Trimethyl-5-oxo-2-phenyl-2,3,5,6,7,7a-hexahydro-1H-indole-1-carboxamide (**17q**). General procedure A*: Aminocyclopropane **16q**[2] (48 mg, 0.18 mmol) was employed and the reaction was stirred for 36 h at 125 °C. Flash column chromatography (100% EtOAc) afforded the title compound **17q** (33 mg, 61%) as a yellow oil. Cyclohexanone **17q** was obtained as a mixture of diastereomers (5:2 d.r.). *General procedure B*: Aminocyclopropane **16q** (48 mg, 0.18 mmol) was employed and the reaction was stirred for 24 h at 130 °C. Flash column chromatography (100% EtOAc) afforded the title compound **17q** (24 mg, 45%) as a yellow oil. Cyclohexanone **17q** was obtained as a mixture of diastereomers (1:1 d.r.). The spectroscopic data for **17q** was consistent with that reported in our previous publication.[2]

4.4.17. (7R,7aS*)-N,N,4,7-Tetramethyl-5-oxo-2,3,5,6,7,7a-hexahydro-1H-indole-1-carboxamide (**17r**) and N,N,4,6-tetramethyl-5-oxo-2,3,5,6,7,7a-hexahydro-1H-indole-1-carboxamide (iso-**17r**). General procedure A*: Aminocyclopropane **16r** (37 mg, 0.18 mmol, 6:1 d.r.) was employed and the reaction was stirred for 108 h at 140 °C. Flash column chromatography (100% EtOAc) afforded a mixture of regioisomers **17r** and *iso*-**17r** (**17r**:*iso*-**17r**, 5:2) (21 mg, 50%) as a yellow oil. Cyclohexenones **17r** and *iso*-**17r** were obtained as a mixture of diastereomers (**17r**: 20:1 d.r., *iso*-**17r**: 1:1 d.r.). *General procedure B*: Aminocyclopropane **16r** (37 mg, 0.18 mmol, 6:1 d.r.) was employed and the reaction was stirred for 38 h at 120 °C. Flash column chromatography (100% EtOAc) afforded a mixture of

regioisomers **17r** and *iso*-**17r** (**17r**:*iso*-**17r**, 4:1) (32 mg, 76%) as a yellow oil. Cyclohexenone **17r** was obtained as a single diastereomer (>20:1 d.r.), *iso*-**17r** was obtained as a mixture of diastereomers (3:1 d.r.). The spectroscopic data for **17r** and *iso*-**17r** was consistent with that reported in our previous publication.[2]

4.4.18. (7R,7aS*)-7-Butyl-N,N,4-trimethyl-5-oxo-2,3,5,6,7,7a-hexahydro-1H-indole-1-carboxamide (**17s**) and 6-butyl-N,N,4-trimethyl-5-oxo-2,3,5,6,7,7a-hexahydro-1H-indole-1-carboxamide (iso-**17s**). General procedure A*: Aminocyclopropane **16s** (45 mg, 0.18 mmol, >20:1 d.r.) was employed and the reaction was stirred for 168 h at 140 °C. Flash column chromatography (50% Et_2O/toluene) afforded a mixture of regioisomers **17s** and *iso*-**17s** (**17s**:*iso*-**17s**, 5:1) (20 mg, 41%) as a yellow oil. Cyclohexenones **17s** and *iso*-**17s** were obtained as a mixture of diastereomers (**17s**: 20:1 d.r., *iso*-**17s**: 1:1 d.r.). *General procedure B*: Aminocyclopropane **16s** (45 mg, 0.18 mmol, >20:1 d.r.) was employed and the reaction was stirred for 40 h at 130 °C. Flash column chromatography (50% Et_2O/toluene) afforded a mixture of regioisomers **17s** and *iso*-**17s** (**17s**:*iso*-**17s**, 8:1) (22 mg, 45%) as a yellow oil. Cyclohexenone **17s** was obtained as a single diastereomer (>20:1 d.r.), *iso*-**17s** was obtained as a mixture of diastereomers (2:1 d.r.). The spectroscopic data for **17s** and *iso*-**17s** was consistent with that reported in our previous publication.[2]

*4.4.19. 3a-Butyl-N,N,4-trimethyl-5-oxooctahydro-1H-indole-1-carboxamide (**18**).* To a solution of CuI (257 mg, 1.35 mmol) in THF (1.5 mL) at 0 °C was added *n*-BuLi (1.70 mL, 2.70 mmol, 1.59 M in hexanes) and the solution was stirred for 10 min. The reaction mixture was cooled to −78 °C and chlorotrimethylsilane (85 μL, 0.675 mmol) and hexamethylphosphoramide (0.16 mL, 0.90 mmol) were added sequentially. The reaction mixture was stirred for 5 min and then **17c**[2] (100 mg, 0.45 mmol) in THF (2 mL) was added. The solution was warmed to rt and stirred for 90 min. Satd aq NH_4Cl solution (20 mL) and Et_2O (30 mL) were added. The organic portion was separated and washed with satd aq NH_4Cl solution (10 mL) and water (2×10 mL). The organic portion was dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in THF (2 mL), tetra-*n*-butylammonium fluoride (0.9 mL, 0.90 mmol, 1 M in THF) was added and the solution was stirred for 20 h. Water (20 mL) was added and the solution was extracted with Et_2O (3×10 mL). The organic portions were combined, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (70% EtOAc/hexane) to afford the title compound **18** (70 mg, 56%) as a colourless oil. Cyclohexanone **18** was obtained as a mixture of diastereomers A and B (2:1, A:B); IR (neat): 2932, 1710, 1633, 1455, 1385, 1353, 1201 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 4.13 (dd, *J*=4.5, 3.0 Hz, 1H, A), 3.89 (dd, *J*=4.0, 4.0 Hz, 1H, B), 3.63 (ddd, *J*=10.0, 10.0, 7.0 Hz, 1H, B), 3.27 (ddd, *J*=10.0, 9.0, 2.5 Hz, 1H, B), 3.20–3.09 (m, 2H, A), 2.89 (s, 6H, B), 2.79 (s, 6H, A), 2.60 (q, *J*=7.0 Hz, 1H, B), 2.55 (q, *J*=6.5 Hz, 1H, A), 2.46 (ddd, *J*=14.0, 12.0, 6.0 Hz, 1H, B), 2.37 (m, 1H, B), 2.27–2.24 (m, 2H, A), 2.17–2.10 (m, 1H (A) and 1H (B)) 2.05 (m, 1H, A), 1.94 (m, 1H, B), 1.83 (m, 1H, B), 1.74 (m, 1H, B), 1.68 (ddd, *J*=13.0, 7.0, 6.0 Hz, 1H, A), 1.53–1.46 (m, 3H, A), 1.41–1.15 (m, 4H (A) and 6H (B)), 1.00 (d, *J*=7.0 Hz, 3H, B), 0.98 (d, *J*=6.5 Hz, 3H, A), 0.91 (t, *J*=7.0 Hz, 3H, A), 0.85 (t, *J*=7.0 Hz, 3H, B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 215.3 (A), 213.8 (B), 164.2 (B), 163.2 (A), 60.3 (A), 60.1 (B), 51.3 (B), 49.5 (A), 48.2 (B), 47.9 (A), 47.2 (B), 47.1 (A), 38.9 (A), 38.1 (A), 38.0 (B), 36.3 (B), 35.1 (A), 34.1 (B), 33.5 (A), 32.2 (B), 26.7 (A), 26.2 (B), 25.8 (B), 24.0 (A), 23.6 (B), 23.4 (A), 14.1 (A), 14.0 (B), 8.8 (B), 8.5 (A); *m/z* (CI^+) 72 (30%), 281 ($[M+H]^+$, 100%); HRMS: (CI^+) calcd for $C_{16}H_{29}N_2O_2$: 281.2229. Found $[M+H]^+$: 281.2223.

*4.4.20. N,N,4-Trimethyl-5-oxooctahydro-1H-indole-1-carboxamide (**19**).* To a three-necked round-bottom flask containing Pd on carbon (20.0 mg, 0.0188 mmol, 10% w/w) under N_2 was added EtOH (2 mL) and the solution was bubbled with H_2 for 10 min. **17c**[2] (30.0 mg, 0.135 mmol) in EtOH (0.7 mL) and Et_3N (0.3 mL) was added and the reaction was stirred under an atmosphere of H_2 for 2 h. The solution was filtered through Celite® and concentrated in vacuo. The residue was purified by flash column chromatography (100% EtOAc) to afford the title compound **19** (24 mg, 80%) as a colourless oil. Cyclohexanone **19** was obtained as a mixture of diastereomers A and B (5:2, A:B); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.50 (m, 1H, B), 4.12 (ddd, *J*=5.5, 5.5, 5.5 Hz, 1H, A), 3.62 (ddd, *J*=10.0, 10.0, 6.5 Hz, 1H, A), 3.40–3.28 (m, 1H (A) and 1H (B)), 3.13 (ddd, *J*=10.0, 7.5, 7.5 Hz, 1H, B), 2.87 (s, 6H, A), 2.81–2.69 (m, 8H, B), 2.43 (m, 1H, A), 2.36–1.85 (m, 6H (A) and 5H (B)), 1.81 (m, 1H, A), 1.51 (m, 1H, B), 1.07 (d, *J*=6.5 Hz, 3H, A), 1.01 (d, *J*=6.5 Hz, 3H, B); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 214.0 (B), 213.7 (A), 163.8 (A), 163.4 (B), 57.0 (A), 56.0 (B), 48.9 (A), 48.2 (B), 46.5 (A), 44.1 (A), 43.5 (2 signals, B), 38.4 (B), 38.1 (A), 36.5 (B), 35.9 (A), 30.5 (A), 27.5 (A), 27.1 (B), 26.3 (B), 13.2 (A), 11.8 (B); *m/z* (CI^+) 72 (100%), 224 ($[M+H]^+$, 30%); HRMS: (CI^+) calcd for $C_{12}H_{20}N_2O_2$: 224.1525. Found $[M+H]^+$: 224.1530.

*4.4.21. 5-Hydroxy-N,N-dimethyl-4-phenylindoline-1-carboxamide (**20**).* To a solution of Pd on carbon (17.0 mg, 0.016 mmol, 10% w/w) and cyclohexene (0.11 mL, 1.06 mmol) in toluene (2 mL) under N_2 was added a solution of **17h**[2] (30.0 mg, 0.106 mmol) in toluene (2 mL). The reaction mixture was heated to 100 °C for 72 h and then cooled to rt and filtered through Celite®. The solution was concentrated in vacuo and purified by flash column chromatography (50% EtOAc/hexane) to afford the title compound **20** (13 mg, 43%) as a white solid; IR (neat): 3204, 2395, 1619, 1472, 1455, 1429, 1389, 1255 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz): δ 7.43–7.29 (m, 5H), 6.84 (d, *J*=8.5 Hz, 1H), 6.73 (d, *J*=8.5 Hz, 1H), 3.82 (t, *J*=8.0 Hz, 2H), 2.95 (s, 6H), 2.84 (t, *J*=8.0 Hz, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 162.7, 150.7, 137.9 (2 signals), 133.1, 130.9, 129.1, 128.0, 127.9, 114.9 (2 signals), 52.1, 38.4, 29.5; *m/z* (CI^+) 72 (30%), 283 ($[M+H]^+$, 100%); HRMS: (CI^+) calcd for $C_{17}H_{19}N_2O_2$: 283.1447. Found $[M+H]^+$: 283.1443.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.08.052.

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19. X-ray structures of **15b**/**c** have been reported previously (see Ref. 5). CCDC 1415293 contains the crystallographic data for **15a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
20. For a review, see Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197–257.
21. We have also studied the use of PhCN as an additive (10–150 mol %) in 1,2-DCB. Reaction rates and yields improved as the amount of PhCN was increased but isolated yields of **17c** remained below 50%.
22. For studies that delineate the donor-acceptor properties of nitrile ligands in manganese-carbonyl complexes, see Herberhold, M.; Brabetz, H. *Chem. Ber.* **1970**, *103*, 3909–3917.
23. A 56% yield of **17c** was obtained after 68 h using 2.5 mol % $[Rh(cod)_2]OTf$ and 5 mol % $P(3,5\text{-}(CF_3)_2C_6H_3)_3$. Even though cationic systems provide greatly accelerated rates at 130 °C we have been unable to obtain satisfactory results at significantly lower reaction temperatures. For example, we obtained only a 50% yield of **17c** after 132 h when the conditions outlined in Table 4, Entry 6 were run at 110 °C.
24. Using 7.5 mol % $[Rh(cod)_2]OTf$ and 15 mol % $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ a 45% yield of **17k** was obtained.
25. At 130 °C $[Rh(cod)_2]OTf$ gives lower selectivity in a shorter reaction time (3:1 **17r**:*iso*-**17r**, 73% yield, 20 h).
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