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Double Gold-Catalysed Annulation of Indoles by Enynones

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Abstract: The gold-catalysed double functionalisation of indoles is presented. Enynones are used to annulate indoles *via* a double sodium tetrachloroaurate-catalysed process involving a mixture of C–H activation and alkyne activation modes of promotion. Good yields for the formation of medicinally relevant [6,5,7]-tricyclic indoles are realised.

Keywords: cascade reactions; catalysis; diversity; gold; indoles

Introduction

Indoles are an extensive and important family of biologically active molecules.[1] The indole nucleus plays a key role in mammalian neurochemistry in the form of the neurotransmitter serotonin and is therefore pivotal to a large number of physiological functions. Additionally, indoles and indole-derived compounds are found in an extraordinary range of secondary natural product metabolites with wide-ranging associated biological activities.[2,3] Thirdly, the indole skeleton has been incorporated into a large number of medicinal chemistry designs and clinical products and as such has been viewed as a privileged structure.[4,5] When considered together, it is therefore understandable why indoles remain an area of intense synthetic exploration,[6] both in terms of *de novo* syntheses[7] but also in the elaboration of pre-existing indole frameworks.[8]

Three structurally related indoles (**1**–**3**, Figure 1), recently reported in the medicinal chemistry literature with potent biological activity, have attracted our interest due to the presence of a shared [6,5,7]-fused tricyclic indole core. Indole **1** displays high potency and excellent oral bioavailability in mouse model tumour xenografts, acting as an aurora kinase inhibitor.[9]

Carboxamide **2** acts as a potent and selective inhibitor of the deacetylase, SIRT1 **2**.[10] This amide represents the most active SIRT1 inhibitor reported to date and with a favourable ADME profile, has been suggested as a lead towards therapeutics. Additionally, indole **3** has been reported as a potent and selective fatty-acid binding protein (FABP) inhibitor.[11] In each instance, the specified [6,5,7]-core offered maximum biological activity in their respective assays in comparison with the [6,5,6]- and [6,5,5]-fused tricyclic homologues.

Accordingly, it is reasonable to suggest that this [6,5,7] indole core displays significant promise in medicinal drug-discovery contexts and would benefit from future exploration. It is noteworthy that the [6,5,7]-indole core in **1**–**3** was constructed through a classical Fischer indole synthesis and therefore accessed from restricted chemical space. With a clear medicinal rationale, we reasoned that novel and flexible approaches to such [6,5,7]-tricyclic indoles might open new areas of chemical space for exploration in a small-molecule discovery context. In addition, a number of natural products with impressive biological activity exist which feature this [6,5,7]-tricyclic core. For example, actinophyllic acid,[12] the ambiguines[13] and the ervatamine-silicine alkaloids[14] all feature this key indole structural unit.

Results and Discussion

Building on our Brønsted acid-catalysed annulation of indoles[15] by divinyl ketones we have sought to expand the scope of such indole-focussed annulations. With this in mind, we chose to consider structurally related ketonic double electrophiles, such as enyn-

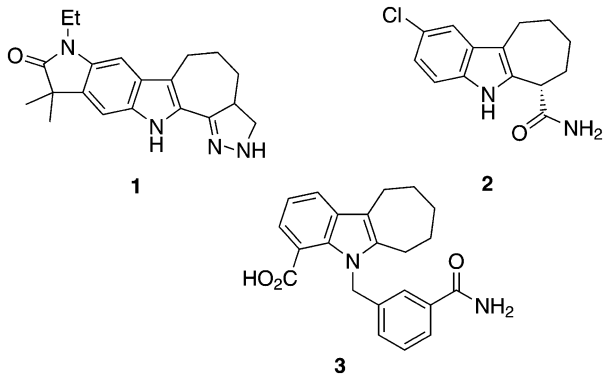


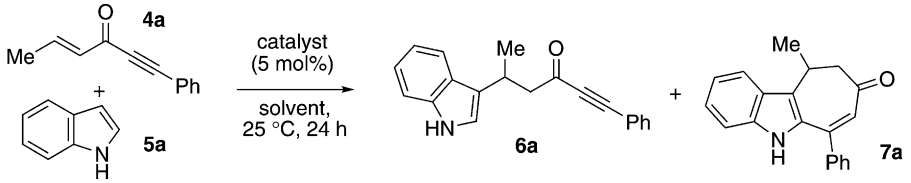
Figure 1. Medicinally active indoles containing a [6,5,7]-fused tricyclic unit.

ones, with a view to rapidly forming new functionalised tricyclic indole structures.[16,17] An initial examination was conducted with ketone **4a** which was reacted with indole in dichloromethane in the presence of the previously successful strong Brønsted acid promoter, 2,4-dinitrobenzenesulfonic acid (Table 1).

A clean *inter*molecular enone Friedel–Crafts reaction occurred, however, no annulation was observed. A range of Lewis acid catalysts, including typical π-acidic metals were subsequently examined yet none were successful in forming tricycle **7a** (Table 1). Metals studied included Fe(III), Pt(II), Cu(I), Pd(II) and Au(I) catalyst systems (Table 1, entries 2–8). The sole exception was the readily available Au(III) catalyst, $NaAuCl_4{\cdot}2H_2O$ (entry 9) offering 22% conversion after 24 h.[18] Subsequent solvent optimisation revealed a marked improvement in reaction efficiency on choosing acetonitrile (entries 9–14). In this initial system, 2 mol% loading was found to be adequate with full conversion observed after 4 h (entry 16). The intermediacy of indole **6a** in this cascade was further supported by *in situ* reaction monitoring by ^{1}H NMR (Figure 2).[19] This experiment confirms the presence of **6a** (20%) before the observable formation of tricycle **7a**. Additionally, isolated **6a** cleanly and quantitatively converts to **7a** under identical reaction conditions.

The majority of Au-catalysed indole cascades are performed in a non-convergent fashion, with reactive functionality attached to the indole core prior to an Au-promoted cascade or cyclisation. We reasoned that suitable discovery reactions for the synthesis of new indoles comprising medium-sized rings should maximise molecular divergency, synthetic convergency and seek to form two C–C bonds as part of a one-pot cascade. An inspection of the literature reveals

Table 1. Metal catalyst screen.



Entry	Catalyst	Solvent	**4a**:**6a**:**7a** [%][a]	Yield **7a** [%]
1	DNsOH[b]	CH_2Cl_2	0:100:0	–
2	$FeCl_3{\cdot}6H_2O$	CH_2Cl_2	25:75:0	–
3	$PtCl_2$	CH_2Cl_2	90:10:0	–
4	CuOTf	CH_2Cl_2	30:70:0	–
5	$PdCl_2$	CH_2Cl_2	83:17:0	–
6	$Pd(PPh_3)_2Cl_2$	CH_2Cl_2	12:88:0	–
7	$AuPPh_3Cl$	CH_2Cl_2	100:0:0	–
8	$AuPPh_3Cl$[c]	CH_2Cl_2	100:0:0	–
9	$NaAuCl_4{\cdot}2H_2O$	CH_2Cl_2	33:45:22	–
10	$NaAuCl_4{\cdot}2H_2O$	PhMe	50:49:1	–
11	$NaAuCl_4{\cdot}2H_2O$	Et_2O	40:30:30	–
12	$NaAuCl_4{\cdot}2H_2O$	DMF	35:65:0	–
13	$NaAuCl_4{\cdot}2H_2O$	EtOH	0:38:62	–
14	$NaAuCl_4{\cdot}2H_2O$	MeCN	0:0:100	96
15	$NaAuCl_4{\cdot}2H_2O$[d]	MeCN	0:0:100	99
16	$NaAuCl_4{\cdot}2H_2O$[d]	MeCN[e]	0:0:100	98

[a] Determined by ^{1}H NMR analysis of crude reaction mixture.
[b] DNsOH = 2,4-dinitrobenzenesulfonic acid.
[c] 5 mol% $AgSbF_6$ additive used.
[d] 2 mol% catalyst used.
[e] Reaction conducted for 4 h.

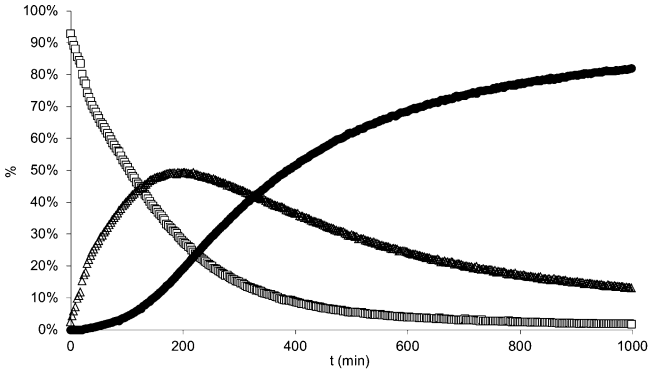
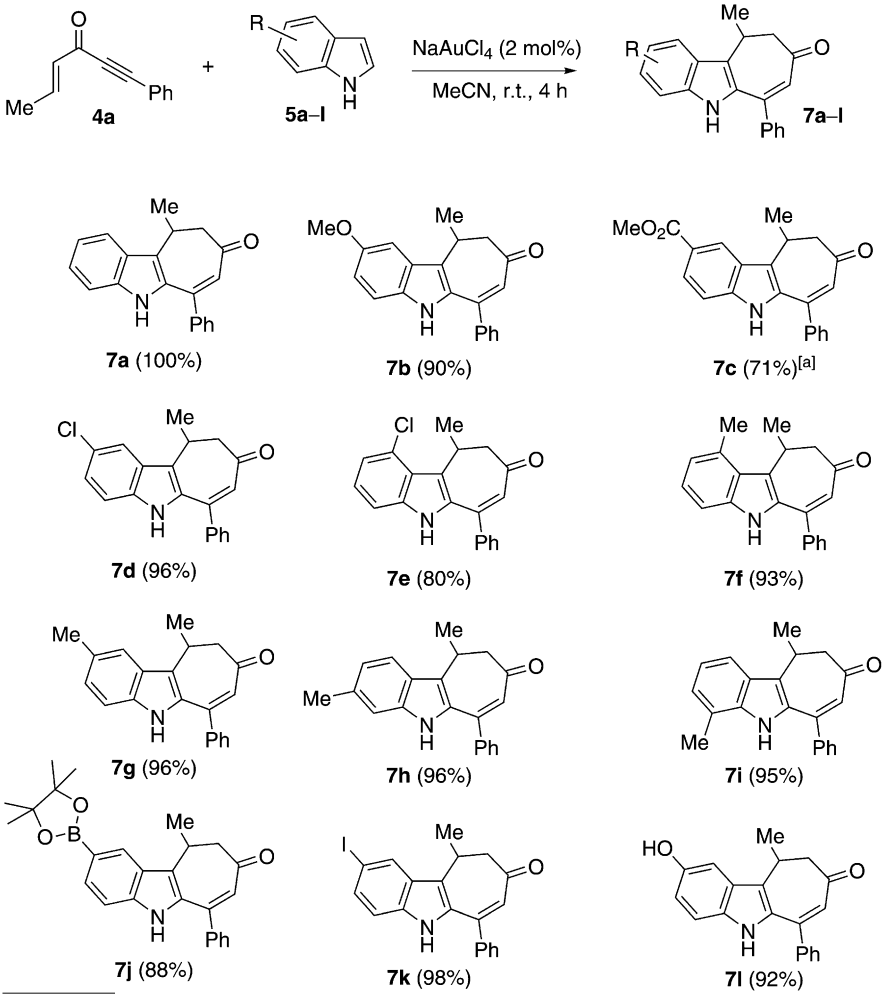


Figure 2. ^{1}H NMR monitoring of the tandem cascade reaction (CD_3CN at 20 °C; 500 MHz). □ = **4a**, △ = **6a**, ■ = **7a**.

that this strategy is uncommon.[20] The clean reaction of these enynone double electrophiles with indoles contrasts to the complex synthetic outcomes reported by Hashmi when an enynone was reacted with a furan.[16a]

A range of indoles has been examined with a view to demonstrating flexibility and diversity (Scheme 3). The system is compatible with electron-rich (**7b** and **7k**) and electron-deficient (**7c**–**e**) indoles. The indole annulation is unaffected by substitution on the benzenoid fragment (**7f**–**i**) as gauged by a range of methylindole regioisomers. In particular, the boronate ester and iodide systems (**7j** and **7k**) are expected to offer flexibility for subsequent synthetic elaboration by employing late-stage diversity strategies. The formation of **7l** is also noteworthy in a context of protecting group-free synthesis as neither the indole N–H or O–H bonds require protection for a clean annulation reaction to occur.[21]

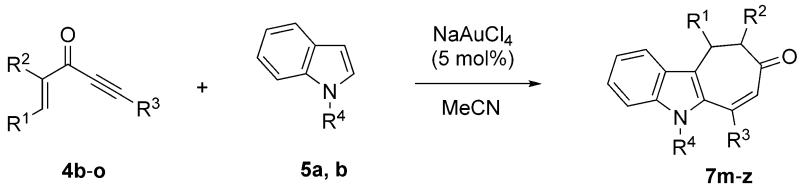
The modularity and ease of substrate synthesis has allowed for the ready examination of substrate scope (Table 2). Accordingly, this annulation shows a good level of structural scope with respect to the enynone.



[a] Reaction conducted for 24 h.

Scheme 1. Indole scope.

Table 2. Scope of the enynone in cascade reactions.



Entry	R^1	R^2	R^3	R^4	Time [h]	Temperature [°C]	Yield [%]
1	Me	H	4-MeC_6H_4 (**4b**)	H (**5a**)	6	23	98 (**7m**)
2	Me	H	4-$OMeC_6H_4$ (**4c**)	H	24	23	82 (**7n**)
3	Me	H	4-$CF_3C_6H_4$ (**4d**)	H	16	23	73 (**7o**)
4	Ph	H	Ph (**4e**)	H	24	82	77 (**7p**)
5	Ph	H	Ph	H	3	82	100[b]
6	Me	H	2-naphthyl (**4f**)	H	8	23	81 (**7q**)
7	Ph	H	2-naphthyl (**4g**)	H	24	23	97 (**7r**)
8	Ph	H	*n*-Bu (**4h**)	H	72	82	47 (**7s**)
9	Ph	H	*n*-Bu	H	18	82	69[b,c]
10	Me	H	*n*-Bu (**4i**)	H	24	82	79 (**7t**)
11	Me	H	*n*-Bu	H	4	82	82[b]
12	H	H	*n*-Bu (**4j**)	H	96	82	60 (**7u**)
13	H	H	Ph (**4k**)	H	12	23	99 (**7v**)
14	*i*-Pr	H	Ph (**4l**)	H	18	23	72 (**7w**)
15	H	Me	Ph (**4m**)	H	8	23	76 (**7x**)
16	Me	Me	Ph(**4n**)	H	8	82	15 (**7y**)[a]
17	Me	Me	Ph	H	18	23	73[a,b]
18	Ph	H	H (**4o**)	H	18	82	0
19	Me	H	Ph (**4a**)	Me (**5b**)	20	23	71 (**7z**)

[a] 4:1 *syn/anti* based on ^1H NMR analysis of crude reaction mixture.
[b] 2 equiv. of H_2O added.
[c] Based on recovery of starting material.

The cascade is general with respect to the enynone double electrophile, accommodating both electron-rich and electron-deficient arylacetylene moieties (entries 1–3). It is possible to construct substrates bearing alkyl or aryl groups on both the enone or ynone fragments, revealing some reactivity trends (entries 1, 4, 8, 10). Alkyl substitution upon the enone and aryl substitution upon the ynone fragment appear to offer optimal substrate reactivity. Monosubstituted enones can be accommodated without incidence (Entry 12), however, terminal alkynes would appear incompatible in this reaction (entry 18), possibly due to the formation of a catalytically inactive Au-acetylide.[22] In contrast, substitution at the indole N-centre is compatible (entry 19). It is worth mentioning that reaction monitoring studies have led us to the observation that small quantites of H_2O (2 equivalents) as an additive can have a pronounced beneficial effect (entries 5, 9, 11, 17). Whilst the reason for this improvement is not entirely clear, we feel that this observation may be linked to an indole auration processes during this cascade (*vide infra*). Finally, the cascade sequence proceeds with substrates containing a trisubstituted enone with tricycle **7y** being formed in good yield with 4:1 *cis*-diastereoselectivity (entry 16). This diastereoselectivity was confirmed by single crystal X-ray diffraction analysis of the major isomer (Figure 3).

The annulation under discussion was initially developed using $NaAuCl_4{\cdot}2H_2O$ for pragmatic reasons as this catalyst is a bench-stable, robust catalyst. However, we felt this salt was acting as a pre-catalyst for $AuCl_3$.[18] To probe this, the annulation reaction between **4a** and **5a** was repeated with $AuCl_3$ and found to promote the reaction with improved reaction efficiency (Scheme 2).

The diastereoselectivity observed in the formation of **7y** is important for two key reasons. Firstly, we believe this diastereoselectivity is kinetic in origin, as judged by attempts to epimerise diastereomerically pure *cis*-**7y** (Scheme 3). Exposure of *cis*-**7y** to acidic (2,4-dinitrobenzenesulfonic acid) or basic (DBU) conditions led to an observed erosion in diastereomeric ratio to 4:1 and 20:1, respectively. However, re-exposure of *cis*-**7y** to 5 mol% $NaAuCl_4{\cdot}2H_2O$ resulted in no loss of diastereomeric purity.

Secondly, the final level of annulation diastereoselectivity is controlled by the diastereoselectivity of the initial *inter*molecular Au-catalysed Friedel–Crafts reaction as isolated mono-addition product **6b** is formed with the same level of diastereoselectivity [Eq. (1),

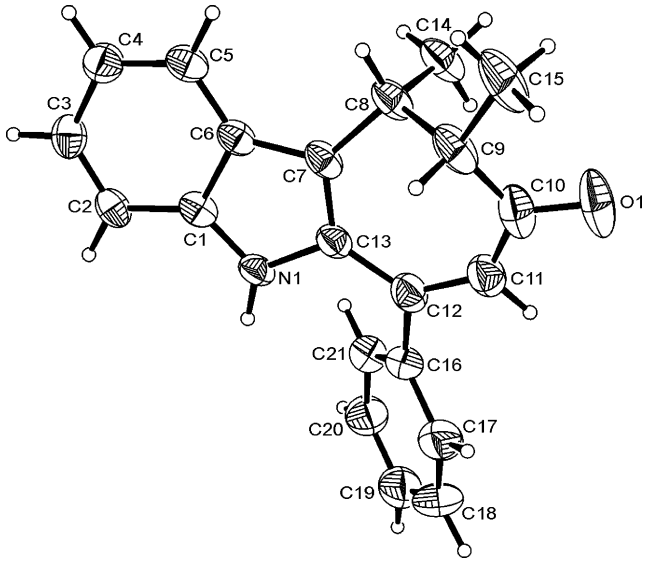
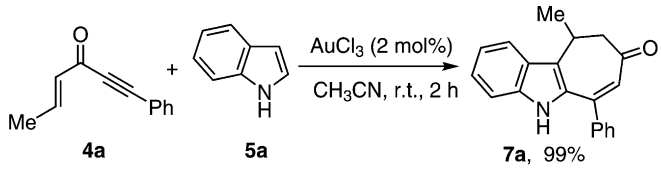
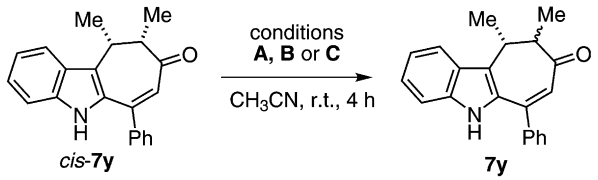


Figure 3. ORTEP Plot of XRD analysis of **7y** (25% probability). Structure is deposited with the CCDC (CCDC 834635; these data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif).



Scheme 2. $AuCl_3$ catalysis of the annulation reaction.



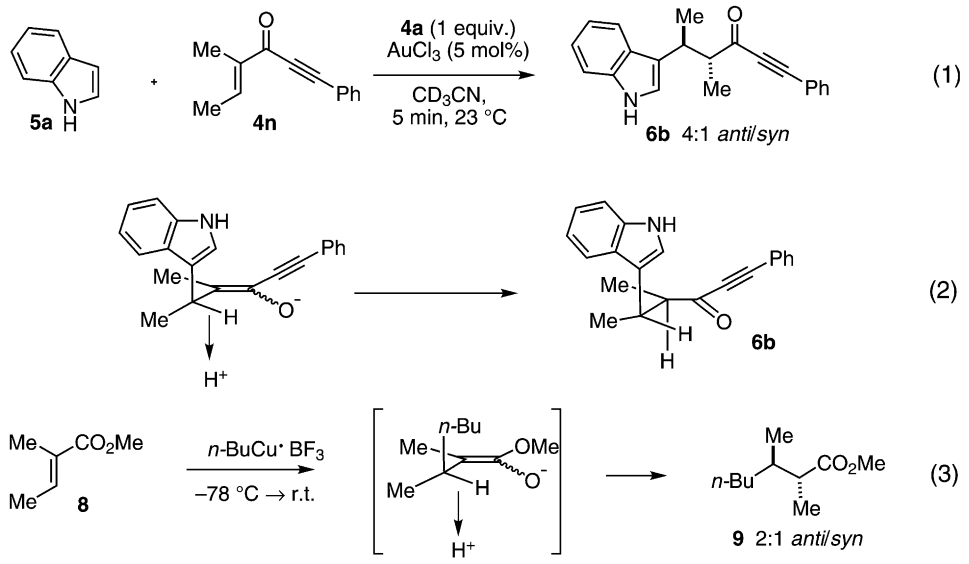
Scheme 3. Probing the possibility of product equilibration.

Scheme 4]. We believe that this stereoselectivity is governed by kinetic protonation of an enolate formed from the addition of the indole nucleophile to **4n** [Eq. (2), Scheme 4]. This scenario mirrors that understood for cuprate addition to α,β-unsaturated carbonyl electrophiles. Significantly, a similar outcome has been reported by Yamamoto where the addition of organocopper reagents to methyl tiglate forms ester **9** in a 2:1 *anti/syn* diastereomeric mixture [Eq. (3), Scheme 4].[23] Key to this understanding was the stereoselective protonation of an oxygen-bound copper enolate.

Friedel–Crafts reactions are highly atom efficient reactions. In this instance, it may be expected that the indolyl C-2 and C-3 protons ultimately become incorporated at the ketonic α-methylene positions. To probe this matter, C-2 and C-3 deuterated analogues of *N*-methylindole have been synthesised and examined (Scheme 5). The *N*-methyl group was chosen to obviate facile H→D exchange during these studies. Unexpectedly, no deuterium incorporation was observed when either labelled indole was reacted with **4a**, as gauged by ^{1}H NMR analysis of the reaction products. In both instances, the reaction was found to proceed without incidence, when compared to the original reaction (Table 2, entry 19).

A possible explanation for the disappearance of the deuterium from the product would be a scrambling of the single deuterium through all positions of **7z** and therefore unidentifiable by ^{1}H NMR integration. However, this was ruled out by HR-MS analysis which was identical to that of product **7z** obtained from the original reaction. We have gone to considerable efforts to try and determine the whereabouts of the indolyl deuterium. We hypothesised that a facile D→H exchange process was occurring. In an attempt to remove adventitious sources of protons, this reaction has been attempted in dried CD_3CN (Table 3, entry 1), however, no deuterium incorporation into **7z** is observed. In the presence of 4 Å molecular sieves, either with (entry 3) or without (entry 2) deuterated solvent one sees no transfer of the indolyl deuterium. Similarly, utilisation of silylated glassware[24,25] (entries 4 and 5) or Teflon reaction vessels (entry 6) results in no D-incorporation into **7z**. Indeed, all scenarios result in a reaction outcome which is relatively invariable with respect to final yield (28–44%) over extended reaction times.

With no transfer of deuterium from indole nucleophile, either from the C-3 or C-2 positions to the annulated product, *at any position*, we wished to examine the behaviour of these labelled indoles in the presence of gold catalyst in the absence of an external electrophile. The contrast between the C-3 and C-2 labelled indoles was strong with the C-3 labelled indole immediately losing a significant level of deuterium after 13 min. In the time it took to add the catalyst and record a ^{1}H NMR spectrum, the amount of observable adventitious H_2O present in the NMR solvent had exchanged both available protons at the C-3 indole position [Eq. (1), Scheme 6]. In contrast, the C-2 position was found to be robust under the same NMR conditions for an extended period [Eq. (2)]. In an attempt to prepare a labelled indole model which more closely resembled an intermediate ynone, C-2-^{2}H-**5b** was reacted, under comparable $AuCl_3$ catalysis in CD_3CN, with enone **10** to afford the Friedel–



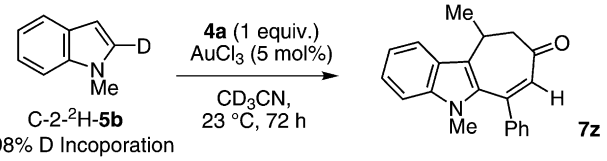
Scheme 4. Significance of diastereoselectivity from an initial *inter*molecular Friedel–Crafts reaction.

Crafts product in 66% yield [Eq. (3), Scheme 6]. However, C-2-^{2}H-**11** was now isolated with a diminished level of ^{2}H-labelling (72% by ^{1}H NMR integration). When C-2-^{2}H-**11** was resubjected to only the $AuCl_3$ catalyst in CD_3CN, a continual erosion of labelling was observed [Scheme 6, Eq. (4)].

These observations demonstrate the rapid Au(III)-catalysed scrambling of these indole nucleophiles. The catalyst aurates the more nucleophilic C-3 indole position and must readily react with electrophiles present in the reaction system, such as protons from adventitious H_2O or an enone. This is further highlighted by the robust nature of the label in the C-2-^{2}H-**5b**, however, when auration is precluded at the C-3 position by substitution, then C-2 auration becomes apparent. This therefore suggests the presence of both C-3 and C-2 auration processes that are operative during this transformation.

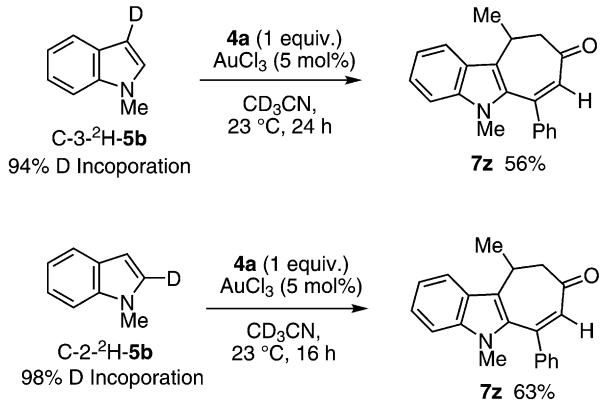
With deuterated *N*-methylindoles offering interesting data but ultimately limited for reaction monitoring by ^{1}H NMR, a substrate was sought which would still offer some real-time information regarding the cyclisation step. We chose to return to an N–H indole, the structural moiety which had been demonstrated to be compatible with NMR monitoring (i.e., Figure 2). It was anticipated that a slow cyclisation may allow an observable population of a C-2 auration complex to form in solution. Enynone **4i** had been a demonstrably difficult substrate, therefore, ynone **6d** was synthesised [Eq. (1), Scheme 7]. Subjection of ynone **6d** to an equivalent of $NaAuCl_4{\cdot}2H_2O$ led to no observable change in the ^{1}H NMR spectrum at

Table 3. Attempted deuterium incorporation.

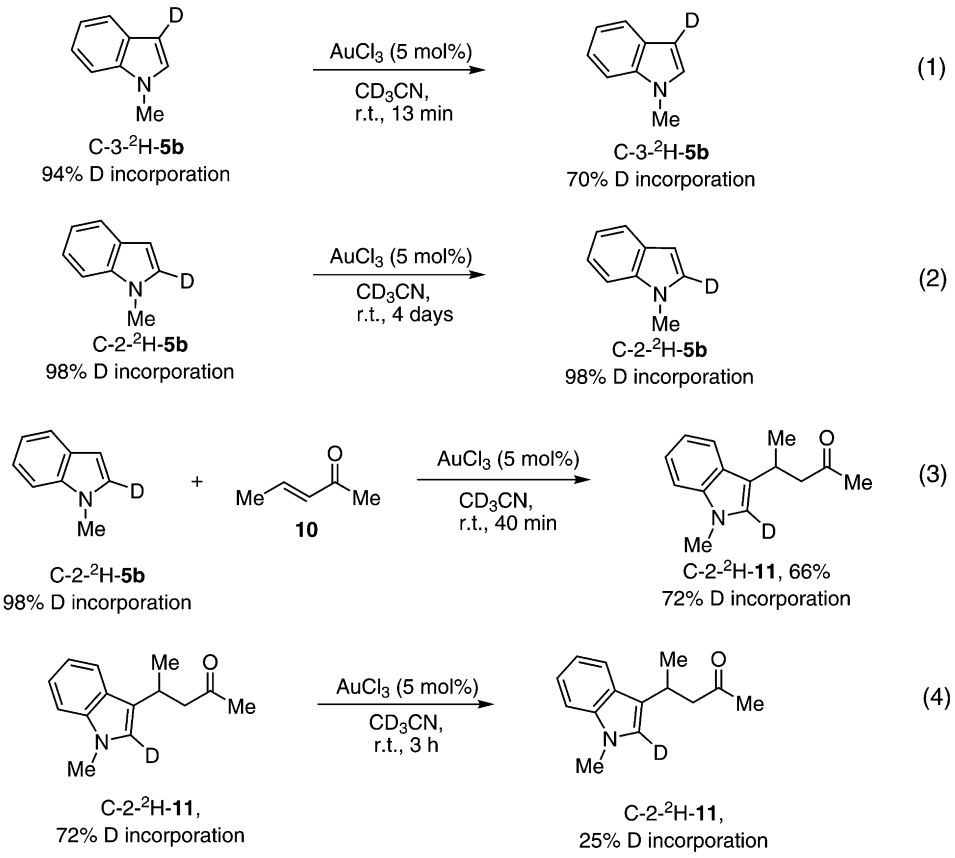


Entry	Solvent	Deuterium Incoporation [%][a]	Yield of **7z** [%]
1	CD_3CN	0	44
2	CH_3CN	0	36[b]
3	CD_3CN	0	26[b]
4	CH_3CN	0	30[c]
5	CD_3CN	0	28[c]
6	CD_3CN	0	34[d]

[a] Assayed by integration of ^{1}H NMR.
[b] Reaction conducted for 24 h.
[c] Reaction conducted with 4 Å molecular sieves.
[d] Reaction conducted in a silylated reaction vessel.
[e] Reaction conducted in a Teflon vessel



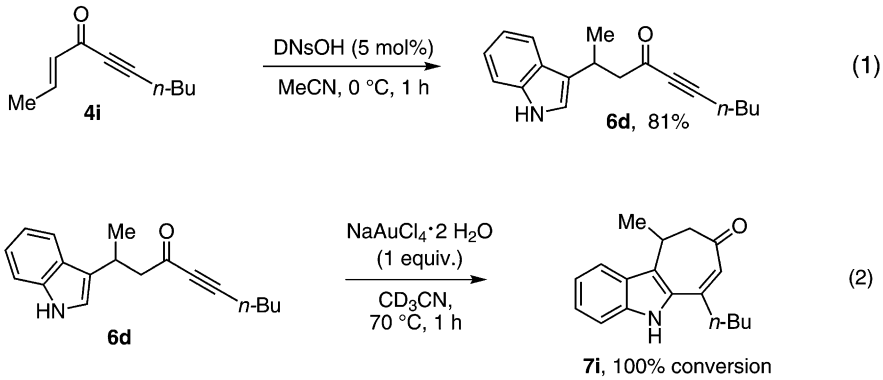
Scheme 5. Reactivity of deuterated indoles.



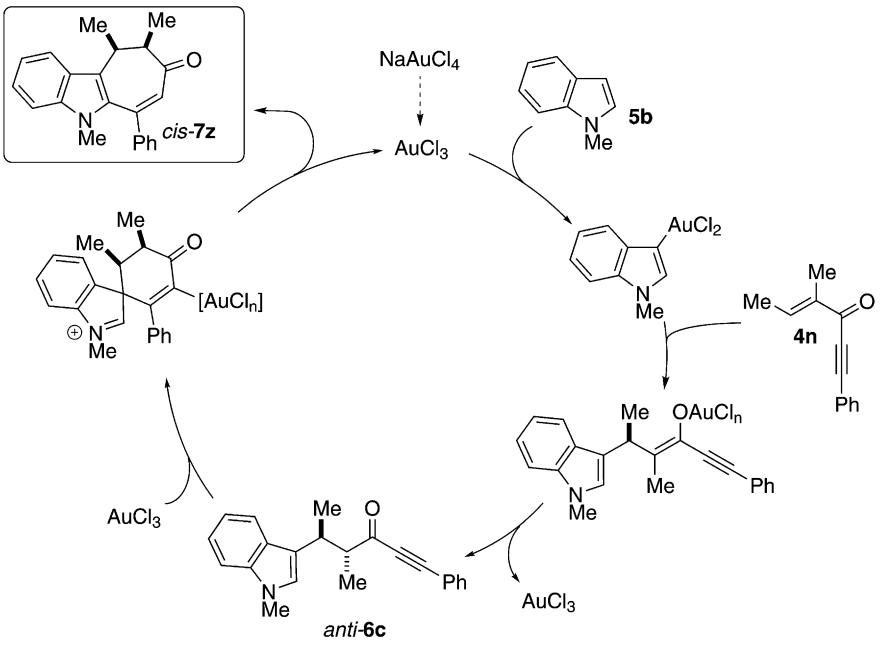
Scheme 6. Deuterium-scrambling studies.

room temperature. However, heating at 70 °C resulted in the rapid formation of **7i** with complete conversion.

Unfortunately, limited resolution of peaks, specifically the indole C-2 proton, has not allowed an unequivocal observation of C-2 auration, although an improvement in reaction efficiency is strong when compared with the case in which a 5% catalyst loading is used. The improvement in reaction efficiency is expected to be assisted by an increased loading of the $NaAuCl_4 \cdot 2H_2O$ catalyst. However, a more subtle issue is the concurrent increase in the loading of H_2O, derived from the hydrated gold catalyst. Having already observed a distinct stalling of reaction efficiency when dried solvent was used, we hypothesised that water is in fact crucial to this process and that the increased water loading was actually the key. Accordingly, we chose to re-examine difficult substrates, now with the addition of 2 equivalents of water in conjunction with catalytic loadings of $NaAuCl_4 \cdot 2H_2O$. A significant improvement in reaction efficiency is observed when comparing reactions with and without



Scheme 7. Attempted ^1H NMR observation of C-2 auration.



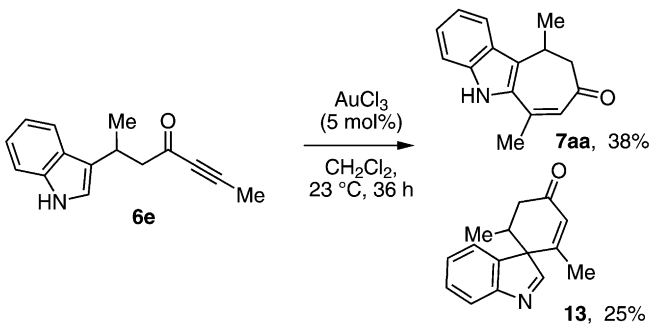
Scheme 8. Proposed catalytic cycle.

the water additive (Table 2 *cf.* entries 4+5, *cf.* entries 8+9, *cf.* 10+11, entries 16+17).

We have therefore incorporated the observations into the proposed mechanism by adapting the mechanism proposed by Arcadi for Au-catalysed enone Friedel–Crafts reactions, namely the C–H activation of the indole nucleus (exemplified using **4n** and **5b**, Scheme 8). Initial indole C-3 auration and subsequent reaction with the enone moiety, generates indole **6a**.[25] The diastereoselectivity is dictated by a kinetic enolate protonation.

A second indole auration, now at C-2, initiates an *intra*molecular addition of the indole to the alkyne, leading to **7z** and the regeneration of the Au(III) catalyst (Scheme 8). In addition, the *intra*molecular attack of indole upon the activated alkyne requires an entropically favoured *intra*molecular scenario as Reetz has demonstrated that Au(III) catalysts will not promote the addition of nucleophilic arenes to internal propiolate electrophiles.[26] We believe that the ring-closure reaction proceeds through an initial *spiro*-cyclisation, as precedented by Echavarren.[19b] The possibility that this annulation could proceed *via* a *spiro*indolene intermediate is supported by an observation made in our laboratory early in our studies of indole cascade chemistry, initially overlooked, whereby annulated and *spiro*-indolene were isolated (**7aa** and **13**, respectively, Scheme 9). This reaction had been conducted in CH_2Cl_2 solvent and using a substrate bearing a propyne fragment. With the hindsight of the extensive studies presented in this report, the combination of an alkyl-substituted ynone moiety and a solvent other than MeCN would combine to retard the overall annulation sequence and in turn lead to a recoverable population of a *spiro* intermediate.

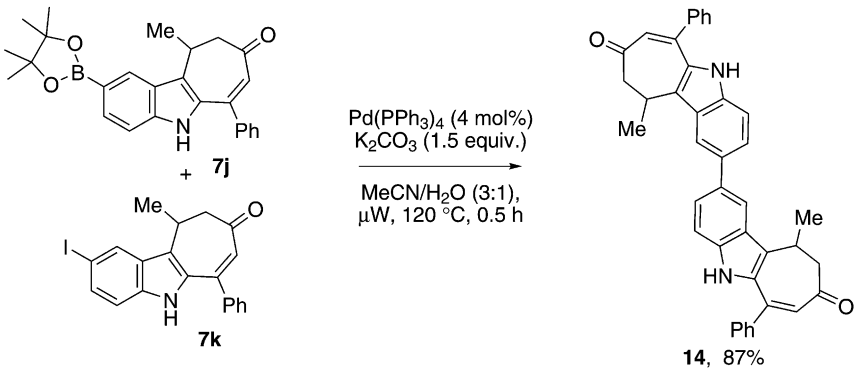
The ability to execute subsequent late-stage diversity transformations is demonstrated by the coupling of boronate **7j** and iodide **7k** in a Pd-catalyzed Suzuki reaction to form dimer **14** (Scheme 10).



Scheme 9. Observation of *spiro*-products.

Conclusions

In conclusion, a highly efficient Au-catalysed cascade process is presented offering access to medicinally relevant [6,5,7]-tricyclic indoles. The reaction is operationally simple, structurally modular and open to subsequent late stage diversity operations. Studies towards absolute stereocontrol and application to target-orientated synthesis are currently ongoing in our laboratory.



Scheme 10. Demonstration of late-stage diversity through Suzuki couplings.

Experimental Section

Synthesis of 4b

To a stirred solution of 1-ethynyl-4-methylbenzene (1.02 mL, 8.0 mmol, 1 equiv.) was added *n*-BuLi (1.6 M in hexane, 5.50 mL, 8.8 mmol, 1.1 equiv.) dropwise and stirred for a further 10 min. Crotonaldehyde (663 μL, 8.0 mmol, 1 equiv.) in THF (5 mL) was added and the reaction stirred for 4 h. Saturated NH_4Cl solution (100 mL) was added and subsequently extracted with EtOAc (3×100 mL), washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under vacuum to afford the crude residue. This crude reaction product was dissolved in CH_2Cl_2 (150 mL) before the addition of MnO_2 (17.39 g, 200 mmol, 25 equiv.), stirred for a further 24 h before filtering through a pad of Celite and solvent removed under vacuum. Enynone **4b** was purified by flash chromatography (8:1 petroleum ether/EtOAc) to afford a yellow oil; yield: 893 mg (60%). FT-IR (thin film): ν_{max} = 3035.4, 2964.5, 2909.0, 2203.0, 1641.1, 1615.5, 1603.5, 1509.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41 (2H, app d, *J* = 8.2 Hz), 7.28–7.14 (1H, m), 7.11 (2H, app d, *J* = 8.2 Hz), 6.18 (1H, dq, *J* = 15.7, 1.6 Hz), 2.31 (3H, s), 1.94 (3H, dd, *J* = 6.9, 1.6 Hz); ^{13}C NMR (75 MHz): δ = 178.5, 149.2, 141.2, 134.0, 132.9, 129.4, 117.1, 91.7, 86.1, 21.7, 18.5. HR-MS (ESI, +ve): *m/z* = 207.0782 $(M+Na)^+$, calcd. for $C_{13}H_{12}ONa$: 207.0786.

Synthesis of 7a

To solid indole **5a** (24.6 mg, 0.21 mmol, 1.05 equiv.) in a round-bottomed flask was added an acetonitrile (1 mL) solution of enynone **4a** (24.6 mg, 0.21 mmol, 1.05 equiv.) followed by a solution of sodium tetrachloroaurate(III) hydrate (0.05 equiv.) in acetonitrile (1 mL). This mixture was stirred at room temperature for 4 h, before filtering through celite and was then concentrated under vacuum. Subsequent purification by flash column chromatography (8:1 Pet/EtOAc) afforded tricycle **7a** as a yellow solid; yield: 57 mg (100%); mp 170–171 °C. FT-IR (thin film): ν_{max} = 3057.3, 2956.7, 2924.5, 1707.5, 1623.3 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.73 (1H, br), 7.70–7.17 (8H, m), 6.20 (1H, s), 3.61–3.38 (1H, m), 3.19 (1H, dd, *J* = 14.4, 3.1 Hz), 2.97 (1H, dd, *J* = 14.4, 1.8 Hz), 1.37 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.9, 145.2, 139.7, 135.5, 129.9, 129.3, 129.0, 128.9, 128.5, 126.8, 126.2, 124.7, 120.4, 119.5, 111.4, 48.2, 25.0, 17.1; HR-MS (ESI, +ve): *m/z* = 310.1606 $(M+Na)^+$, calcd. for $C_{20}H_{17}ONNa$: 310.1208.

Synthesis of 7p

To solid indole **5a** (42.9 mg, 0.42 mmol, 1.05 equiv.) in a round-bottom flask was added an acetonitrile solution (1 mL) of (*E*)-1,5-diphenylpent-1-en-4-yn-3-one **4e** (94 mg, 0.4 mmol, 1 equiv.) followed by a solution sodium tetrachloroaurate(III) hydrate (8 mg, 0.02 mmol, 0.05 equiv.) in acetonitrile (1 mL). Water (0.84 mmol, 2 equiv.) was finally added before heating the reaction mixture to reflux for 3 h. The reaction was cooled before filtering through Celite and concentration under vacuum. Purification was achieved by flash chromatography (8:1 petroleum ether/EtOAc) which afforded **7p** as a yellow oil; yield: 140 mg (100%). FTI-R (thin film): ν_{max} = 3057.5, 2952.2, 1624.3, 1536.6 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.90 (1H, br), 7.53–7.46 (6H, m), 7.32–7.11 (8H, m), 6.12 (1H, d, *J* = 1.3 Hz), 4.86–4.84 (1H, m), 3.52 (1H, dd, *J* = 14.9, 6.0 Hz), 3.43 (1H, dd, *J* = 14.9, 3.4 Hz). ^{13}C NMR (125 MHz, CDCl3) δ: 198.9, 145.0, 139.8, 139.6, 135.6, 131.2, 129.4 (×2), 129.0, 128.6 (×2), 127.4 (×2), 126.8, 124.8, 122.9, 120.7, 119.8, 111.4, 48.7, 35.3; HR-MS (ESI, +ve): *m/z* = 350.1554 $(M+H)^+$. calcd. for $C_{25}H_{20}NO$: 350.1544.

Synthesis of 14

To a microwave vial was added **7j** (62 mg, 0.15 mmol, 1 equiv.), **7k** (62 mg, 0.15 mmol, 1 equiv.), K_2CO_3 (31 mg, 0.225 mmol, 1.5 equiv.) and $Pd(PPh_3)_4$ (7 mg, 0.006 mmol, 0.04 equiv.). Acetonitrile (3 mL) and water (1 mL) were added and the vessel was sealed, followed by sonication and purging with nitrogen concurrently for 10 min. The reaction mixture was then subjected to microwave irradiation at 120 °C for 30 min. The reaction mixture was then passed through a plug of silica gel before concentration under vacuum. Purification was achieved by flash chromatography (8:1 petroleum ether /EtOAc) which afforded **14** as a yellow oil; yield: 75 mg (87%). FT-IR (thin film): ν_{max} = 3353.4, 2960.1, 1630.0, 1583.4, 1565.5, 1531.6 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.93–7.87 (2H, m), 7.79 (2H, s), 7.63–7.57 (10H, m), 7.36 (2H, app. d, *J* = 8.5 Hz), 6.22 (2H, d, *J* = 1.5 Hz), 3.80 (2H, m), 3.23 (2H, dt, *J* = 14.5, 2.9 Hz), 3.00 (2H, ddd, *J* = 14.5, 6.5, 1.1 Hz), 1.41 (3H, d, *J* = 7.3 Hz), 1.40 (3H, d, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 199.8, 145.0, 139.7, 134.9, 134.8, 130.6, 129.3, 129.0 (×2),

128.5, 127.4, 126.4, 125.1, 117.6, 111.7, 48.2, 25.0, 17.1; HR-MS (ESI, +ve): $m/z = 573.2535$ $(M+H)^+$, calcd. for $C_{40}H_{33}N_2O_2$: 573.2542.

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