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Divergent synthesis of indenoisoquinolines and indenoisochromenes by rhodium-catalysed cyclocondensation of *N*-substituted benzamides with 2-diazoindenediones†

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An atom-and step-economical method for the synthesis of indenoisoquinolines as a scaffold of topoisomerase I inhibitors was developed using rhodium-catalysed cyclocondensation of *N*-monosubstituted benzamides with 2-diazoindenedione, where the unexpected indenoisochromenes were obtained in high yields with high selectivity through rhodium-catalysed cyclocondensation of *N*-*tert*-butylbenzamides with 2-diazoindenediones (**2**). These results indicated that the kinds of substituents on a nitrogen atom of the starting benzamides controlled which product—indenoisoquinolines or indenoisochromenes—could be obtained selectively by the tuning of rhodium catalyst systems under optimal reaction conditions. Namely, indeno[1,2-*c*]isoquinolin-5,11-diones (**3** and **5**) were formed directly from 1,3-dicarbonyl intermediates by intramolecular nucleophilic attack of an amide nitrogen atom on a carbonyl group in 1,3-dicarbonyl intermediates, followed by dehydration, whereas indeno[1,2-*c*]isochromene-5,11-diones (**7**) were obtained from enol tautomers of 1,3-dicarbonyl intermediates by intramolecular nucleophilic attack of a hydroxyl group on an amide carbonyl group together with liberation of an amine.

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Introduction

Recently, considerable attention has been focused on the transition-metal complex-catalysed synthesis of fused heterocycles in one step.[1] Among the various possibilities, we focused our attention on the development of atom- and step-economical methods for the synthesis of indenoisoquinolines, which are highly fused *N*-heterocyclic compounds bearing a planar tetracyclic structure. The topoisomerase I (Top I) inhibitory activity of indenoisoquinolines[2] was proved by a COMPARE analysis,[3] which also showed better pharmacokinetic features and stability than those of the known Top I inhibitors such as naturally occurring camptothecins (CPTs) (Fig. 1).[4] Indeed, two water-soluble CPTs, irinotecan (LMP400) and topotecan, have been used for clinical cancer therapy to date.[5] However, CPTs have serious drawbacks, such as significant dose-limiting toxicity and instability of the DNA binding complex after removal of CPTs.[4]

Top I inhibition activity, DNA interaction, and cytotoxicity of indenoisoquinolines in human cancer cell cultures have been individually evaluated and reported by Cushman,[6] Kiem,[7] and Ryckebusch;[8] these studies proved the biological and pharmacological importance of indenoisoquinolines.[9] However, only multi-step syntheses of indenoisoquinolines have been reported so far through the simple combination of well-known traditional reagents and reactions.[10] Recently, transition-metal complex-catalysed approaches have emerged as alternative methods for the synthesis of indenoisoquinolines. Representative examples are summarised in Scheme 1: The ammonia-based four-component Ugi reaction, followed by a Cu(II)-catalysed annulation reaction to give indeno[1,2-*c*]isoquinoline-5,11-diones (Scheme 1a);[11] the Pd(II)-catalysed coupling reaction of amino acids with 2-(2-bromophenyl)-1*H*-indene-1,3(2*H*)-diones, generated from the modified Dieckmann condensation

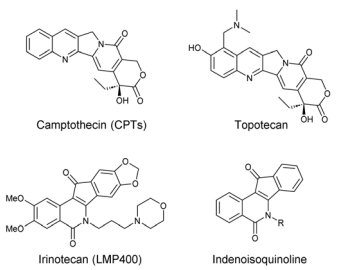

Fig. 1 Structures of camptothecin, irinotecan, topotecan, and indenoisoquinoline.

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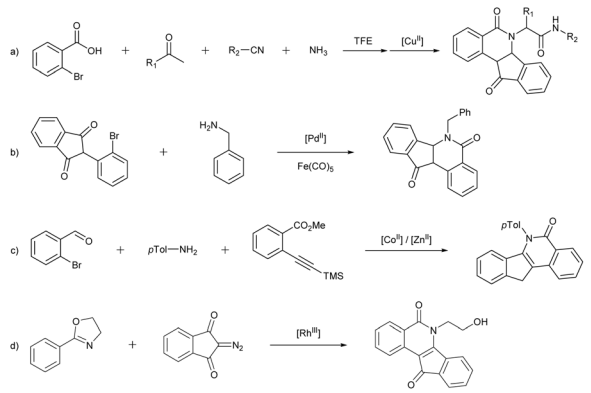
† Dedicated to Prof. Christian Bruneau for his outstanding contribution to catalysis.

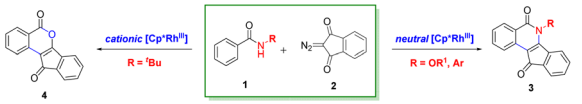


Scheme 1 Transition-metal complex-catalysed synthesis of indenoisoquinolines.

of phthalides with *o*-bromobenzaldehydes, followed by Heck-type carbonylative cycloamination with amino acids in the presence of a stoichiometric amount of $Fe(CO)_5$ (Scheme 1b);[12] the Co(II)/Zn-catalysed dual annulation reaction of 2-bromobenzaldehydes, amines, and alkynes to highly substituted indeno[1,2-*c*]-isoquinolin-5-ones, which were easily converted into indeno[1,2-*c*]isoquinoline-5,11-diones by oxidation with SeO_2 (Scheme 1c);[13] and a Rh(III)-catalysed [4 + 2] cascade annulation of 2-phenyloxazolines with 2-diazo-1,3-indandiones to afford indeno[1,2-*c*]isoquinoline-5,11-diones (Scheme 1d).[14] Thus, the development of a novel atom- and step-economical synthetic method for a variety of indeno[1,2-*c*]isoquinoline-5,11-diones is urgently desired.

In our continuing interest in transition-metal-catalysed syntheses of various biologically important heterocyclic compounds,[15] we focused our attention on the development of the straightforward synthesis of indeno[1,2-*c*]isoquinoline-5,11-diones. After many trials, we succeeded in developing the divergent synthesis of indenoisoquinolines, *i.e.* indeno[1,2-*c*]isoquinoline-5,11-diones (**3** and **5**) from **1**, **4**, and 2-diazo-1,3-indandione (**2**), and indenoisochromenes, *i.e.* indeno[1,2-*c*]isochromene-5,11-diones (**7**) from *N*-*tert*-butylbenzamides (**6**) and **2** by a Cp*Rh(III)-catalysed cyclocondensation reaction (Scheme 2). These results indicate that the present divergent synthesis of indenoisoquinolines and indenoisochromenes is dominated by a steric effect rather than an electronic effect of the substituents on a nitrogen atom of the starting benzamides. Recently, fierce competition has emerged in this research area,[16] but no one has succeeded in developing a rhodium-catalysed divergent synthesis of the fused heterocyclic compounds so far.

Indeno[1,2-*c*]isochromene-5,11-diones (**7**) are key scaffolds in a large number of natural products that exhibit broad



Scheme 2 [Cp*Rh]-catalysed divergent synthesis of indenoisochromenes and indenoisoquinolines.

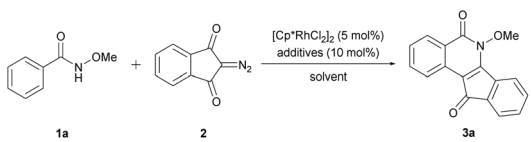
biological and clinical activities, such as anti-fungal, anti-tumour, anti-allergic, and anti-inflammatory activities.[17] In addition, indeno[1,2-*c*]isochromene-5,11-diones (**7**) are one of the most important types of synthetic intermediates for the synthesis of indeno[1,2-*c*]isoquinoline-5,11-diones (*vide infra*).[18]

Results and discussion

The reaction of *N*-methoxybenzamide **1a** with 2-diazo-1*H*-indene-1,3(2*H*)-dione **2** was carried out in the presence of $[Cp^*RhCl_2]_2$ (5.0 mol%) in 1,2-dichloroethane at 120 °C for 12 h in air (1 atm, balloon), and the desired indeno[1,2-*c*]isoquinoline-5,11-dione **3a** was obtained in 26% yield (Table 1, entry 1).

First, the effect of additives was examined; the addition of several silver salts increased the yield of **3a** (entries 2–5). Addition of NaOAc was also effective to give **3a** in 60% yield (entry 6). However, no promoting effect was observed for $Cu(OAc)_2 \cdot H_2O$ (entry 7, **3a**, 38%). Among the metal salts examined, AgOAc was the most effective, and **3a** was obtained in an isolated yield of 89% (entry 3). Other silver salts, such as $AgSbF_6$, $AgPF_6$, and $AgBF_4$, released the chloride ligand from $[Cp^*RhCl_2]_2$ to generate a coordinatively unsaturated cationic rhodium species, $[Cp^*Rh]^+$, but **3a** was obtained in moderate yields. These results indicate that the present reaction proceeds by a neutral, rather than cationic, rhodium species, such as

Table 1 Optimisation of the selective synthesis of indenoisoquinoline **3a** [a]



Entry	Additives	Solvent	Temp (°C)	Isolated yield of **3a** (%)
1	—	DCE	120	26
2	$AgSbF_6$	DCE	120	62
3	AgOAc	DCE	120	89
4	$AgPF_6$	DCE	120	82
5	$AgBF_4$	DCE	120	47
6	NaOAc	DCE	120	60
7	$Cu(OAc)_2 \cdot H_2O$	DCE	120	38
8[b]	AgOAc	MeOH	120	92
9	AgOAc	Toluene	120	83
10	AgOAc	MeCN	120	88
11	AgOAc	1,4-Dioxane	120	75
12[b]	AgOAc	MeOH	60	92
13[b]	AgOAc	MeOH	r.t.	85
14[b,c]	AgOAc	MeOH	60	88
15[b,d]	AgOAc	MeOH	60	42
16[b,e]	AgOAc	MeOH	60	92

[a] Reaction conditions: **1** (0.20 mmol), **2** (0.24 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), additives (10 mol%) in solvent (4.0 mL) for 12 h in air (1 atm, balloon). [b] 1 h. [c] $[Cp^*RhCl_2]_2$ (4 mol%). [d] Additives (5 mol%). [e] Additives (20 mol%). DCE = 1,2-dichloroethane, MeOH = methanol, MeCN = acetonitrile, OAc = acetate, r.t. = room temperature.

$Cp^*Rh(OAc)_2$ (*vide infra*). Next, the effect of solvents was investigated, and methanol was the best solvent (**3a**, 92%), with markedly faster conversion than the other solvents examined (entries 8–11). In addition, the present reaction proceeded well at 60 °C (**3a**, 92%, entry 12), and **3a** was also obtained in 85% yield even at room temperature (entry 13). The loadings of $[Cp^*RhCl_2]_2$ and AgOAc were then optimised (entries 14–16). Reducing the amount of $[Cp^*RhCl_2]_2$ to 4 mol% slightly decreased the yield of **3a** to 88% (entry 14). Notably, lowering the amount of AgOAc to 5 mol% resulted in a pronounced drop in yield (42%, entry 15), whereas increasing AgOAc to 20 mol% maintained high efficiency to give **3a** in 92% yield (entry 16).

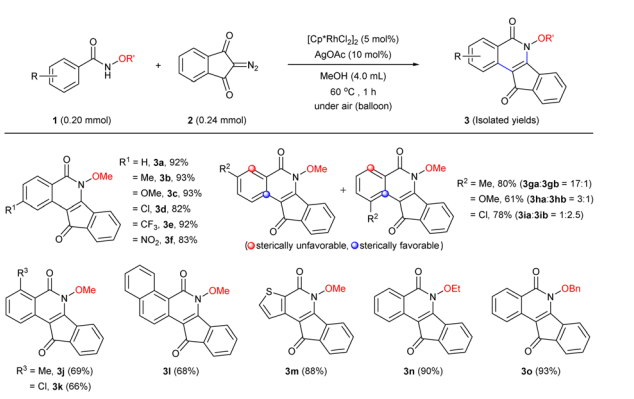
Under the optimal reaction conditions, the scope of *N*-monoalkoxybenzamides (**1a–1o**) was examined in the reaction with **2**, and the results are summarised in Scheme 3. *N*-Methoxybenzamides bearing 4-methyl (**1b**), 4-methoxy (**1c**), 4-chloro (**1d**), 4-trifluoromethyl (**1e**), and 4-nitro (**1f**) substituents on a phenyl group smoothly reacted with **2** to give the corresponding indeno[1,2-*c*]isoquinoline-5,11-diones (**3b–3f**) in isolated yields of 82–93%.

To investigate regioselectivity, *meta*-substituted *N*-methoxybenzamides **1g–1i** were examined. While high yields were generally obtained, **1g** furnished **3ga** as the major regioisomer (**3ga** : **3gb** = 17 : 1), indicating preferential C(sp^2)-H activation at the less hindered 6-position.[19] In contrast, **1h** and **1i** gave regioisomeric mixtures (**3ha** : **3hb** = 3 : 1 and **3ia** : **3ib** = 1 : 2.5). Notably, **1i** preferentially afforded the 2-substituted regioisomer, which may be rationalised by differences in C–H bond acidity and/or the stability of the corresponding the metal–carbon bond.[20] In addition, the reaction of 2-substituted *N*-methoxybenzamides (**1j** and **1k**) with **2** gave the corresponding indeno[1,2-*c*]isoquinoline-5,11-diones (**3j** and **3k**) in moderate yields. The reactions of both 1-naphthamide (**1l**) and thiophene-2-carboxamide (**1m**) with **2** also proceeded to give the corresponding **3l** and **3m** in 68% and 88% yields, respectively. *N*-Ethoxybenzamide (**1n**) and *N*-benzyloxybenzamide (**1o**) also reacted with **2** smoothly to give **3n** and **3o** in 90% and 93% yields, respectively.

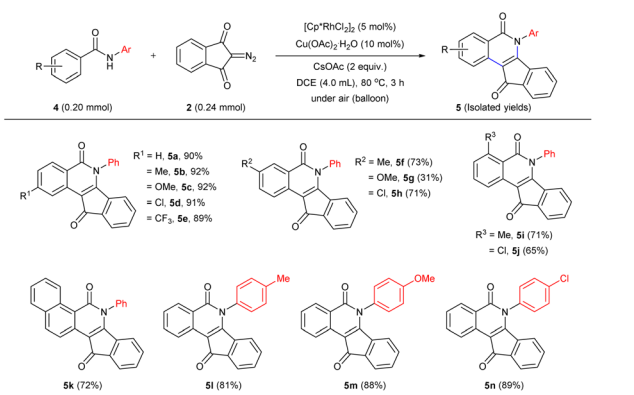
In sharp contrast, when the reactions of *N*-aryl-substituted benzamides (**4a–4n**) with **2** were carried out in MeOH at 60 °C for 1 h using the same catalyst system of $[Cp^*RhCl_2]_2$ combined with AgOAc, no indeno[1,2-*c*]isoquinoline-5,11-diones **5** were obtained. Thus, fine tuning of the rhodium catalyst system as well as the reaction conditions was apparently required. After many trials, we found that the catalyst system of $[Cp^*RhCl_2]_2$ combined with both $Cu(OAc)_2 \cdot H_2O$ and CsOAc showed the highest catalytic activity for the reactions of *N*-monoaryl-substituted benzamides (**4a–4n**) with **2** in 1,2-dichloroethane at 80 °C for 3 h to give the desired indeno[1,2-*c*]isoquinoline-5,11-diones (**5a–5n**) in high yields with high selectivity (Scheme 4). Notably, intramolecular competition reactions using *meta*-substituted *N*-aryl benzamides **4f–4h** were largely governed by steric effects to give **5f–5h** as the single regioisomer in the yields of 31–73% with high selectivity. Substituents on the *N*-aryl ring (**4l–4n**) had only a minor effect on the reaction outcome, and the corresponding products **5l–5n** were obtained in moderate to good yields (81–89%).

Besides, further improvements to the rhodium catalyst system as well as the reaction conditions were required for the reaction of *N*-*tert*-butylbenzamide (**6a**) with **2**. As a result, the catalyst system of $[Cp^*RhCl_2]_2$ combined with both $AgSbF_6$ and $Cu(OAc)_2 \cdot H_2O$ showed the highest catalytic activity for the reaction of **6a** with **2** in 1,2-dichloroethane at 110 °C for 2 h, giving the unexpected indeno[1,2-*c*]isochromene-5,11-dione (**7a**) in 82% yield. The yields of indeno[1,2-*c*]isochromene-5,11-diones (**7a–7f**) were higher than those of **7g–7k**. For **7g–7k**, the lower isolated yields are mainly attributed to incomplete conversion, and the corresponding benzamides **6g–6k** were partially recovered. All reactions gave indeno[1,2-*c*]isochromene-5,11-diones (**7**) as the sole cyclised products (Scheme 5).

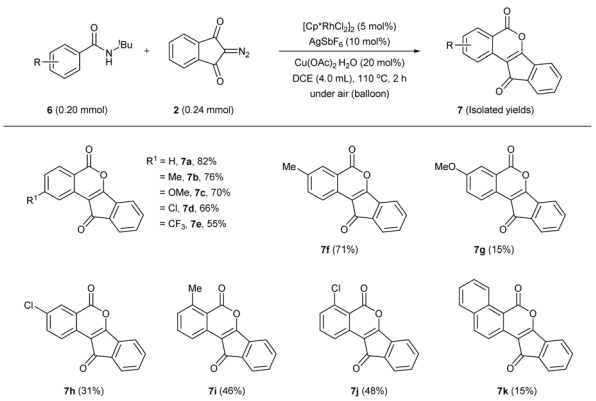
Regarding the divergent cyclocondensation selectivity, the Cp*Rh(III)-catalysed annulation was primarily governed by the steric effect of the *N*-substituent of the starting benzamides, rather than by electronic effects. These results indicate that an appropriate combination of the rhodium catalyst system and the *N*-substituent under the optimised conditions enables the divergent synthesis of indeno[1,2-*c*]isoquinoline-5,11-diones



Scheme 3 Selective synthesis of *N*-alkoxyindeno[1,2-*c*]isoquinoline-5,11-diones by a catalyst system of $[Cp^*RhCl_2]_2$ combined with AgOAc.



Scheme 4 Selective synthesis of *N*-arylindeno[1,2-*c*]isoquinoline-5,11-diones by a catalyst system of $[Cp^*RhCl_2]_2$ combined with both $Cu(OAc)_2 \cdot H_2O$ and CsOAc.



Scheme 5 $[Cp^*RhCl_2]_2/AgSbF_6$-catalysed synthesis of indeno[1,2-*c*] isochromene-5,11-dione.

and indeno[1,2-*c*]isochromene-5,11-diones in high yields with high selectivity.

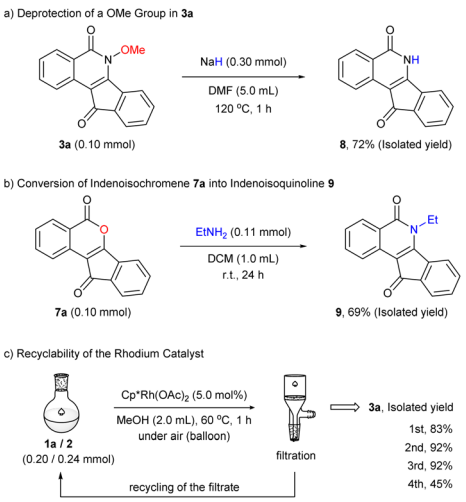
The synthetic utility of the present reaction was demonstrated by the deprotection of a methoxy group of *N*-methoxyindeno[1,2-*c*]isoquinoline-5,11-dione (**3a**). For example, treatment of **3a** with NaH in DMF at 120 °C for 1 h gave the deprotected **8** in 72% yield (Scheme 6a).[21] When indeno[1,2-*c*] isochromene-5,11-dione (**7a**) was treated with ethanamine in CH_2Cl_2 at room temperature for 24 h with stirring, 6-ethyl-5*H*-indeno[1,2-*c*]isoquinoline-5,11(6*H*)-dione (**9**) was obtained in 69% yield (Scheme 6b).[18] In addition, the recyclability of the rhodium catalyst was investigated in the cyclocondensation reaction of **1a** with **2** in methanol at 60 °C for 1 h under air. After the reaction, the resulting mixture was cooled to room temperature, and the product **3a** was obtained as a solid, which was filtered and then washed with as little methanol as possible. Subsequently, both **1a** and **2** were added to the organic layer containing the active rhodium catalyst, and the reaction was carried out at 60 °C for 1 h in air. The present rhodium catalyst can be cycled at least three times, and **3a** was obtained in high yield with high selectivity (1st 83%, 2nd 92%, 3rd 92%), where the slightly lower yield in the first run is mainly attributed to partial loss of **3a** during isolation owing to its slight solubility in methanol and partial retention in the mother liquor. But the yield of **3a** decreased to 45% with the fourth reuse (Scheme 6c).[22]

To obtain further insights into the reaction mechanism, the following reactions were investigated (Scheme 7). When **1a** was treated with a catalyst system of $[Cp^*RhCl_2]_2$ (5 mol%) and AgOAc (10 mol%) in the presence of 20 equiv. of methanol-d_4 in 1,2-dichloroethane at room temperature for 1 h, H/D exchange at the 2- and 6-positions (*ortho*-positions) of a phenyl group in **1a** occurred smoothly to give 83% of deuterium incorporation (Scheme 7a). This result could explain the reason why the catalytic activity of $[Cp^*RhCl_2]_2$ increased remarkably upon addition of AgOAc, $Cu(OAc)_2 \cdot H_2O$, or CsOAc (*vide supra*).

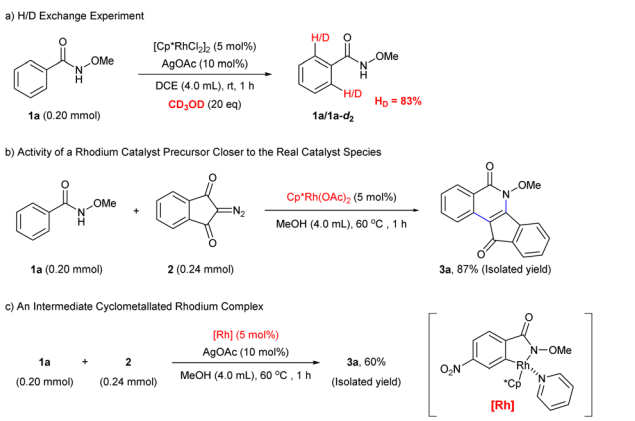
As a result, the coordination of acetate ligand to an active rhodium species is essential for high catalytic activity. Therefore, the catalytic activity of $Cp^*Rh(OAc)_2$ in the absence of AgOAc was investigated in the reaction of **1a** with **2** to give the desired **3a** in 87% yield (Scheme 7b). In addition, the catalytic activity of the reported five-membered rhodacycle, [Rh] (5 mol%) coordinated by a pyridine ligand,[23] was examined for the cyclocondensation reaction of **1a** with **2** in the presence of AgOAc (10 mol%) in MeOH at 60 °C for 1 h to give **3a** in 60% yield (Scheme 7c).

When typical silver salts, such as $AgSbF_6$, $AgPF_6$, and $AgBF_4$, were added to the chlorine-bridged rhodium dimer complex, $[Cp^*RhCl_2]_2$, the chlorine ligand was released from the rhodium centre to give a cationic and coordinatively unsaturated mononuclear rhodium species. The anions of these silver salts are highly stable and have no interaction with the cationic rhodium species in solution. As a result, the catalyst system of $[Cp^*RhCl_2]_2$ combined with AgOAc showed the best catalytic activity in the cyclocondensation of **1a** with **2** to give **3a** in the isolated yield of 87%, which strongly suggests that neutral $Cp^*Rh(OAc)_2$ is the active catalyst species.

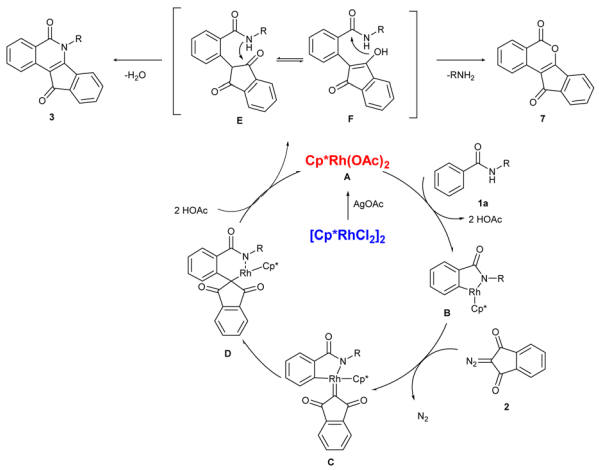
Considering all results obtained in this study, the most plausible mechanism of the present reaction is illustrated in Scheme 8. First, $[Cp^*RhCl_2]_2$ is converted into a neutral and



Scheme 6 Synthetic transformation.



Scheme 7 Mechanistic study.



Scheme 8 A plausible mechanism.

catalytically active Cp*Rh(OAc)$_2$ species (**A**) in the presence of AgOAc with deposition of AgCl. Subsequently, the reaction of Cp*Rh(OAc)$_2$ occurs with *N*-monosubstituted benzamides **1**, followed by intramolecular *ortho*-C(sp^2)–H bond cleavage of a phenyl group to generate a five-membered rhodacyclic intermediate (**B**)[23] with liberation of two molecules of acetic acid. Next, the reaction of intermediate (**B**) with 2-diazo-1*H*-indene-1,3(2*H*)-diones (**2**) proceeds with evolution of N_2 to give a carbene-coordinated rhodacyclic intermediate (**C**).[24] Then, insertion of a carbene ligand into a rhodium–C(sp^2) bond in intermediate **C** proceeds to give a six-membered rhodacyclic intermediate (**D**). Finally, the protonation of intermediate **D** proceeds by the first liberated acetic acid (two equivalents) to give a 1,3-dicarbonyl product (**E**) together with the regeneration of a neutral and catalytically active Cp*Rh(OAc)$_2$ species (**A**).

About the products **3** and **5**, indeno[1,2-*c*]isoquinolin-5.11-dione (**3**) was directly formed from a 1,3-dicarbonyl product (**E**) through the intramolecular nucleophilic attack of an amide nitrogen atom together with the liberation of water. In addition, the intramolecular migration of a carbonyl α-hydrogen in a 1,3-dicarbonyl product (**E**) gives an enol (**F**) through keto–enol tautomerism. For an enol (**F**), the intramolecular nucleophilic attack of a hydroxyl group on a carbonyl group occurred to give indeno[1,2-*c*]isochromene-5,11-dione (**7**) together with liberation of an amine. With the fine tuning of rhodium catalyst systems as well as the reaction conditions, the kinds of substituents on a nitrogen atom in amides (**1**) perfectly controlled which product, indenoisoquinoline (**3**) or indenoisochromene (**7**), was obtained in high yield with high selectivity, where the steric hindrance of the substituent such as a *tert*-butyl group on a nitrogen atom in amides (**1**) operates more effectively than the electronic effect of the substituents (OMe, OEt, C_6H_5, 4-MeC_6H_4, 4-MeOC_6H_4, and 4-ClC_6H_4) (*vide supra*).

Conclusion

In this study, a novel divergent synthesis of indeno[1,2-*c*]isoquinoline-5,11-diones and indeno[1,2-*c*]isochromene-5,11-diones was developed through Cp*Rh(III)-catalysed C(sp^2)–H bond cleavage followed by cyclocondensation reactions that are applicable to a wide range of both benzamides. In addition, the present reaction has the following four characteristics. (1) During the reaction, there was no change in the oxidation state of an active rhodium species, and the reaction proceeds with a neutral trivalent, not cationic trivalent, rhodium species. (2) The final divergent cyclocondensation step was fully controlled by changing the steric effect of substituents on a nitrogen atom of the starting benzamides. (3) The fine tuning of both the rhodium catalyst systems and the reaction conditions was essential for the present Cp*Rh-catalysed divergent synthesis of indeno[1,2-*c*]isoquinoline-5,11-diones and indeno[1,2-*c*]isochromene-5,11-diones, probably due to the weak coordinating ability of an acetate ligand to the rhodium centre. (4) Furthermore, Cp*Rh(OAc)$_2$ catalyst can be cycled at least three times only through the filtration of the reaction mixture.

This work provides divergent access to fused heterocycles, indeno[1,2-*c*]isoquinoline-5,11-diones and indeno[1,2-*c*]isochromene-5,11-diones, and will be of interest to both synthetic organic chemistry and medicinal chemistry.

Author contributions

DYK contributed to experiments and product characterisation. DYK and YK contributed to product characterisation. TK conceived the project. DYK and TK prepared the manuscript, and DYK, YK, RM, and TK contributed to discussions.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supporting information (SI). Supplementary information: experimental data, materials and methods, NMR spectra, and HRMS data can be found in the SI file. See DOI: https://doi.org/10.1039/d6ra01058j.

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References

1 (*a*) D. Ye, H. Lu, Y. He, Z. Zheng, J. Wu and H. Wei, *Nat. Commun.*, 2022, **13**, 3337–3346; (*b*) M. Choury, A. B. Lopes, G. Blond and M. Gulea, *Molecules*, 2020, **25**, 3147–3165; (*c*) J. P. Wolfe, Synthesis of Heterocycles via Metal–Catalysed Reactions that Generate One or More Carbon–Heteroatom Bonds, In *Topics in Heterocyclic Chemistry (TOPICS*, Springer–Verlag, Berlin, Heidelberg, 2013, Vol. 32.

2 (*a*) X. Xiao, S. Antony, Y. Pommier and M. Cushman, *J. Med. Chem.*, 2005, **48**, 3231–3238; (*b*) X. Liang, Q. Wu, S. Luan, Z. Yin, C. He, L. Yin, Y. Zou, Z. Yuan, L. Li, X. Song, M. He, C. Lv and W. Zhang, *Eur. J. Med. Chem.*, 2019, **171**, 129–168; (*c*) M. Chauhan and R. Kumar, *Med. Chem. Res.*, 2015, **24**, 2259–2282; (*d*) K. E. Peterson, M. A. Cinelli, A. Morrell, A. Mehta, T. S. Dexheimer, S. Antony, Y. Pommier and M. Cushman, *J. Med. Chem.*, 2011, **54**, 4937–4953; (*e*) Y. Pommier and M. Cushman, *Mol. Cancer Ther.*, 2009, **8**, 1008–1014; (*f*) P. Botella and E. Rivero-Buceta, *J. Control. Release*, 2017, **247**, 28–54; (*g*) Y.-Q. Liu, W.-Q. Li, S. L. Morris-Natschke, K. Qian, L. Yang, G.-X. Zhu, X.-B. Wu, A.-L. Chen, S.-Y. Zhang, X. Nan and K.-H. Lee, *Med. Res. Rev.*, 2015, **35**, 753–789; (*h*) L. Chen and F.-E. Chen, *Synlett*, 2017, **28**, 1134–1150; (*i*) W.-J. Cho, Q. M. Le, H. T. M. Van, K. Y. Lee, B. Y. Kang, E.-S. Lee, S. K. Lee and Y. Kwon, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3531–3534; (*j*) H. T. M. Van, Q. M. Le, K. Y. Lee, E.-S. Lee, Y. Kwon, T. S. Kim, T. N. Le, S.-H. Lee and W. A. Cho, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 5763–5767.

3 K. D. Paull, R. H. Shoemaker, L. Hodes, A. Monks, D. A. Scudiero, L. Rubinstein, J. Plowman and M. R. Boyd, *J. Natl. Cancer Inst.*, 1989, **81**, 1088–1092.

4 (*a*) M. E. Wall, *Med. Res. Rev.*, 1998, **18**, 299–314; (*b*) W. Du, *Tetrahedron*, 2003, **59**, 8649–8687; (*c*) E. Martino, S. D. Volpe, E. Terribile, E. Benetti, M. Sakaj, A. Centamore, A. Sala and S. Collina, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 701–707; (*d*) Y. Pommier, *Nat. Rev.*, 2006, **6**, 789–802; (*e*) D. E. Beck, P. V. N. Reddy, W. Lv, M. Abdelmalak, G. S. Tender, S. Lopez, K. Agama, C. Marchand, Y. Pommier and M. Cushman, *J. Med. Chem.*, 2016, **59**, 3840–3853.

5 (*a*) W. E. Hardman, M. P. Moyer and I. L. Cameron, *Anticancer Res.*, 1999, **19**, 2269–2274; (*b*) R. Balaña-Fouce, C. F. Prada, J. M. Requena, M. Cushman, Y. Pommier, R. Álvarez-Velilla, J. M. Escudero, E. Calvo-Álvarez, Y. Pérez-Pertejo and R. M. Reguera, *Antimicrob. Agents Chemother.*, 2012, **56**, 5264–5270.

6 (*a*) M. Cushman and L. Cheng, *J. Org. Chem.*, 1978, **43**, 3781–3783; (*b*) D. Strumberg, Y. Pommier, K. Paull, M. Jayaraman, P. Nagafuji and M. Cushman, *J. Med. Chem.*, 1999, **42**, 446–457.

7 N. T. Dung, L. N. T. Giang, P. H. Thu, N. H. Thuong, D. T. T. Anh, L. Q. Tan, N. H. Thanh, L. T. T. Anh, N. T. Anh, B. L. Giang, N. V. Tuyen and P. V. Kiem, *Nat. Prod. Commun.*, 2019, **14**, 1–6.

8 A. Ryckebusch, D. Garcin, A. Lansiaux, J.-F. Goossens, B. Baldeyrou, R. Houssin, C. Bailly and J.-P. Hénichart, *J. Med. Chem.*, 2008, **51**, 3617–3629.

9 (*a*) Y. Pommier and M. Cushman, *Mol. Cancer Ther.*, 2009, **8**, 1008–1014; (*b*) M. A. Cinelli, *Med. Res. Rev.*, 2019, **39**, 1294–1337; (*c*) D. E. Beck, K. Agama, C. Marchand, A. Chergui and Y. Pommier, *J. Med. Chem.*, 2014, **57**, 1495–1512.

10 (*a*) M. Conda-Sheridan, E.-J. Park, D. E. Beck, P. V. N. Reddy, T. X. Nguyen, B. Hu, L. Chen, J. J. White, R. B. van Breemen, J. M. Pezzuto and M. Cushman, *J. Med. Chem.*, 2013, **56**, 2581–2605; (*b*) G. Ahn, A. Lansiaux, J.-F. Goossens, C. Bailly, B. Baldeyrou, N. Schifano-Faux, P. Grandclaudon, A. Couture and A. Ryckebusch, *Bioorg. Med. Chem.*, 2010, **18**, 8119–8133; (*c*) M. R. Mahmoud, M. M. El-Shahawi, E. A. A. El-Bordany and F. S. M. A. El-Azm, *Synth. Commun.*, 2010, **40**, 666–676; (*d*) D. E. Beck, W. Lv, M. Abdelmalak, C. B. Plescia, K. Agama, C. Marchand, Y. Pommier and M. Cushman, *Bioorg. Med. Chem.*, 2016, **24**, 1469–1479; (*e*) M. Cushman, M. Jayaraman, J. A. Vroman, A. K. Fukunaga, B. M. Fox, G. Kohlhagen, D. Strumberg and Y. Pommier, *J. Med. Chem.*, 2000, **43**, 3688–3698; (*f*) T. T. Jayanth, L. Zhang, T. S. Johnson and H. C. Malinakova, *Org. Lett.*, 2009, **11**, 815–818.

11 (*a*) C.-Y. Huang, V. Kavala, C.-W. Kuo, A. Konala, T.-H. Yang and C.-F. Yao, *J. Org. Chem.*, 2017, **82**, 1961–1968; (*b*) Q. Wang, J. Tuinhof, K. C. Mgimpatsang, K. Kurpiewska, J. Kalinowska-Tluscik and A. Dömling, *J. Org. Chem.*, 2020, **85**, 9915–9927; (*c*) M. Rawat and D. S. Rawat, *ACS Sustainable Chem. Eng.*, 2020, **8**, 13701–13712; (*d*) C.-Y. Huang, V. Kavala, C.-W. Kuo, A. Konala, T.-H. Yang and C.-F. Yao, *J. Org. Chem.*, 2017, **82**, 1961–1968.

12 B. Slatkovská, J. Ondriaš, J. Doháňošová, T. Gracza and M. Babjak, *ChemistrySelect*, 2017, **2**, 3948–3951.

13 C.-C. Liu, J.-C. Hsieh, R. P. Korivi and C.-H. Cheng, *Chem. Eur. J.*, 2015, **21**, 9544–9549.

14 (*a*) X. Yue, Y. Gao, J. Huang, Y. Feng and X. Cui, *Org. Lett.*, 2023, **25**, 2923–2927; (*b*) H. Li, Y. Lu, N. Xu, X. Jin, T. Chen, J. Yu and J. Liu, *J. Org. Chem.*, 2024, **89**, 1301–1309; (*c*) Q. Wang and X. Li, *Org. Chem. Front.*, 2016, **3**, 1159–1162.

15 (*a*) T. Kondo, Y. Kaneko, Y. Taguchi, A. Nakamura, T. Okada, M. Shiotsuki, Y. Ura, K. Wada and T. Mitsudo, *J. Am. Chem. Soc.*, 2002, **124**, 6824–6825; (*b*) T. Kondo, T. Okada and T. Mitsudo, *J. Am. Chem. Soc.*, 2002, **124**, 186–187; (*c*) T. Kondo, Y. Taguchi, Y. Kaneko, M. Niimi and T. Mitsudo, *Angew. Chem., Int. Ed.*, 2004, **43**, 5369–5372; (*d*) T. Kondo, M. Nomura, Y. Ura, K. Wada and T. Mitsudo, *J. Am. Chem. Soc.*, 2006, **128**, 14816–14817; (*e*) D. Y. Kim, Y. Kimura, R. Miura and T. Kondo, *Chem. Lett.*, 2026, **55**, upag017.

16 (*a*) R. D. Barry, *Chem. Rev.*, 1964, **64**, 229–260; (*b*) S. Pal and M. Pal, *Isocoumarin, Thiaisocoumarin and Phosphaisocoumarin: Natural Occurrences, Synthetic Approaches and Pharmaceutical Applications*, Elsevier, Amsterdam, 2019; (*c*) Y. Xiang, C. Wang, Q. Ding and Y. Peng, *Adv. Synth. Catal.*, 2019, **361**, 919–944; (*d*) N. Gogoi, R. Parhi, R. K. P. Tripathi, L. Pachuau and P. P. Kaishap, *Tetrahedron*, 2024, **150**, 133740.

17 (*a*) L. Pochet, R. Frédérick and B. Masereel, *Curr. Pharm. Des.*, 2004, **10**, 3781–3796; (*b*) A. Saeed, *Eur. J. Med. Chem.*, 2016, **116**, 290–317; (*c*) A. O. Noor, D. M. Almasri, A. A. Bagalagel, H. M. Abdallah, S. G. A. Mohamed, G. A. Mohamed and S. R. M. Ibrahim, *Molecules*, 2020, **25**, 395; (*d*) G. Shabir, A. Saeed and H. R. El-Seed, *Phytochemistry*, 2021, **181**, 112568; (*e*) M. A. Tammam, M. I. G. El-Din, A. Abood and A. R. El-Demerdash, *RSC Adv.*, 2023, **13**, 8049–8089; (*f*) C. Wang, H. Xu, J. Wang,

C. Wei, S. Zheng, R. Xu, S. Wang, Z. Li, P. Li and F. Kong, *J. Nat. Prod.*, 2025, **88**, 757–767.

18 S. Wawzonek, *Org. Prep. Proced. Int.*, 1982, **14**, 163–168.

19 (*a*) J. D. Neuhaus and M. C. Willis, *Org. Biomol. Chem.*, 2016, **14**, 4986–5000; (*b*) M. Peng, H. Doucet and J.-F. Soulé, *ChemCatChem*, 2024, **16**, e202400279; (*c*) F. Doraghi, S. Kermaninia, H. Afaridoun, B. Larijani and M. Mahdavi, *Asian J. Org. Chem.*, 2025, **14**, e202400617.

20 (*a*) L. Ackermann, A. V. Lygin and N. Hofmann, *Angew. Chem., Int. Ed.*, 2011, **50**, 6379–6382; (*b*) E. Clot, C. Mégret, O. Eisenstein and R. N. Perutz, *J. Am. Chem. Soc.*, 2009, **131**, 7817–7827.

21 (*a*) H. Zhong, D. Y. Songqing, S. Wang and J. Huang, *Chem. Commun.*, 2012, **48**, 3236–3238; (*b*) N. Sharma, R. Saha, N. Parveen and G. Sekar, *Adv. Synth. Catal.*, 2017, **359**, 1947–1958.

22 (*a*) T. A. Fassbach, J.-M. Ji, A. J. Vorholt and W. Leitner, *ACS Catal.*, 2024, **14**, 7289–7298; (*b*) Z.-P. Han, M.-M. Xu, R.-Y. Zhang, X.-P. Xu and S.-J. Ji, *Green Chem.*, 2021, **23**, 6337–6340; (*c*) H. Meng, H. Xu, Z. Zhou, Z. Tang, Y. Li, Y. Zhou, W. Yi and X. Wu, *Green Chem.*, 2022, **24**, 7012–7021; (*d*) X. Liu, S. Zheng, Q. Ge, T. Cao, F. Zeng, F. Tian, Z. He, Z. Gao and X. Wu, *J. Org. Chem.*, 2025, **90**, 4646–4651.

23 T. Zhou, L. Li, B. Li, H. Song and B. Wang, *Organometallics*, 2018, **37**, 476–481.

24 (*a*) J. Wang, C.-M. Che and M. P. Doyle, *Transition Metal–Catalyzed Carbene Transformation*, Wiley–VCH, Weinheim, Germany, 2022; (*b*) F. Hu, Y. Xia, C. Ma, Y. Zhang and J. Wang, *Chem. Commun.*, 2015, **51**, 7986–7995; (*c*) N. Jha, N. P. Khot and N. Kapur, *Chem. Rec.*, 2021, **21**, 4088–4122; (*d*) D. Yadagiri and P. Anbarasan, *Chem. Rec.*, 2021, **21**, 3872–3883; (*e*) F. Doraghi, P. Baghershahi, M. Ghasemi, M. Mahdavi and A. Al-Harrasi, *RSC Adv.*, 2024, **14**, 39337–39352.