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Transition metal catalyzed carboannulation of diazabicyclic alkenes with ambiphilic bifunctional reagents: a facile route towards functionalized indanones and indanols

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ABSTRACT

Functionalized indanones are readily prepared in good to excellent yields by the Pd/Rh catalyzed carboannulation of bicyclic and tricyclic hydrazines with 2-iodobenzonitrile, 2-cyanophenylboronic acid and 2-formylphenylboronic acid. The reaction with 2-formylphenylboronic acid afforded 3,4-disubstituted cyclopentenes as minor product along with indanones under Rh catalyzed conditions, whereas indanols were obtained as the major product under Pd catalyzed conditions. The products obtained can be synthetically manipulated easily to pharmaceutically important molecules.

1. Introduction

In recent years, transition metal catalyzed annulation processes have gained popularity as an attractive strategy in organic synthesis for the efficient construction of complex molecular frameworks.[1,2] Various transition metals, such as palladium,[3] nickel[4] and rhodium[5] were found to be effective catalysts in the hetero- and carboannulation of unsaturated cyclopropanes and cyclobutanes,[6] 1,2-dienes,[7] 1,3-dienes[8] and alkynes[9] leading to a wide variety of arene-containing heterocycles and carbocycles. Among the various unsaturated compounds, azabicyclic alkenes prepared by the Diels–Alder cycloaddition between cyclopentadiene and diazocompounds,[10] possess great synthetic potential. The combination of a strained carbon–carbon double bond and an N–N bond in the symmetrical bi and polycyclic hydrazines allows them to be easily activated by the metal catalysts.

The reactivity of azabicyclic alkenes have been extensively investigated with monocentered nucleophiles under transition metal catalyzed conditions.[11,12] These investigations resulted in the formation of either 3,4- or 3,5-disubstituted cyclopentenes. Kaufmann and co-workers reported the stereoselective ring opening of bicyclic hydrazine with aryl iodides under palladium catalysis resulting in the formation of substituted cyclopentene and hydroarylated adduct.[11a,h] Desymmetrization of bicyclic hydrazine with organoboronic acid affording *trans*-3,4-disubstituted hydrazino cyclopentenes under Pd/iodine condition have been reported by our group.[12d] Pineschi and later Lautens have explored the asymmetric ring opening of bicyclic hydrazine with boronic acids under rhodium catalysis.[11i,13] Lautens and co-workers have also reported a Rh(I) catalyzed carbonylative ring opening of diazabicycles with aryl anion equivalents generated from boronic acids.[14] Acid catalyzed rearrangements of these bicyclic alkenes leading to several polyfunctional diaminocyclopentanes have also been reported.[11b,15] The investigations of the reactivity of azabicyclic alkenes towards aromatic species (Fig. 1), with *ortho* bicentered reactive sites, have been limited. The reactive sites, FG_1 and FG_2 in such compounds can both be nucleophilic or electrophilic or one can be nucleophilic and the other electrophilic. We have recently explored the palladium catalyzed ring opening of azabicyclic alkenes with 2-iodophenol or 2-iodoaniline, which served as a two-fold nucleophile in enabling the stereoselective synthesis of cyclopentene-annulated benzofuran and indole derivatives.[16] A rhodium catalyzed tandem cyclization of various strained olefins with bifunctional arylboronic esters providing access to highly functionalized polycylic systems was reported by Lautens and co-workers.[17]

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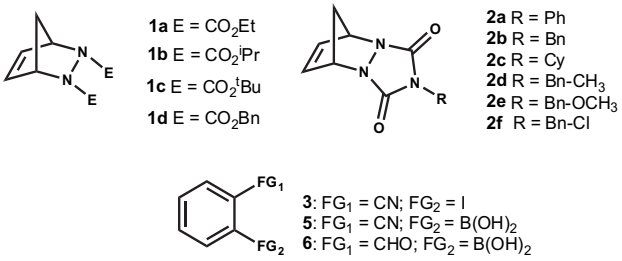


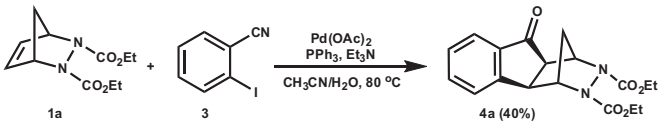
Fig. 1. Bicyclic and tricyclic hydrazines and bifunctional reagents used for the study.

Our interest in the metal catalyzed annulation process prompted us to examine the reactivity of various *o*-functionalized aryl halides like *o*-iodobenzonitrile and boronic acids towards azabicyclic olefins under palladium and rhodium catalysis. Herein, we provide a detailed report on the carboannulation of bicyclic hydrazines with 2-iodobenzonitrile, 2-cyanophenylboronic acid and 2-formylphenylboronic acid leading to the synthesis of highly functionalized indanones and indanols.

2. Results and discussion

2.1. Palladium catalyzed cyanoannulation with 2-iodobenzonitrile

The bicyclic hydrazines selected for our studies are shown in Fig. 1. We initiated our experiments with the reaction of 2,3-diazabicyclo[2.2.1]heptene **1a** with 2-iodobenzonitrile **3** in the presence of $Pd(OAc)_2$ as catalyst, PPh_3 as ligand and Et_3N as base in 9:1 mixture of CH_3CN/H_2O (Scheme 1). The reaction afforded substituted indanone **4a** in 40% yield. The structure of the product was assigned with the help of various spectroscopic techniques.



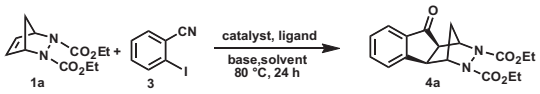
Scheme 1. Palladium catalyzed annulation of azabicyclic olefin.

Detailed optimization studies were carried out to find the best condition for this transformation (Table 1). Among the different catalysts tried (Table 1, entries 1, 13–15), $Pd_2(dba)_3\cdot CHCl_3/PPh_3$ was found to be the best catalyst system (entry 14). The next variable examined was the solvent (entries 1–5). A 9:1 mixture of CH_3CN/H_2O gave the best yield of the product compared to toluene, THF and MeOH. The next task was to find out the best base for the reaction. A series of organic and inorganic bases were examined (entries 1, 7–12) and Et_3N was found to furnish the highest yield (entry 1). On the basis of these investigations, the optimal conditions for this reaction are as follows: 1:1 mixture of iodobenzonitrile/olefin with 10 mol % $Pd_2(dba)_3\cdot CHCl_3$, 10 mol % PPh_3, 2.0 equiv of Et_3N and 2 mL of CH_3CN/H_2O (9:1) for 24 h (entry 14).

The scope of the reaction was then explored under optimized conditions. In all the cases, the azabicyclic alkene **1a**–**d** reacted with 2-iodobenzonitrile **3** leading to corresponding carboannulated products in good yields and the results are summarized in Table 2. In the case of tricyclic substrates, the reaction did not take place because of the low stability of the starting material under basic condition.[11h]

On the basis of previous work on bicyclic annulation chemistry,[18] we propose the following mechanism for the formation of

Table 1
Optimization studies for the annulation reaction



Entry	Catalyst	Solvent	Base	Ligand	Yield (%)[a]
1	$Pd(OAc)_2$	CH_3CN/H_2O (9:1)	Et_3N	PPh_3	40
2	$Pd(OAc)_2$	DMF/H_2O (9:1)	Et_3N	PPh_3	31
3	$Pd(OAc)_2$	$Toluene/H_2O$ (9:1)	Et_3N	PPh_3	17
4	$Pd(OAc)_2$	$Dioxane/H_2O$ (9:1)	Et_3N	PPh_3	11
5	$Pd(OAc)_2$	THF	Et_3N	PPh_3	No reaction
6	$Pd(OAc)_2$	MeOH	Et_3N	PPh_3	No reaction
7	$Pd(OAc)_2$	CH_3CN/H_2O (9:1)	K_2CO_3	PPh_3	No reaction
8	$Pd(OAc)_2$	CH_3CN/H_2O (9:1)	Cs_2CO_3	PPh_3	No reaction
9	$Pd(OAc)_2$	CH_3CN/H_2O (9:1)	NaOAc	PPh_3	No reaction
10	$Pd(OAc)_2$	CH_3CN/H_2O (9:1)	DIEA	PPh_3	38
11	$Pd(OAc)_2$	CH_3CN/H_2O (9:1)	$^tBuNH_2$	PPh_3	Trace
12	$Pd(OAc)_2$	CH_3CN/H_2O (9:1)	Pyridine	PPh_3	17
13	$PdCl_2$	CH_3CN/H_2O (9:1)	Et_3N	PPh_3	No reaction
14	*$Pd_2(dba)_3CHCl_3$*	*CH_3CN/H_2O*(9:1)	*Et_3N*	*PPh_3*	68
15	$Pd(PPh_3)_4$	CH_3CN/H_2O(9:1)	Et_3N	PPh_3	Trace
16	$Pd_2(dba)_3CHCl_3$	CH_3CN/H_2O(9:1)	Et_3N	—	60
17	$Pd_2(dba)_3CHCl_3$	CH_3CN/H_2O(9:1)	Et_3N	dppe	64
18	$Pd_2(dba)_3CHCl_3$	CH_3CN/H_2O(9:1)	Et_3N	PPh_3Bu_4NCl	25
19	$Pd_2(dba)_3CHCl_3$	CH_3CN/H_2O(9:1)	Et_3N	PPh_3,LiCl	20

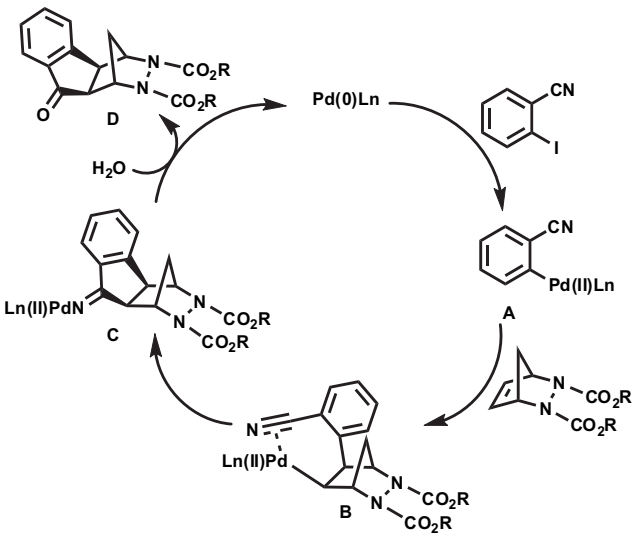
Reaction conditions: Alkene (1.0 equiv) 3 (1.0 equiv), Catalyst (10 mol %), Base (2.0 equiv), Ligand (10 mol %), Solvent (2 mL), 80 °C, 24 h. The condition in italics denotes the optimized conditions for the relevant reactions.
[a] Isolated yield.

Table 2
Generality of the palladium catalyzed annulation reaction

Entry	Alkene	Product	Yield (%)[a]
1	**1a**	**4a**	68
2	**1b**	**4b**	69
3	**1c**	**4c**	61
4	**1d**	**4d**	66

Reaction conditions: Alkene (1.0 equiv), 3 (1.0 equiv), $Pd_2(dba)_3\cdot CHCl_3$ (10mol%), PPh_3 (10mol%), Et_3N(2.0 equiv), CH_3CN/H_2O (2 mL), 80 °C, 24 h.
[a] Isolated yield.

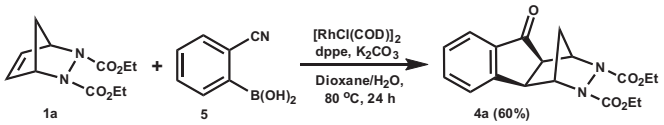
indanone. The first step of the catalytic cycle involves oxidative addition of aryl halide to form $Ar-PdL_2-X$ and subsequent coordination to the alkene. Next step is the carbopalladation, which is followed by hydration to form indanone (Scheme 2).



Scheme 2. Proposed mechanism of the reaction.

2.2. Rhodium catalyzed cyanoannulation with 2-cyanophenylboronic acid and 2-formylphenylboronic acid

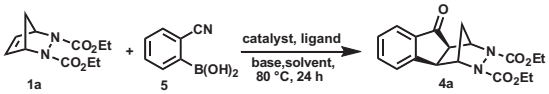
2-Cyanophenylboronic acid and 2-formylphenylboronic acid are attractive molecules due to the presence of both nucleophilic and electrophilic centres in them. The nucleophilic carbon–boron linkage can be transmetalated to an organorhodium(I) species and the electrophilic cyano/formyl group can act as an acceptor for an organorhodium(I) species.[19] Murakami and co-workers reported the rhodium catalyzed annulation reactions of 2-cyanophenylboronic acid and 2-formylphenylboronic acid with alkynes and strained alkenes.[20,21] Inspired by this work, we checked the reactivity of these ambiphilic boronic acids towards azabicyclic and tricyclic olefins under rhodium catalyzed conditions. Initially, we carried out the reaction of 2-cyanophenylboronic acid **5** with bicyclic olefin **1a** in presence of catalyst $[RhCl(COD)]_2$, ligand dppe and base K_2CO_3 in (9:1) dioxane/H_2O at 80 °C under argon atmosphere (Scheme 3). The reaction afforded the product **4a** in 60% yield.



Scheme 3. Rhodium catalyzed annulation of azabicyclic olefin.

On the basis of this preliminary result, we set out to investigate the best conditions for the reaction to occur. The parameters screened were rhodium catalysts, ligands, bases and solvents. A number of rhodium catalysts and ligands were surveyed for the reaction of azabicyclic alkene **1a** and 2-cyanophenylboronic acid **5**, among which $[RhCl(COD)]_2$/BINAP gave the highest yield of 74% for the indanone derivative **4a**. Among the bases examined, Cs_2CO_3 gave the best yield: K_2CO_3 (68%), KF (63%). While a number of solvent systems were studied, 9:1 dioxane/H_2O was found to be the best solvent for the transformation. Table 3 describes our efforts towards optimizing various reaction parameters.

Table 3
Optimization studies for the annulation reaction



Entry	Catalyst	Solvent	Base	Ligand	Yield (%)[a]
1	$[RhCl(COD)]_2$	Dioxane/H_2O (9:1)	K_2CO_3	dppe	60
2	$[RhCl(COD)]_2$	Dioxane/H_2O (9:1)	K_2CO_3	dppe	62
3	$[RhCl(COD)]_2$	Dioxane/H_2O (9:1)	K_2CO_3	dppe	64
4	$[RhCl(COD)]_2$	Dioxane/H_2O (9:1)	K_2CO_3	BINAP	65
5	$[RhCl(COD)]_2$	Dioxane/H_2O (9:1)	K_2CO_3	Monophos	62
6	$[RhCl(COD)]_2$	Dioxane/H_2O (9:1)	KF	BINAP	63
7	*$[RhCl(COD)]_2$*	*Dioxane/H_2O* (9:1)	*Cs_2CO_3*	*BINAP*	74
8	$[RhCl(COD)]_2$	Dioxane/H_2O (9:1)	K_2CO_3	BINAP	68
9	$[RhCl(COE)_2]_2$	Dioxane/H_2O (9:1)	Cs_2CO_3	BINAP	21
10	[Rh(acac)(COD)]	Dioxane/H_2O (9:1)	Cs_2CO_3	BINAP	15
11	$[Rh(OH)(COD)]_2$	Dioxane/H_2O (9:1)	Cs_2CO_3	BINAP	35
12	$[RhCl(COD)]_2$	Toluene/H_2O (9:1)	Cs_2CO_3	BINAP	33
13	$[RhCl(COD)]_2$	THF/H_2O (9:1)	Cs_2CO_3	BINAP	8
14	$[RhCl(COD)]_2$	Methanol	Cs_2CO_3	BINAP	16

Reaction conditions: Alkene (1.0 equiv), 5 (1.0 equiv), Catalyst (5 mol %), Base (2.0 equiv), Ligand (10 mol %), Solvent (2 mL), 80 °C, 24 h. The condition in italics denotes the optimized conditions for the relevant reactions.
[a] Isolated yield.

The scope of this reaction was then investigated under optimized conditions [alkene (1.0 equiv), 2-cyanophenylboronic acid (1.0 equiv), $[RhCl(COD)]_2$ (5 mol %), BINAP (10 mol %), Cs_2CO_3 (2.0 equiv) in (9:1) dioxane/H_2O at 80 °C for 24 h]. In all the cases, the azabicyclic alkene **1a**–**d** reacted with 2-cyanophenylboronic acid **5** affording the corresponding functionalized indanones **4a**–**d** in good to excellent yields. The reaction was also extended to sterically more hindered tricyclic adducts **2a**–**f** derived from cyclopentadiene and urazole.[10b] The results are summarized in Table 4.

The product **4e** was crystallized from dichloromethane and the structure and stereochemistry of the product was unambiguously confirmed by single crystal X-ray analysis of **4e** (Fig. 2).[22]

Table 4
Generality of the rhodium catalyzed annulation reaction

Entry	Alkene	Product	Yield (%)[a]
1	**1a**	**4a**	74
2	**1b**	**4b**	67
3	**1c**	**4c**	90
4	**1d**	**4d**	78
5	**2a**	**4e**	70
6	**2b**	**4f**	78
7	**2c**	**4g**	96
8	**2d**	**4h**	80
9	**2e**	**4i**	77
10	**2f**	**4j**	83

Reaction conditions: Alkene (1.0 equiv), 5 (1.0 equiv), $[RhCl(COD)]_2$ (5 mol %), BINAP (10 mol %), Cs_2CO_3 (2.0 equiv), 9:1 Dioxane/H_2O (2 mL), 80 °C, 24.h.
[a] Isolated yield.

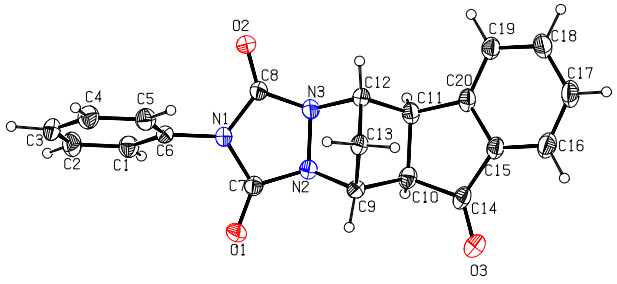
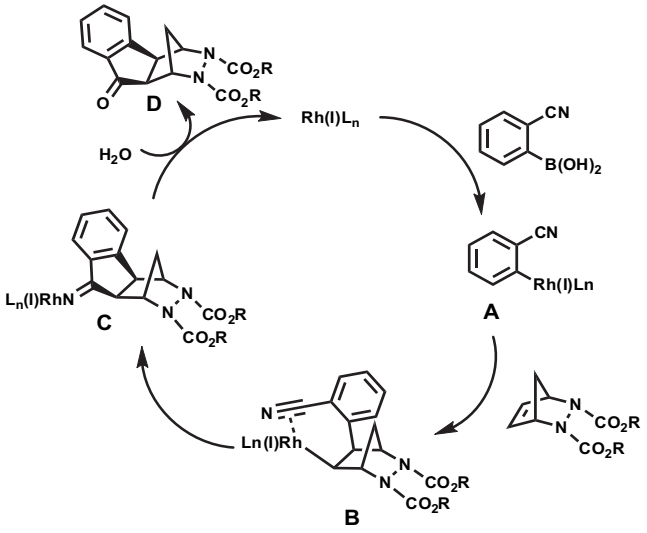


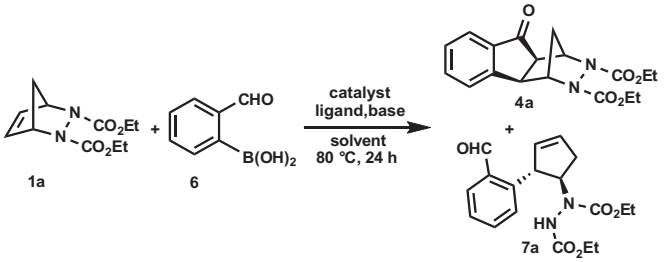
Fig. 2. ORTEP diagram of annulated product **4e**.

Based on these results, we propose a plausible mechanism for the annulation reaction.[20] The first step of the catalytic cycle involves transmetalation of 2-cyanophenylboronic acid to Rh(I) species to generate the intermediate **A**, which then undergoes '*syn*' addition to the alkene double bond through the '*exo*' phase resulting in the formation of intermediate **B**. Coordination of Rh(I) Ln to the electrophilic cyano group occurs, which is followed by intramolecular addition to generate the intermediate **C**. Hydrolysis of the imine bond results in the formation of the annulated product and regeneration of the Rh(I) species to continue the catalytic cycle (Scheme 4).



Scheme 4. Plausible mechanism for the annulation reaction.

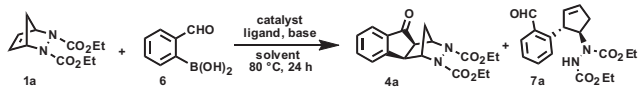
We then turned our attention towards the reaction of olefins with 2-formylphenylboronic acid and accordingly the bicyclic alkene **1a** was treated with 2-formylphenylboronic acid **6** in the presence of rhodium catalyst $[RhCl(COD)]_2$, ligand BINAP and base K_2CO_3, in CH_3CN at 80 °C. The reaction afforded a mixture of 3,4-disubstituted cyclopentene **7** along with the functionally substituted indanone **4a** (Scheme 5).



Scheme 5. Rhodium catalyzed annulation of azabicyclic olefin.

In order to develop conditions suitable for this transformation we surveyed a variety of rhodium catalysts, ligands, bases, solvents, and temperatures and optimization reactions are summarized in Table 5. Temperature showed a dramatic effect in the cyclization process. No cyclization product was observed when bicyclic alkene **1a** was treated with 2-formylphenylboronic acid **6** in the presence of rhodium catalyst ligated with nonchiral ligands at room temperature. The effects of different phosphine ligands and different bases were also studied. Best results were obtained using chiral bidentate ligands (entries 4, 5). Among the bases examined, K_2CO_3 gave the best results. Other bases, such as Cs_2CO_3, KOH, Et_3N, NaOAc etc. have also been employed in this reaction but none of them gave a better yield than K_2CO_3. From the optimization studies carried out for rhodium catalysts, we found that $[Rh(OH)(COD)]_2$ also gave products in good yield. Using $[RhCl(COD)]_2$ as catalyst and Monophos as ligand, the effect of different solvents were studied, among which CH_3CN was found to be the best. On the basis of the above results, the following reaction condition has been chosen as the standard reaction condition: 1.0 equiv of 2-formylphenylboronic acid, 1.25 equiv of bicyclic alkene, 5 mol % of $[RhCl(COD)]_2$, 10 mol % of Monophos and 1.5 equiv of K_2CO_3, in 2 mL of CH_3CN at 80 °C (Table 5).

Table 5
Optimization studies for the annulation reaction



Entry	Catalyst	Solvent	Base	Ligand	Yields (%)[a]	
					4a	7a
1	$[RhCl(COD)]_2$	CH_3CN	K_2CO_3	dppe	0	15
2	$[RhCl(COD)]_2$	CH_3CN	K_2CO_3	dppm	0	16
3	$[RhCl(COD)]_2$	CH_3CN	K_2CO_3	PPh_3	0	23
4	$[RhCl(COD)]_2$	CH_3CN	K_2CO_3	BINAP	40	22
5	*$[RhCl(COD)]_2$*	*CH_3CN*	*K_2CO_3*	*Monophos*	49	38
6	$[RhCl(COD)]_2$	CH_3CN	KF	Monophos	23	25
7	$[RhCl(COD)]_2$	CH_3CN	Cs_2CO_3	Monophos	43	32
8	$[RhCl(COD)]_2$	CH_3CN	KOH	Monophos	21	29
9	$[RhCl(COD)]_2$	CH_3CN	NaOAc	Monophos	12	10
10	$[RhCl(COD)]_2$	CH_3CN	Et_3N	Monophos	21	35
11	$[RhCl(COE)_2]_2$	CH_3CN	K_2CO_3	Monophos	Trace	Trace
12	[Rh(acac)(COD)]	CH_3CN	K_2CO_3	Monophos	15	14
13	$[Rh(OH)(COD)]_2$	CH_3CN	K_2CO_3	Monophos	49	24
14	$[RhCl(COD)]_2$	Toluene	K_2CO_3	Monophos	21	17
15	$[RhCl(COD)]_2$	THF	K_2CO_3	Monophos	8	27
16	$[RhCl(COD)]_2$	Methanol	K_2CO_3	Monophos	16	44
17	$[RhCl(COD)]_2$	DMF	K_2CO_3	Monophos	28	24

Reaction conditions: Alkene (1.25 equiv), 6 (1.0 equiv), Catalyst (5 mol %), Ligand (10 mol %), Base (1.5 equiv), Solvent (2 mL), 80 °C, 24 h. The condition in italics denotes the optimized conditions for the relevant reactions.
[a] Isolated yield.

Various bicyclic alkenes **1a**–**d** and tricyclic alkenes **2a**, **2b** and **2d** were treated with 2-formylphenylboronic acid **6** under the optimized conditions. All the attempts resulted in the formation of functionally substituted indanones as the major product and 3,4-disubstituted cyclopentene as the minor product (Table 6).

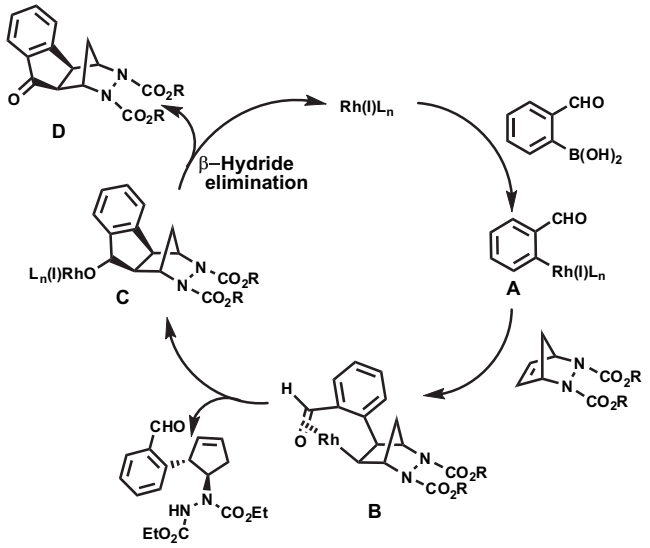
Table 6
Generality of the rhodium catalyzed annulation reaction

Entry	Alkene	Products		Yields(%)[a]	
		4	7	4	7
1	**1a**	**4a**	**7a**	49	38
2	**1b**	**4b**	**7b**	47	40
3	**1c**	**4c**	**7c**	45	41
4	**1d**	**4d**	**7d**	45	30
5	**2a**	**4e**	**7e**	37	31
6	**2b**	**4f**	**7f**	36	27
7	**2d**	**4h**	**7g**	39	25

Reaction conditions: Alkene (1.25 equiv), 6 (1.0 equiv), $[RhCl(COD)]_2$ (5 mol %), Monophos (10 mol %), K_2CO_3 (1.5 equiv), CH_3CN (2 mL), 80 °C, 24 h.
[a] Isolated yield.

The products were characterized on the basis of their spectral data. The structure and stereochemistry were unambiguously supported by an X-ray analysis (Fig. 2).[22]

The mechanism shown in Scheme 6 is proposed for this annulation process. The mechanism may involve two stages, the initial one being the ring opening of bicyclic alkene.[11e,i] The first step of the catalytic cycle involves transmetalation of 2-formylphenylboronic acid to Rh(I) species to generate the intermediate **A**, which then undergoes '*syn*' addition to the alkene double bond through the '*exo*' phase and results in the formation of intermediate **B**. Coordination of Rh(I)Ln to the electrophilic aldehydic group occurs, which is followed by intramolecular addition to generate the intermediate **C**. β-Hydride elimination results in the formation of the annulated product and regeneration of the Rh(I) species to continue the catalytic cycle.[23] β-elimination facilitated by the ligands could lead to the formation of the ring opened 3,4-disubstituted cyclopentene.[11e,i]



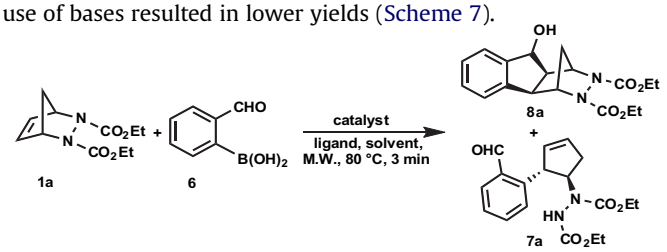
Scheme 6. Plausible mechanism for the annulation reaction.

2.3. Palladium catalyzed carbonylative cyclization with 2-formylphenylboronic acid

We were then interested in checking the reactivity of 2-formylphenylboronic acid towards bicyclic and tricyclic alkenes under Pd catalyzed conditions. Our initial studies focused on the palladium catalyzed carbonylation of azabicyclic alkenes employing the 2-formylphenylboronic acid **6** in the presence of palladium catalyst

$Pd(OAc)_2$, ligand dppe, in MeOH solvent at room temperature, and the reaction afforded the 3,4-disubstituted cyclopentene **7** in good yields.

No cyclization product was observed when bicyclic alkene **1a** was treated with 2-formylphenylboronic acid **6** in the presence of palladium catalyst at room temperature. When the solvent was changed from MeOH to CH_3CN at 80 °C, to our delight, the major product (49%) was found to be indanol **8a**, along with the 3,4-disubstituted cyclopentene **7a**. From the solvents tested, CH_3CN/H_2O (9:1) was found to be the best for the formation of annulation product. The catalysts screened were $Pd(OAc)_2$, $[Pd(allyl)Cl]_2$, $PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd_2dba_3\cdot CHCl_3$ and $Pd(PPh_3)_4$, from which $Pd(OAc)_2$ gave the highest yield. Among the palladium catalysts that were examined $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ were found to be ineffective. Among the various ligands screened, dppe gave the highest yield. Finally we studied the effect of bases in this reaction and found that use of bases resulted in lower yields (Scheme 7).



Scheme 7. Palladium catalyzed annulation of azabicyclic olefin.

The low yields of the products in the carboannulation of diazabicyclic alkenes with 2-formylphenylboronic acid in conventional heating prompted us to conduct the reaction using microwave heating. The key advantage of the microwave heating process over conventional heating method is the nature of fast internal heating by microwave irradiation. Microwave energy deposition in the dielectric loss mode of heating can cause spatially uniform heating and help to reduce the reaction time drastically.[24] The reaction under microwave condition gave the expected indanol in 76% yield. Thus optimized conditions for the reaction was found to be a 1:1 mixture of 2-formylphenylboronic acid/olefin with 5 mol % $Pd(OAc)_2$, 10 mol % dppe and 2 mL of CH_3CN/H_2O solvent (9:1) at 80 °C under microwave heating for 3 min (Table 7).

Table 7
Optimization studies for the annulation reaction

Entry	Catalyst	Solvent, Temp	Ligand	Yields (%)[a]	
				8a	7a
1	$Pd(OAc)_2$	MeOH, rt	dppe	0	57
2	$Pd(OAc)_2$	MeOH, 60 °C	dppe	0	67
3	$Pd(OAc)_2$	THF, 60 °C	dppe	11	47
4	$Pd(OAc)_2$	CH_3CN, 60 °C	dppe	40	23
5	$Pd(OAc)_2$	CH_3CN, 80 °C	dppe	49	17
6	$Pd(OAc)_2$	CH_3CN/H_2O, 80 °C	dppe	55	18
7	$Pd(OAc)_2$	Toluene	dppe	0	10
8	$Pd(OAc)_2$	DMF	dppe	trace	27
9	$Pd_2(dba)_3\cdot CHCl_3$	CH_3CN/H_2O, 80 °C	dppe	45	14
10	$PdCl_2$	CH_3CN/H_2O, 80 °C	dppe	25	8
11	$Pd[(allyl)Cl]_2$	CH_3CN/H_2O, 80 °C	dppe	32	13
12	$PdCl_2(PPh_3)_2$	CH_3CN/H_2O, 80 °C	dppe	0	0
13	Pd(PPh3)4	CH_3CN/H_2O, 80 °C	dppe	0	0
14	$Pd(OAc)_2$	CH_3CN/H_2O, 80 °C	dppf	45	17
15	$Pd(OAc)_2$	CH_3CN/H_2O, 80 °C	PPh_3	42	16
16	$Pd(OAc)_2$	CH_3CN/H_2O, 80 °C	P(o-tolyl Ph)$_3$	43	15
17	*$Pd(OAc)_2$*	*CH_3CN/H_2O, M.W.*, 80 °C	*dppe*	76	7

Reaction conditions: Alkene (1.0 equiv), 6(1.0 equiv), Catalyst (5 mol %), Ligand (10 mol %), Solvent (2 mL), M.W., 80 °C, 3 min. The condition in italics denotes the optimized conditions for the relevant reactions.
[a] Isolated yield.

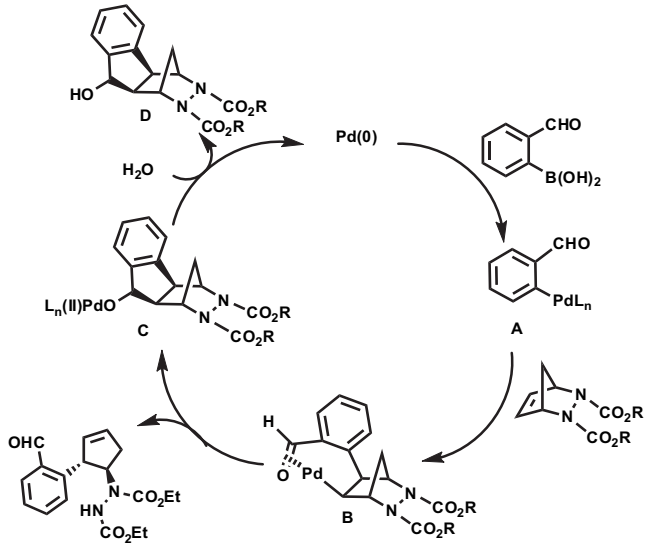
Similar reactivity was observed with other bicyclic alkenes and the results obtained are summarized in Table 8. The products were characterized on the basis of their spectral data. The tricyclic olefins derived from triazolinedione and cyclopentadiene gave exclusively the 3,4-disubstituted cyclopentene in good yields.

Table 8
Generality of the palladium catalyzed annulation reaction

Entry	Alkene	Products		Yields(%)[a]	
		8	**7**	8	7
1	**1a**	**8a**	**7a**	76	7
2	**1b**	**8b**	**7b**	79	9
3	**1c**	**8c**	**7c**	77	11
4	**1d**	**8d**	**7d**	83	8
5	**2a**	—	**7e**	—	87
6	**2b**	—	**7f**	—	85
7	**2d**	—	**7g**	—	90

Reaction conditions: Alkene (1.0 equiv), 6 (1.0 equiv), $Pd(OAc)_2$ (5 mol %), dppe (10 mol %), CH_3CN/H_2O (2 mL) (9:1), M.W., 80 °C, 3 min.
[a] Isolated yield.

The mechanism shown in Scheme 8 is proposed for this annulation process. The mechanism may involve two stages, the initial one being the ring opening of bicyclic alkene.[12d] The first step of the catalytic cycle involves transmetalation of 2-formylphenylboronic acid to PdL_2 giving ArPdL to generate the intermediate **A**. **A** then undergoes '*syn*' addition to the alkene double bond through the '*exo*' phase and results in the formation of intermediate **B**. Coordination of Pd to the electrophilic aldehydic group occurs, which is followed by intramolecular addition to generate the intermediate **C**. Hydrolysis in the final step results in the formation of the annulated product and regeneration of the palladium to continue the catalytic cycle.[25]



Scheme 8. Plausible mechanism for the annulation reaction.

1-Indanones occur as structural subunits in a number of natural products that exhibit a wide range of biological activity[26] and it is prominently featured in many pharmaceutical products.[27–32] Further synthetic transformations of functionalized indanones, such as deprotection of the ester group and cleavage of N–N bond by platinum catalyzed hydrogenation can lead to the formation of cyclopentane fused diaminoindanones of potential utility in pharmaceuticals and material science. Some of the bioactive molecules containing indanone core are shown in Fig. 3.

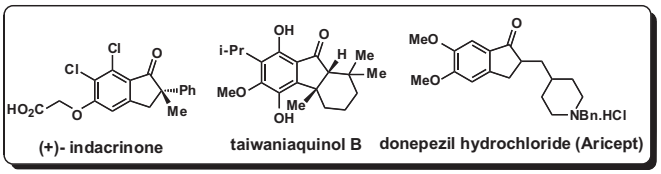


Fig. 3. Bioactive 1-indanone derivatives.

3. Conclusion

In conclusion, a direct and efficient transition metal catalyzed method for the synthesis of substituted indanones has been developed. The methodology assumes significance as indanones constitute the core structures of many biologically active compounds, synthetic intermediates for pharmaceuticals, ligands for olefin polymerization catalysts and discotic liquid crystals. Further work to utilize the fused indanones towards functionalized diaminoindanone derivatives are in progress and will be reported in due course.

4. Experimental section

4.1. General

All reactions were carried out in oven dried Schlenk tube under argon atmosphere. Progress of the reaction was monitored by Thin Layer Chromatography, which was performed on Merck precoated plates (silica gel. 60 F_{254}, 0.25 mm) and was visualized by fluorescence quenching under UV light or by staining with Enholm yellow solution. Column chromatography was done using 100–200 mesh silica gel and appropriate mixture of petroleum ether (60–80 °C) and ethyl acetate for elution. The solvents were removed using Buchi rotary evaporator. The microwave reactions were performed in a microwave synthesis reactor (Shanghai Sineo Microwave Chemistry Technology Co. Ltd., MAS-II) with temperature control, using the instrument's in-built IR sensor. The IR spectra were recorded on Bruker FT-IR spectrometer. NMR spectra were recorded on Bruker FT-NMR spectrometer using $CDCl_3$ or $CDCl_3$–CCl_4 mixture (7:3) as solvent. TMS was used as an internal standard and chemical shifts are in δ-scale. High resolution mass spectra were recorded under EI/HRMS (at 5000 resolution) using JEOL JMS 600H mass spectrometer. Abbreviations used in ^{1}H NMR are s-singlet, br s-broad singlet, d-doublet, dd-doublet of doublet, q-quartet and m-multiplet.

4.1.1. General procedure for the palladium catalyzed carboannulation of bicyclic hydrazines with 2-iodobenzonitrile. Bicyclic hydrazine (1.0 equiv), 2-iodobenzonitrile (1.0 equiv), Et_3N (2.0 equiv), PPh_3 (10 mol %) and $Pd_2(dba)_3 \cdot CHCl_3$ (10 mol %) were taken in a Schlenk tube and degassed. The mixture was dissolved in acetonitrile/water (9:1) (2 mL) and stirred at 80 °C for 24 h under Argon atmosphere. After the completion of the reaction, the reaction mixture was diluted with dichloromethane (50 mL) and washed with water (2×25 mL) and saturated brine (25 mL) solution. The organic layer was then dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo. The residue on silica gel (100–200 mesh) column chromatography using 30% ethyl acetate in hexane afforded the product in good yield.

4.1.2. General procedure for the rhodium catalyzed carboannulation of bicyclic hydrazines with 2-cyanophenylboronic acid. Bicyclic hydrazine (1.0 equiv), 2-cyanophenylboronic acid (1.0 equiv), $[RhCl(COD)]_2$ (5 mol %), BINAP (10 mol %), Cs_2CO_3 (2 equiv) were charged in a Schlenk flask, degassed with argon and the mixture was dissolved in dioxane/water (9:1) (2 mL). The reaction mixture was stirred at 80 °C for 24 h. The contents were transferred to a round-bottom flask, and volatiles were removed in vacuo. The residue on silica gel (100–200 mesh) column chromatography using 30% ethyl acetate in hexane afforded the product in good yield.

4.1.3. General procedure for the rhodium catalyzed carboannulation of bicyclic hydrazines with 2-formylphenylboronic acid. Bicyclic hydrazine (1.25 equiv), 2-formylphenylboronic acid (1 equiv), $[RhCl(COD)]_2$ (5 mol %), Monophos (10 mol %), K_2CO_3 (1.5 equiv) were charged in a Schlenk flask, degassed with argon and the mixture was dissolved in acetonitrile (2 mL). The reaction mixture was stirred at 80 °C for 24 h. The contents were transferred to a round-bottom flask, and volatiles were removed in vacuo. The residue on silica gel (100–200 mesh) column chromatography using ethyl acetate in hexane afforded the products in good yield.

4.1.4. General procedure for the palladium catalyzed carboannulation of bicyclic hydrazines with 2-formylphenylboronic acid. Bicyclic hydrazine (1.0 equiv), 2-formylphenylboronic acid (1 equiv), $Pd(OAc)_2$ (5 mol %), dppe (10 mol %), were charged in a 10 ml glass tube, degassed with argon and the mixture was dissolved in CH_3CN/H_2O (9:1) (2 mL) and the vessel was placed into the microwave cavity. Microwave irradiation of 500 W was used, the temperature being ramped from room temperature to 80 °C. The reaction mixture was stirred at 80 °C for 3 min. After the mixture was allowed to cool to room temperature, the contents were transferred to a round-bottom flask, and volatiles were removed in vacuo. The residue on silica gel (100–200 mesh) column chromatography using 40% ethyl acetate in hexane afforded the products in good yield.

4.1.5. Spectroscopic data for new compounds.

*4.1.5.1. Compound **4a**.* Yield: 74% as pale yellow viscous liquid; R_f: (40% EtOAc/hexane) 0.36; IR (Neat) ν_{max}: 3016, 2997, 2926, 1711, 1606, 1466, 1325, 1255, 1169, 1040, 870, 727 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (m, 1H), 7.76–7.59 (m, 2H), 7.43–7.38 (m, 1H), 4.69 (br s, 2H), 4.23 (br s, 4H), 3.71 (br s, 1H), 3.07 (br s, 1H), 1.48 (m, 1H), 1.38–1.11 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.1, 157.1, 156.5, 152.8, 138.7, 135.5, 128.7, 126.4, 124.4, 62.7, 61.0, 53.4, 45.5, 32.0, 14.6; HRMS (EI): calcd for $C_{18}H_{20}N_2O_5$ (M^+): 344.1372, found: 344.1365.

*4.1.5.2. Compound **4b**.* Yield: 67% as pale yellow viscous liquid; R_f: (40% EtOAc/hexane) 0.46; IR (Neat) ν_{max}: 3021, 2993, 2932, 1712, 1604, 1468, 1330, 1256, 1169, 1099, 855, 730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, 1H, J=7.5 Hz), 7.69–7.66 (m, 1H), 7.62 (s, 1H), 7.46–7.43 (m, 1H), 5.03 (br s, 2H), 4.78–4.62 (m, 2H), 3.73 (br s, 1H), 3.10 (br s, 1H), 1.49 (d, 1H, J=11.0 Hz), 1.32–1.25 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.3, 157.4, 152.9, 138.7, 135.5, 128.6, 126.4, 124.3, 70.5, 62.1, 61.8, 53.5, 45.5, 31.9, 22.0; HRMS (EI): calcd for $C_{20}H_{24}N_2O_5$ (M^+): 372.1685, found: 372.1675.

*4.1.5.3. Compound **4c**.* Yield: 90% as white solid; R_f: (40% EtOAc/hexane) 0.56; mp=154 °C; IR (Neat) ν_{max}: 3051, 2991, 2951, 1719, 1608, 1505, 1450, 1333, 1240, 1145, 966, 751 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, 1H, J=8.0 Hz), 7.60 (t, 1H, J=7.5 Hz), 7.54 (br s, 1H), 7.37 (t, 1H, J=7.5 Hz), 4.75–4.67 (m, 1H), 4.55–4.51(m, 1H) 3.65 (br s, 1H), 3.00 (br s, 1H), 1.53–1.40 (m, 19H), 1.12 (d, 1H, J=8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.3, 157.6, 153.1, 138.7, 135.5, 128.6, 126.5, 124.2, 81.9, 62.6, 61.0, 53.0, 45.4, 31.9, 29.7, 28.2; HRMS (EI): calcd for $C_{22}H_{28}N_2O_5$ (M^+): 400.1998, found: 400.1993.

*4.1.5.4. Compound **4d**.* Yield: 78% as pale yellow viscous liquid; R_f: 0.41 (6:4 hexane/EtOAc); IR (Neat) ν_{max}: 3032, 2952, 2919, 1719, 1603, 1474, 1314, 1248, 1129, 1091, 970, 751 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, 1H, J=7.5 Hz), 7.66–7.65 (m, 2H), 7.46–7.28 (m, 11H), 5.26–5.24 (m, 4H), 4.77–4.70 (m, 2H) 3.69 (br s, 1H), 3.06 (br s, 1H), 1.52 (d, 1H, J=11.0 Hz) 1.24 (d, 1H, J=11.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.4, 157.1, 153.1, 138.8, 135.8, 128.6,

128.5, 128.2, 128.0, 126.5, 124.3, 62.3, 61.3, 53.3, 45.4, 43.6, 32.0; HRMS (EI): calcd for $C_{28}H_{24}N_2O_5$ (M^+): 468.1685, found: 468.1689.

4.1.5.5. Compound ***4e***. Yield: 70% as white solid; R_f: (40% EtOAc/hexane) 0.33; mp=256 °C; IR (Neat) ν_{max}: 3030, 2998, 2928, 1781, 1710, 1606, 1505, 1423, 1286, 1137, 1091, 852, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, 1H, J=7.5 Hz), 7.74 (d, 1H, J=7.0 Hz), 7.68 (d, 1H, J=7.5 Hz), 7.51 (br s, 5H), 7.41(br s, 1H), 4.95 (s, 1H), 4.84 (s, 1H), 3.96 (d, 1H, J=5.5 Hz), 3.32 (d, 1H, J=5.5 Hz), 1.77 (d, 1H, J=11.5 Hz), 1.49 (d, 1H, J=12.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.7, 157.0, 156.5, 151.7, 138.5, 135.9, 131.4, 129.2, 128.4, 126.4, 125.3, 124.7, 62.7, 60.8, 53.2, 46.0, 33.1; HRMS (EI): calcd for $C_{20}H_{15}N_3O_3$ (M^+): 345.1113, found: 345.1111.

4.1.5.6. Compound ***4f***. Yield: 78% as pale yellow viscous liquid; R_f: (40% EtOAc/hexane) 0.38; IR (Neat) ν_{max}: 3033, 2980, 2945, 1780, 1711, 1604, 1514, 1420, 1270, 1124, 1036, 922, 728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, 1H, J=7.5 Hz), 7.71–7.70 (m, 1H), 7.63–7.61 (m, 1H), 7.50–7.47 (m, 1H), 7.42–7.40 (m, 1H), 7.35–7.29 (m, 4H), 4.81 (s, 1H), 4.70 (s, 1H), 4.69 (s, 2H), 3.76 (d, 1H, J=6.5 Hz), 3.15 (d, 1H, J=6.5 Hz), 1.59 (d, 1H, J=11.5 Hz), 1.37 (d, 1H, J=11.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.8, 158.2, 157.7, 151.8, 138.5, 135.9, 135.3, 129.1, 128.8, 128.6, 128.4, 128.2, 128.0, 126.4, 124.6, 62.4, 60.5, 53.1, 45.8, 43.5, 33.9; HRMS (EI): calcd for $C_{21}H_{17}N_3O_3$ (M^+): 359.1270, found: 359.1277.

4.1.5.7. Compound ***4g***. Yield: 96% as white solid; R_f: (40% EtOAc/hexane) 0.54; mp=214 °C; IR (Neat) ν_{max}: 3011, 2988, 2939, 1780, 1712, 1604, 1518, 1440, 1288, 1132, 1096, 911, 782 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, 1H, J=8.0 Hz), 7.65–7.62 (m, 1H), 7.56 (d, 1H, J=8.0 Hz), 7.41 (t, 1H, J=7.5 Hz), 4.70 (s, 1H), 4.59 (s, 1H), 3.75–3.73 (m, 2H), 3.09 (d, 1H, J=6.0 Hz), 2.06–2.03 (m, 2H), 1.78 (d, 1H, J=13.5 Hz), 1.65–1.59 (m, 4H), 1.51–1.48 (m, 2H), 1.20–1.29 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.0, 158.6, 158.1, 152.0, 138.5, 135.8, 129.0, 126.4, 124.6, 62.5, 60.5, 53.0, 52.8, 45.8, 32.4, 29.3, 25.7, 24.9; HRMS (EI): calcd for $C_{20}H_{21}N_3O_3$ (M^+): 351.1583, found: 351.1572.

4.1.5.8. Compound ***4h***. Yield: 80% as pale yellow viscous liquid; R_f: (40% EtOAc/hexane) 0.38; IR (Neat) ν_{max}: 3036, 2978, 2935, 1779, 1713, 1609, 1515, 1427, 1260, 1114, 1037, 912, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, 1H, J=7.8 Hz), 7.72–7.68 (m, 1H), 7.60 (d, 1H, J=7.5 Hz), 7.49–7.44 (m, 1H), 7.29–7.20 (m, 2H), 7.12–7.10 (m, 2H), 4.78 (s, 1H), 4.67 (s, 1H), 4.60 (s, 2H), 3.76 (d, 1H, J=6.0 Hz), 3.12 (d, 1H, J=6.0 Hz), 2.31 (s, 3H), 1.56 (d, 1H, J=11.7 Hz), 1.34 (d, 1H, J=11.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.7, 158.1, 157.7, 151.7, 138.4, 137.7, 135.7, 132.3, 129.3, 129.2, 128.9, 128.4, 128.3, 126.3, 124.5, 62.3, 60.4, 52.9, 45.7, 43.2, 32.8, 21.1; HRMS (EI): calcd for $C_{22}H_{19}N_3O_3$ (M^+): 373.1426, found: 373.1422.

4.1.5.9. Compound ***4i***. Yield: 77% as pale yellow viscous liquid; R_f: (40% EtOAc/hexane) 0.26; IR (Neat) ν_{max}: 3023, 2980, 2965, 1784, 1711, 1626, 1524, 1440, 1280, 1124, 1039, 927, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, 1H, J=7.5 Hz), 7.71–7.68 (m, 1H), 7.61 (d, 1H, J=7.5 Hz), 7.48–7.46 (m, 1H), 7.43–7.42 (m, 1H), 7.29–7.27 (m, 2H), 6.86–6.84 (m, 1H), 4.79 (s, 1H), 4.68 (s, 1H), 4.56 (s, 2H), 3.87 (s, 3H), 3.77 (d, 1H, J=6.5 Hz), 3.12 (d, 1H, J=6.5 Hz), 1.56 (d, 1H, J=12.0 Hz), 1.36 (d, 1H, J=11.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.7, 157.9, 157.5, 154.9, 151.6, 138.4, 135.8, 130.5, 129.0, 128.1, 126.3, 124.5, 122.7, 111.9, 62.3, 60.4, 55.9, 53.0, 45.8, 42.5, 32.9; HRMS (EI): calcd for $C_{22}H_{19}N_3O_4$ (M^+): 389.1376, found: 389.1369.

4.1.5.10. Compound ***4j***. Yield: 83% as white solid; R_f: (40% EtOAc/hexane) 0.51; mp=152 °C; IR (Neat) ν_{max}: 3039, 2998, 2975, 1767, 1712, 1609, 1524, 1431, 1271, 1125, 1037, 931, 717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, 1H, J=7.5 Hz), 7.70 (t, 1H, J=7.5 Hz), 7.61 (d, 1H, J=7.5 Hz), 7.47 (t, 1H, J=7.5 Hz), 7.36–7.27 (m, 4H), 4.79 (s, 1H), 4.68 (s, 1H), 4.61 (s, 2H), 3.76 (d, 1H, J=6.0 Hz), 3.12 (d, 1H, J=6.0 Hz), 1.57 (d, 1H, J=11.7 Hz), 1.36 (d, 1H, J=11.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.5, 157.8, 157.4, 151.6, 138.4, 135.8, 134.3, 133.7, 129.9, 129.0, 128.9, 126.3, 124.5, 62.3, 60.4, 52.9, 45.7, 42.7, 32.9; HRMS (EI): calcd for $C_{21}H_{16}ClN_3O_3$ (M^+): 393.0880, found: 393.0871.

4.1.5.11. Compound ***7a***. Yield: 38% as pale yellow viscous liquid; R_f: (30% EtOAc/hexane) 0.27; IR (Neat) ν_{max}: 3296, 3060, 2983, 2934, 2872, 2751, 1714, 1600, 1574, 1482, 1414, 1330, 1241, 1131, 1060, 951, 817, 762, 654 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 10.04 (s, 1H), 7.72–7.71 (m, 1H), 7.59–7.57 (m, 1H), 7.46–7.43 (m, 2H), 5.95–5.93 (m, 1H), 5.59 (s, 1H), 5.15 (s, 1H), 4.88–4.72 (m, 1H), 4.27–4.21 (m, 2H), 4.00 (br s, 1H), 3.77 (br s, 1H), 2.72–2.64 (m, 2H), 1.35–1.16 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.7, 156.7, 155.8, 146.0, 135.3, 132.0, 131.0, 129.0, 126.9, 67.4, 62.0, 46.9, 35.0, 14.5; HRMS (EI): calcd for $C_{18}H_{22}N_2O_5$ (M^+): 346.1529, found: 346.1539.

4.1.5.12. Compound ***7b***. Yield: 40% as pale yellow viscous liquid; R_f: (30% EtOAc/hexane) 0.43; IR (Neat) ν_{max}: 3298, 3061, 2982, 2936, 2748, 1714, 1601, 1574, 1469, 1386, 1242, 1181, 1108, 1041, 960, 817, 762, 658 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 10.04 (s, 1H), 7.70–7.68 (m, 1H), 7.58–7.56 (m, 1H), 7.46–7.43 (m, 1H), 7.33–7.32 (m, 1H), 5.93–5.92 (m, 1H), 5.58–5.57 (m, 1H), 5.14–5.13 (m, 1H), 5.07–5.05 (m, 2H), 4.72–4.69 (m, 1H), 2.69–2.59 (m, 2H), 1.23–1.21 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.1, 156.5, 155.3, 146.1, 134.3, 132.0, 131.1, 129.0, 126.8, 70.0, 69.5, 67.1, 47.8, 34.9, 22.0, 21.9; HRMS (EI): calcd for $C_{20}H_{26}N_2O_5$ (M^+): 374.1842, found: 374.1853.

4.1.5.13. Compound ***7c***. Yield: 41% as pale yellow viscous liquid; R_f: (30% EtOAc/hexane) 0.49; IR (Neat) ν_{max}: 3370, 3331, 3059, 2979, 2933, 2747, 1703, 1600, 1573, 1478, 1394, 1368, 1251, 1157, 1052, 953, 855, 759, 607 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 10.07 (s, 1H), 7.73–7.72 (m, 1H), 7.67–7.66 (m, 1H), 7.57–7.44 (m, 2H), 5.94–5.92 (m, 1H), 5.58–5.57 (m, 1H), 5.13–5.12 (m, 1H), 4.81–4.68 (m, 1H), 2.69–2.61 (m, 2H), 1.47 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.4, 156.1, 155.6, 146.4, 136.1, 134.3, 133.5, 132.0, 131.1, 128.7, 126.7, 80.9, 69.1, 66.7, 47.8, 34.7, 28.2; HRMS (EI): calcd for $C_{22}H_{30}N_2O_5$ (M^+): 402.2155, found: 402.2159.

4.1.5.14. Compound ***7d***. Yield: 30% as pale yellow viscous liquid; R_f: (30% EtOAc/hexane) 0.41; IR (Neat) ν_{max}: 3300, 3063, 3034, 2956, 2925, 2855, 2751, 1716, 1600, 1574, 1454, 1409, 1260, 1128, 1052, 819, 756, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.88 (s, 1H), 7.63–7.61 (m, 2H), 7.39–7.20 (m, 12H), 5.90–5.84 (m, 1H), 5.55–5.50 (m, 1H), 5.24–5.13 (m, 5H), 4.74–4.72 (m, 1H), 2.71–2.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.1, 156.4, 155.5, 145.6, 136.0, 135.8, 134.3, 130.9, 128.8, 128.4, 128.1, 127.8, 126.8, 67.6, 46.8, 35.0; HRMS (EI): calcd for $C_{28}H_{26}N_2O_5$ (M^+): 470.1842, found: 470.1837.

4.1.5.15. Compound ***7e***. Yield: 87% as white solid; R_f: (30% EtOAc/hexane) 0.32; mp=96 °C; IR (Neat) ν_{max}: 3367, 3060, 2924, 2854, 1769, 1706, 1601, 1502, 1422, 1268, 1157, 1073, 956, 763, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.97 (s, 1H), 7.71–7.70 (m, 1H), 7.57–7.54 (m, 1H), 7.46–7.35 (m, 5H), 7.31–7.26 (m, 2H), 5.94–5.92 (m, 1H), 5.62–5.61 (m, 1H), 5.29–5.27 (m, 1H), 4.62–4.57 (m, 1H), 2.71–2.68 (m, 1H), 2.62–2.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.5, 153.3, 152.8, 143.2, 133.6, 130.2, 128.2, 128.1, 127.9, 127.5, 127.3, 124.6, 65.7, 45.8, 33.2; HRMS (EI): calcd for $C_{20}H_{17}N_3O_3$ (M^+): 347.1270, found: 347.1277.

4.1.5.16. Compound ***7f***. Yield: 85% as white solid; R_f: (30% EtOAc/hexane) 0.24; mp=88 °C; IR (Neat) ν_{max}: 3353, 3064, 2927, 2856, 1767, 1703, 1600, 1452, 1418, 1357, 1261, 1169, 1075, 820, 763, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.95 (s, 1H), 7.73–7.71 (m, 1H), 7.60–7.57 (m, 1H), 7.48–7.42 (m, 2H), 7.37–7.33 (m, 2H),

7.31–7.24 (m, 3H), 5.95–5.94 (m, 1H), 5.64–5.63 (m, 1H), 5.26–5.25 (m, 1H), 4.65–4.54 (m, 3H), 2.71–2.66 (m, 1H), 2.58–2.57 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.1, 155.2, 155.1, 144.2, 135.4, 134.4, 133.5, 132.4, 130.5, 129.4, 128.9, 128.8, 128.7, 128.6, 128.3, 127.9, 126.9, 125.6, 66.5, 46.6, 42.9, 33.8; HRMS (EI): calcd for $C_{21}H_{19}N_3O_3$ (M^+): 361.1426, found: 361.1421.

4.1.5.17. Compound ***7g***. Yield: 90% as white solid; R_f: (30% EtOAc/hexane) 0.24; mp=94 °C; IR (Neat) ν_{max}: 3361, 3061, 2925, 2848, 1767, 1703, 1601, 1515, 1453, 1356, 1242, 1106, 1039, 870, 767, 647 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.89 (s, 1H), 7.67–7.65 (m, 1H), 7.54–7.51 (m, 1H), 7.43–7.37 (m, 2H), 7.26–7.17 (m, 2H), 7.04–7.02 (m, 2H), 5.89–5.87 (m, 1H), 5.58–5.56 (m, 1H), 5.20–5.18 (m, 1H), 4.57–4.47 (m, 3H), 2.62–2.57 (m, 1H), 2.51–2.49 (m, 1H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.7, 155.5, 155.4, 144.3, 137.7, 136.6, 134.6, 133.5, 132.5, 130.4, 129.4, 128.6, 127.6, 67.2, 46.4, 42.9, 33.5, 21.1; HRMS (EI): calcd for $C_{22}H_{21}N_3O_3$ (M^+): 375.1583, found: 375.1581.

4.1.5.18. Compound ***8a***. Yield: 76% as pale yellow viscous liquid; R_f: (50% EtOAc/hexane) 0.34; IR (Neat) ν_{max}: 3458, 2982, 2934, 1709, 1463, 1403, 1375, 1324, 1256, 1171, 1132, 1104, 1040, 947, 870, 760, 734 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, 1H, J=7.0 Hz), 7.31–7.25 (m, 3H), 4.81 (br s, 1H), 4.59–4.52 (m, 2H), 4.23–4.09 (m, 4H), 3.73 (br s, 1H), 3.13 (br s, 1H), 2.75 (br s, 1H) 1.47 (d, 1H, J=9.5 Hz), 1.37–1.25 (m, 6H), 1.15 (d, 1H, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.6, 145.2, 141.7, 129.3, 128.7, 128.2, 125.7, 62.5, 51.2, 32.5, 14.5; HRMS (EI): calcd for $C_{18}H_{22}N_2O_5$ (M^+): 346.1529, found: 346.1523.

4.1.5.19. Compound ***8b***. Yield: 79% as pale yellow viscous liquid; R_f: (50% EtOAc/hexane) 0.43; IR (Neat) ν_{max}: 3026, 2990, 2937, 1712, 1466, 1339, 1256, 1174, 1069, 865, 731 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, 1H, J=7.0 Hz), 7.30–7.27 (m, 3H), 4.97 (br s, 2H), 4.81 (br s, 1H), 4.71–4.43 (m, 2H), 3.73 (br s, 1H), 2.78 (br s, 1H), 1.44–1.38 (m, 1H), 1.30–1.20 (m, 12H), 1.19–1.44 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.5, 145.1, 141.7, 129.3, 128.2, 125.6, 124.7, 70.2, 63.2, 53.3, 32.3, 21.9; HRMS (EI): calcd for $C_{20}H_{26}N_2O_5$ (M^+): 374.1842, found: 374.1849.

4.1.5.20. Compound ***8c***. Yield: 77% as pale yellow viscous liquid; R_f: (50% EtOAc/hexane) 0.50; IR (Neat) ν_{max}: 3041, 2993, 2954, 1713, 1506, 1460, 1323, 1250, 1143, 974, 759 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, 1H, J=7.5 Hz), 7.26–7.20 (m, 3H), 4.81–4.76 (m, s, 1H), 2.74–2.65 (m, 1H), 1.53–1.39 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7, 144.1, 141.0, 128.4, 127.2, 124.6, 123.2, 80.5, 63.3, 62.4, 50.2, 31.3, 29.8, 28.3; HRMS (EI): calcd for $C_{22}H_{30}N_2O_5$ (M^+): 402.2155, found: 402.2159.

4.1.5.21. Compound ***8d***. Yield: 83% as pale yellow viscous liquid; R_f: (50% EtOAc/hexane) 0.43; IR (Neat) ν_{max}: 3042, 2962, 2929, 1712, 1509, 1494, 1312, 1258, 1167, 1088, 977, 754 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, 1H, J=7.0 Hz), 7.29–7.23 (m, 13H), 5.26–5.18 (m, 4H), 4.76 (br s, 1H), 4.62–4.53 (m, 2H), 3.68 (br s, 1H), 2.70 (br s, 1H), 1.45 (d, 1H, J=10.5 Hz) 1.10 (d, 1H, J=9.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.8, 145.0, 141.6, 135.9, 129.4, 128.3, 125.7, 124.7, 124.4, 68.2, 62.3, 53.3, 43.6, 32.0; HRMS (EI): calcd for $C_{28}H_{26}N_2O_5$ (M^+): 470.1842, found: 470.1847.

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22. X-ray crystal data of compound **4e**: empirical formula $C_{20}H_{15}N_3O_3$; Formula weight 345.35; Temperature 293(2) K; Wavelength 0.71073 Å; Crystal system Monoclinic; Space group P21/c; Unit cell dimensions a = 14.1108(16), A alpha =90 deg, b = 5.8515(7) Å, beta = 93.655(2) deg, c = 19.352(2) Å, gama =90 deg; Volume = 1594.6(3) A^3, Z = 4, Density (calculated) 1.439 Mg/m^3, Absorption coefficient = 0.099 mm^{-1}; F(000) 720; Crystal size = 0.45×0.35×0.14 mm; Theta range for data collection 2.11–28.00 deg; Index ranges −18i ≤h ≤14, −7 ≤k ≤7, −22 ≤l≤ 25; Reflections collected 8883; Independent reflections 3669 [R(int)=0.0284]; Absorption correction semi-empirical from equivalents; Max. and min. transmission 0.9862 and 0.9567 Refinement method; Full-matrix least-squares on F^2; Data/restraints/parameters 3669/0/295; Goodness-of-fit on F^2 1.320; Final R indices [I>2sigma(I)] $R1$=0.0802, $wR2$ =0.1576, R indices (all data) $R1$ =0.0874, $wR2$ =0.1613; Largest diff. peak and hole 0.232 and −0.204 e A^{-3}. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 749784.
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