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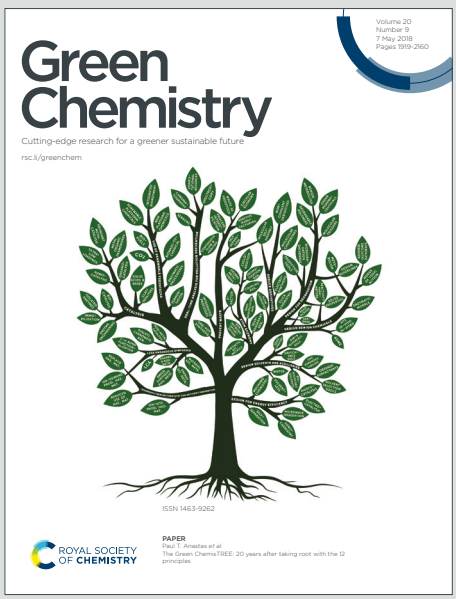

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DOI: 10.1039/D0GC03572F

ARTICLE

A metal-free method for facile synthesis of indanones *via* intramolecular hydroacylation of 2-vinylbenzaldehydes†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A facile method access to indanones was developed under metal- and additive-free conditions in which *L*-proline served as efficient and environmentally benign catalysts. Compared with previous indanones synthesis by transition-metal-catalyzed intramolecular hydroacylations of 2-vinylbenzaldehyde, this protocol provided a more green synthetic pathway to indanone scaffolds in good to excellent yields. More importantly, it could be used to synthsize anti-AD drug donepezil.

Introduction

1-Indanone is a common molecule scaffold widely used in pharmaceutical chemistry and organic synthesis, which exhibit a broad spectrum of biological activities.[1-21] For instance, indacrinone, a racemic mixture, is a loop-blocking diuretic drug.[1] Donepezil, an AChE inhibitor, used for the treatment of Alzheimer's disease.[2] Other indanone frameworks originated from nature, including Pterosin B and C,[3] substituted methoxy-indanone,[4] and Pauciflorol F,[5, 22] were found to have intriguing antibacterial activity, anticancer activity and HIV-inhibitory activity, respectively.

These significant biological value has attracted chemists widespread attention to develop efficient strategies to construct these intriguing molecule scaffolds,[23-42] such as Pd,[23-25] In,[26, 27] Au[28-34] or Cu[39] complex catalyzed intramolecular annulation or multiple-step cascade reactions were usually reported. Recently, an increasing number of studies indicated that the hydroacylation is a very important and efficient strategy to build C-C bonds by inserting alkene into the C-H bond of aldehyde group, which provides a direct pathway to form ketones from simple starting materials.[43-45] Most remarkably, Morehead's group reported a pioneering Rh(I)-catalyzed intramolecular asymmetric hydroacylation of 2-vinylbenzaldehyde to fulfill the synthesis of chiral 3-substituted indanones with high conversions and enantioselectivities (Scheme 1a).[46] Breit's group[47] and Coltart's group[48] also reported similar works to build indanones *via* an intramolecular hydroacylation of 2-vinylbenzaldehyde employing different Rh(I)-catalyst system, respectively. Besides, other metal-catalysts were also used to fulfill the intramolecular hydroacylation, for example Yoshikai's group finished a cobalt-chiral diphoshines catalyzed enantioselective intramolecular hydroacylation reaction of 2-alkenylbenzaldehyde to afford indanone derivatives (Scheme 1a).[49] However, these transition-metal-catalyzed hydroacylation represents a highly attractive synthetic approach to these intriguing ketone compounds, but they usually need an expensive transition-metal catalysts or undergo a decarbonylation competing side reaction.[26, 43, 50-52] Therefore, the alternative synthetic methods are highly desired. Recently, using *N*-heterocyclic carbenes (NHCs) to avoid these issues seems to be a logical idea,[53] for example, Glorius's group reported *N*-heterocyclic carbenes (NHCs) catalyzed strategy to synthesize indanones *via* intramolecular hydroacylation from unactivated olefin-substituted aldehydes (Scheme 1b).[54] Whereas the intricate starting materials and limited scope of substrates restricted its further application.

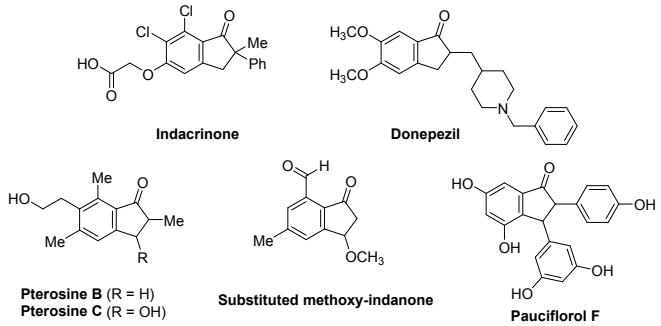

Figure 1 Some drugs containing 1-indanone cores.

Our group has also attempted to develop some efficient methods to construct indanone derivatives for the discovery of AChE inhibitors against Alzheimer's disease, and we have obtained a new anti-AD drug Fluoropezil fused indanone scaffold that is in a phase I clinical trial. In 2013, we reported an efficient strategy to prepare chiral 3-alkyl substituted indanones *via* an asymmetric Michael addition of *N*-tert-butanesulfinyl imidates with α,β-unsaturated diesters with excellent enantioselectivities.[55] Recently, we reported another facile and efficient copper-catalyzed method to construct 3-hydroxy-1-indanones employing simple 2-ethynylbenzaldehyde as starting

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†Electronic Supplementary Information (ESI) available: Experimental procedures and spectral data. For ESI data see DOI:10.1039/x0xx00000x
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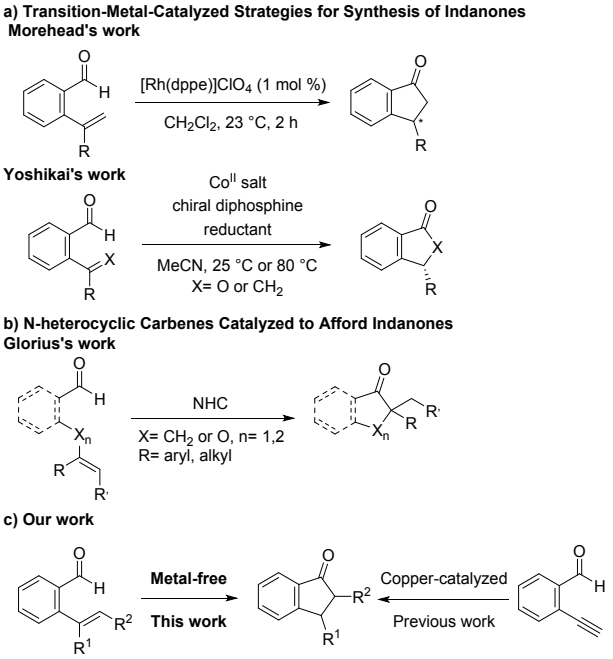


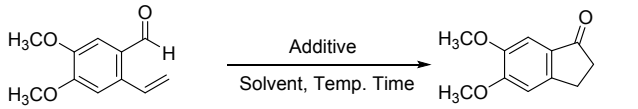
Scheme 1 Strategies for synthesis of indanones.

materials *via* an intramolecular annulation strategy (Scheme 1c).[39] However, the two methods still undergo some deficiencies, such as long synthetic route or the use of metal catalysts. Here, we offer a more facile strategy to prepare indanone scaffold *via* an efficient intramolecular hydroacylation under a metal-free reaction condition. The biggest feature is able to fulfil the construction of indanone scaffolds with a green hydroacylation condition, avoiding of the use of expensive and polluting metal catalysts. More importantly, it could be used to synthsize anti-AD drug donepezil.

Results and discussion

Based on our previous studies,[39] we have attempted to synthesize 4,5-dimethoxyindanone (**2a**) by treatment of 4,5-dimethoxy-2-vinylbenzaldehyde (**1a**) with CuI/pyrrolidine/AcOH catalytic system in 1,2-dichloroethane (DCE), but we have not detected the indanone scaffold **2a** (Table 1, entry 1). To our great surprise, when we used acetic acid as solvent, the indanone product could be observed in 74% yield (Table 1, entry 2). Further explorations showed that abolishing CuI in catalytic system is favourable for this transformation, but the absence of pyrrolidine will result in losing the target product (Table 1, entries 3-4). Encouraged by findings, we further evaluated pyrrolidine analogues as the single additive, such as piperidine, tetrahydroisoquinoline (THIQ) or L-proline in AcOH as solvent at 100 °C (Table 1, entries 5-7). To our delight, the desired product **2a** was up to 95% when L-proline was used as additive (Table 1, entry 7). The screening of reaction temperatures indicated that it has a very great influence on this transformation (Table 1, entries 8-9), which did not work below 80 °C. We speculated that required a high energy to get involved in the activation step of olefin. Subsequently, we continued to optimize reaction solvents among HCO_2H, Toluene, 1,4-Dioxane, DCE, CH_3OH and their mixed solvents (Table 1, entries 10-

Table 1 Optimization of metal-free mediated reactions of **1a**[a]

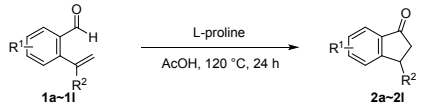


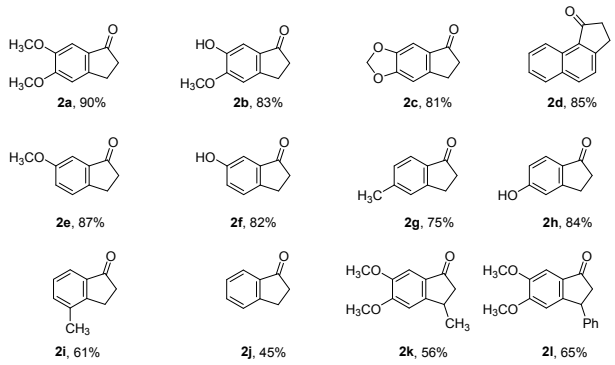
1a **2a**

entry	additive	solvent	T (°C)	yield (%)[b]
1	CuI/pyrrolidine/AcOH	DCE	100	0
2	CuI/pyrrolidine	AcOH	100	74
3	Pyrrolidine	AcOH	100	77
4	-	AcOH	100	0
5	Piperidine	AcOH	100	82
6	THIQ	AcOH	100	90
7	L-proline	AcOH	100	95
8	L-proline	AcOH	80	trace
9	L-proline	AcOH	110	94
10	L-proline	HCO_2H	100	0
11	L-proline	Toluene	100	0
12	L-proline	1,4-Dioxane	100	0
13	L-proline	DCE	100	0
14	L-proline	CH_3OH	100	0
15[c]	L-proline	AcOH/Toluene	100	0
16[c]	L-proline	AcOH/1,4-Dioxane	100	0
17[c]	L-proline	AcOH/DCE	100	0
18[c]	L-proline	AcOH/CH_3OH	100	0
19[d]	L-proline	AcOH	100	53
20[e]	L-proline	AcOH	100	66
21[d]	L-proline	AcOH	80	trace
22[d]	L-proline	AcOH	120	90
23[d]	L-proline	AcOH	130	87

[a] Reaction conditions: **1a** (0.2 mmol), additive (2 equiv), solvent (3 mL), for 12 h; [b] Isolated yields. [c] AcOH (2 equiv). [d] Additive (20 mol %), for 24 h. [e] Additive (50 mol %), for 24 h.

Table 2 The scope for the synthesis of indanones **2a**-**2l**[a, b]



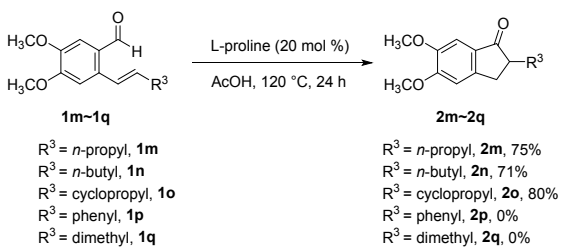


[a] Reaction conditions: **1a** (0.3 mmol), additive (20 mol %), solvent (3 mL), for 24 h; [b] Isolated yields.

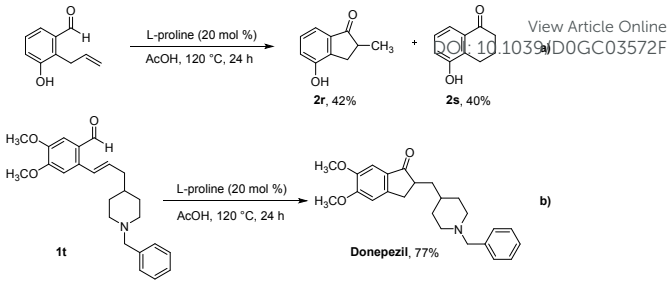
18). The results showed AcOH is still the desirable solvent, indicating it maybe acts a key role for this transformation. When we changed the amount of additive to 20 mol % and 50 mol %, respectively, the yield was only 53% and 66% (Table 1, entries 19-20). However, we can achieve 90% yield at 120 °C for 24 h (Table 1, entries 21-23). Taken together, the optimum reaction condition for this strategy was to use L-proline (20 mol %) as the catalyst and AcOH as solvent at 120 °C.

With the optimal conditions in hand, we further explored the scope of substrates, and the results are showed in Table 2. When we varied the R^1 or R^2 group, the substrates **1a–1l** reacted smoothly to afford corresponding desired products **2a–2j** with moderate to good yields (Table 2), in which disubstitutents (**2b**), polycyclic compounds (**2c** and **2d**), and monosubstituted groups as methoxyl (**2e**), methyl (**2g** and **2i**), hydroxyl (**2h** and**2f**) or hydrogen (**2j**) were all tolerated and could give the target product with excellent yields. However, it seemed that electron-withdrawing groups were harmful to this transformation and could not produce the target indanone scaffold (such as F, Cl, CN, and NO_2, data not shown).

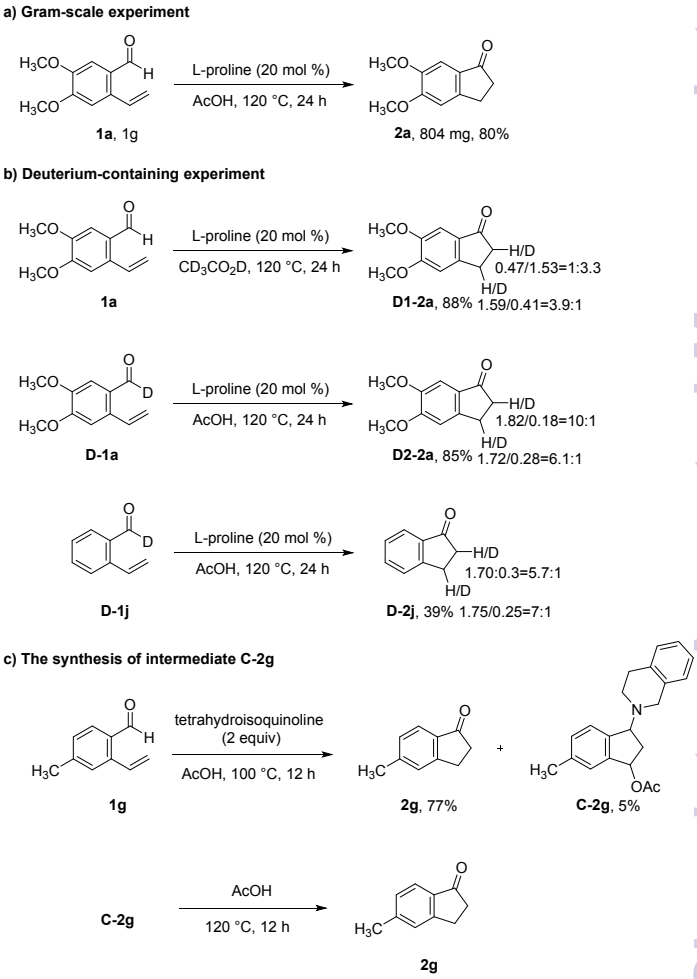
Transition-metal-catalyzed hydroacylation usually from terminal alkenyl aldehydes, as showed in Scheme 2, we can achieve unactivated olefin-substituted aldehydes with long-chain alkenes (**2m** and **2n**), and cycloalkenes (**2o**) with good yields. In addition, aryl-substituted alkenes (**2p**) and dimethyl-substituted alkenes (**2q**) have been exploited. Unfortunately, no target products were observed, correlated with high steric hindrance or electron-deficient.



Scheme 2 The scope for the synthesis of indanones **2m**-**2q**.



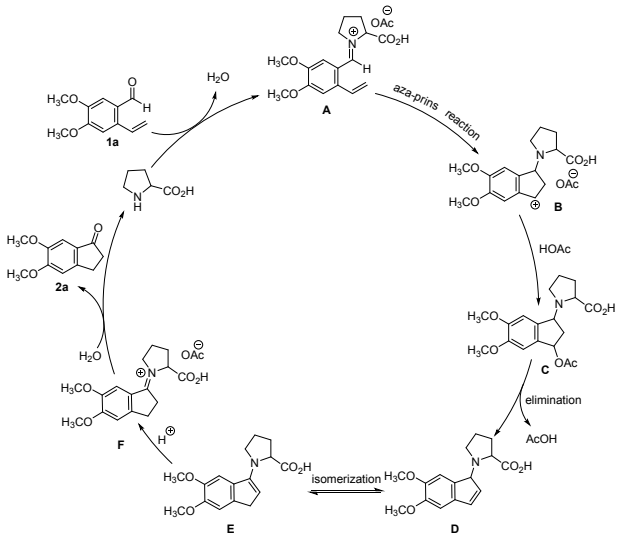
Scheme 3 The synthesis of indanone **2r**, **2s** and donepezil.



Scheme 4 Gram-scale experiment and further mechanism study.

Interestingly, as showed in Scheme 3a, a long chain allyl-substituted alkenes as starting material, 5- and 6-membered rings products (**2r** and **2s**) can be furnished in moderate yields, respectively. More intriguing, this strategy could be used to synthesize the anti-AD drug donepezil in an excellent yield (Scheme 3b), indicating a potential use for its production process.

To further evaluate the efficiency of this reaction, we performed the reaction on a gram-scale preparation with **1a**, and the yield of isolated product with 80% (Scheme 4a). Also, the explorations for possible reaction mechanism were firstly launched under the standard condition with CD_3CO_2D, and the results displayed that a part of deuterium-containing product **D1-2a** was obtained as expected (Scheme 4b). When the deuterium-aldehyde was used as the starting material, deuterium-containing product **D2-2a** and **D-2j**



Scheme 5 Proposed mechanism for the formation of **2a**.

was also detected, these resulting indicated that the hydrogen atom on indanone scaffold may come from acetic acid and aldehydes, respectively, maybe undergoing a hydrogen migration.A plausible mechanism is proposed for this transformation, as illustrated in Scheme 5. Firstly, compound **1a** reacts with L-proline through an initial activation to form the intermediate **A**, which was then through an aza-prins reaction[56] to give the intermediate **B**, followed by a nucleophilic attack to attain the intermediate **C**. Subsequently, an elimination[57] to afford intermediate **D**. The resulting **D** undergoes isomerization[58] under acid and high temperature to gain **E**, and protonation to form intermediate **F**, then hydration to furnish the final target product **2a**. During our studies, we fortunately captured a key intermediate **C** (**C-2g**) in 5% yield when replacing L-proline with tetrahydroisoquinoline, the intermediate **C-2g** could be further convert into the target product **2g** under acetic acid. This indirect proof maybe further supports this proposed mechanism (Scheme 4c).

Conclusions

Herein, we developed a highly efficient versatile strategy to afford indanones under metal-free conditions. Compared with transition-metal-catalyzed hydroacylation usually need terminal alkenyl substrates, we can achieve unactivated olefin-substituted substrates. This paper presents a simple, practical, green and environmentally benign protocol to prepare 1-indanones in moderate to good yields *via* an intramolecular hydroacylation of 2-vinylbenzaldehyde that avoiding the use of transition-metal-catalyst and reductant as co-catalyst altogether. More importantly, this strategy could be used to synthesize the anti-AD drug donepezil in an excellent yield, indicating a potential use for its production process.

Experimental

General Procedure for the Synthesis of Target Products (2a as an example).

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A 25 mL round bottom flask, 4,5-dimethoxy-2-vinylbenzaldehyde (**1a**) (58 mg, 0.3 mmol), L-proline (7 mg, 20 mol %) in glacial acetic acid (3 mL) was added and stirred at 120 °C for about 24 h under an air atmosphere (monitored by TLC). Upon completion, the reaction mixture was cooled to room temperature and removal of the solvent under vacuum, the resulting mixture was extracted with ethyl acetate (10 mLx2), the combined organic layers were washed with saturated sodium bicarbonate, brine, dried over $MgSO_4$, concentrated under reduced pressure. and the residue was purified on a silica gel column chromatography (eluent: EtOAc/PE=1:6) to provide the corresponding product **2a** (52 mg, 90%).5,6-Dimethoxy-2,3-dihydro-1*H*-inden-1-one **(2a)**. Brown solid, 52 mg, 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 6.90 (s, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.10~2.98 (m, 2H), 2.71~2.60 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.7, 155.4, 150.4, 149.4, 129.9, 107.5, 104.1, 56.1, 56.1, 36.5, 25.6. HRMS (EI-DFS) *m/z* calcd for $C_{11}H_{12}O_3$ $[M]^+$ 192.0786, found 192.0779.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (No. 21977106, 21672232, 21632008, 81903434), Shanghai Science and Technology Development Funds (Grant 19431901000) for financial support.

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