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Construction of novel bridged aromatic ring-fused oxazocine frameworks *via* an N-heterocyclic carbene-catalyzed azabenzoin reaction and radical-initiated cascade cyclization[†]

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Shuang-Shuo Niu and Ying Cheng 🕩 *

A novel and efficient method for the construction of 1,5-methanobenzo[*f*][1,3]oxazocin-6-one compounds from *o*-vinyl benzaldehydes and *N*-acylarylimines has been developed. The synthesis proceeded through the sequential NHC-catalyzed azabenzoin reaction and radical-initiated regioselective intramolecular cascade cyclizations. This protocol features mild conditions, good functional group tolerance and high yields of products. Novel 6,10-methanopyrido[3,2-*f*][1,3]oxazocin-5-ones could also be synthesized from 2-vinylnicotinaldehyde and *N*-acylarylimines based on this method. Capitalizing on the operational simplicity and use of efficient C–C and C–X bond-forming reactions, this protocol combining NHC-catalyzed and radical-initiated reactions enables the assembly of bridged aromatic ring-fused oxazocine derivatives with versatile functional and structural diversities.

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Introduction

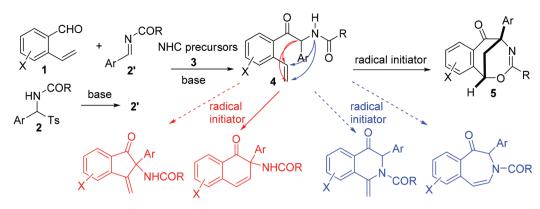
Over the last few decades, radical-initiated cyclization reactions¹ have been shown to be powerful methods for the construction of structurally diverse complex carbocyclic and heterocyclic compounds.² They have often been used as key steps in the total synthesis of biologically active natural products and pharmaceuticals.^{3,4} For example, the TBPB-initiated cascade cyclization between 3-arylethynyl-[1,1'-biphenyl]-2-carbonitriles and sulfinic acids produced tetracyclic cyclopenta [gh]phenanthridines,^{2a} while the SmI₂-triggered radicalradical cyclization cascades of barbiturates produced tricyclic 2a¹-hydroxy-hexahydro-4,5a-diazaacenaphthylene-3,5-diones containing up to five contiguous stereocenters.^{2b} On the other hand, nickel-catalyzed intramolecular radical tandem cyclization of alkyl bromide-tethered alkylidenecyclopropanes furnished benzo[*b*]naphtho[1,2-*d*]azepines.^{2*c*} Remarkably, the radical reactions proceed smoothly under relatively mild reaction conditions with a high level of regio- and stereocontrol,⁵ and particularly a high degree of functional group tolerance.

College of Chemistry, Beijing Normal University, Beijing 100875, China. E-mail: ycheng2@bnu.edu.cn

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Furthermore, the radical cascade cyclizations are able to efficiently deliver unprecedented polycyclic molecular architectures from simple starting materials in a single synthetic operation.^{1,2} As a consequence, the development of novel radical-initiated cascade cyclization reactions is of great importance and highly desirable.

We have been interested for many years in the exploration of new multicatalytic systems enabling the divergent synthesis of complex molecules from simple and inexpensive chemicals, mainly combining N-heterocyclic carbenes with Lewis acids, Brønsted bases and transition metal catalysts.⁶ Since N-heterocyclic carbenes are well-known organic catalysts for the azabenzoin reaction between aldehydes and imines to produce various α -aminoketones,⁷ we envisioned that 2-amido-2-aryl-1-(o-alkenylphenyl)ethanone 4 derived from the NHC-catalyzed reaction of o-alkenyl benzaldehydes with N-acylarylimines would undergo different intramolecular radical cyclizations in the presence of radical initiators to form fused five-, six- or seven-membered carbocyclic or heterocyclic compounds (Scheme 1). To our surprise, under the sequential NHC- and radical-mediated reaction conditions, the reaction of o-vinyl benzaldehyde 1a with N-(phenyl(tosyl) methyl)benzamide 2a, which is the precursor of N-benzoylphenylmethanimine, afforded unexpectedly a novel bridged eight-membered heterocycle 5a (Scheme 1). Reported herein is a novel and highly efficient method for the construction of complex 1,5-methanobenzo[f][1,3]oxazocin-6-one compounds.



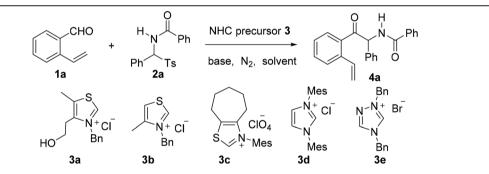
Scheme 1 Proposed NHC- and radical-mediated cascade reactions between o-vinyl benzaldehydes and N-acylarylimines.

Results and discussion

Aiming to develop a cascade reaction, we commenced our study with the examination of the NHC-catalyzed reaction of *o*-vinyl benzaldehyde **1a** with *N*-benzoylphenylimine **2a**' and the radical-mediated reaction of the resulting adduct **4a**, separ-

ately. *N*-Benzoylphenylimine **2a**' was generated *in situ* from the reaction of *N*-(phenyl(tosyl)methyl)benzamide **2a** with a base. A series of heterocyclic azolium salts including thiazolium salts **3a–3c**, imidazolium salt **3d** and triazolium salt **3e** were employed as NHC precursors. In acetonitrile and at ambient temperature, thiazoliums **3a–3c** (20 mol%) upon reaction with

Table 1Optimization of the reaction conditions for the NHC-catalyzed azabenzoin reaction of o-vinyl benzaldehyde 1a with N-(phenyl(tosyl)methyl)benzamide $2a^a$



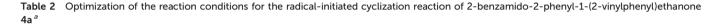
| Entry | NHC catalyst 3 (mol%) | Base (equiv.) | Solvent | Temp. (°C) | Yield of $4a^{b}$ (%) |
|-------|-----------------------|------------------|----------|------------|-----------------------|
| 1 | 3a (20) | $Et_{3}N(1.5)$ | MeCN | r.t. | 35 |
| 2 | 3b (20) | $Et_3N(1.5)$ | MeCN | r.t. | 31 |
| 3 | 3c (20) | $Et_{3}N(1.5)$ | MeCN | r.t. | 13 |
| 4 | 3d (20) | $Et_{3}N(1.5)$ | MeCN | r.t. | _ |
| 5 | 3e (20) | $Et_{3}N(1.5)$ | MeCN | r.t. | _ |
| 6 | 3a (30) | $Et_{3}N(1.5)$ | MeCN | r.t. | 39 |
| 7 | 3a (10) | $Et_{3}N(1.5)$ | MeCN | r.t. | 9 |
| 8 | 3a (30) | $Et_3N(2.5)$ | MeCN | r.t. | 71 |
| 9 | 3a (30) | DABCO (2.5) | MeCN | r.t. | 63 |
| 10 | 3a (30) | $Na_2CO_3(2.5)$ | MeCN | r.t. | 80 |
| 11 | 3a (30) | NaOAc (2.5) | MeCN | r.t. | 15 |
| 12 | 3a (30) | Cs_2CO_3 (2.5) | MeCN | r.t. | 29 |
| 13 | 3a (30) | $Na_2CO_3(2.5)$ | DCM | r.t. | 61 |
| 14 | 3a (30) | Na_2CO_3 (2.5) | $CHCl_3$ | r.t. | 45 |
| 15 | 3a (30) | Na_2CO_3 (2.5) | DMF | r.t. | 51 |
| 16 | 3a (30) | $Na_2CO_3(2.5)$ | THF | r.t. | 14 |
| 17 | 3a(30) | Na_2CO_3 (2.5) | Dioxane | r.t. | |
| 18 | 3a (30) | $Na_2CO_3(2.5)$ | MeCN | 40 | 75 |
| 19 | 3a (30) | $Na_2CO_3(2.5)$ | MeCN | Reflux | 43 |
| 20 | 3a (30) | $Na_2CO_3(2.5)$ | MeCN | 0 | 7 |

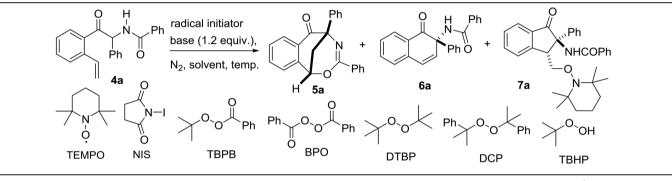
^{*a*} Reaction conditions: Under nitrogen protection, a mixture of reactants **1a** (0.5 mmol) and **2a** (0.5 mmol), catalyst **3** and a base in a dry solvent (5 mL) was stirred for 12 h at the temperature indicated in the table. ^{*b*} Isolated yield.

Research Article

 Et_3N (1.5 equiv.) were able to promote the azabenzoin reaction of 1a with 2a to give 2-benzamido-2-phenyl-1-(2-vinylphenyl) ethanone 4a in 13-35% yields (Table 1, entries 1-3). The highest yield of 4a was obtained from the reaction catalyzed by thiazolium salt 3a. In contrast, imidazolium 3d and triazolium 3e were virtually ineffective towards the azabenzoin reaction of 1a with 2a. Increasing the loading of thiazolium salt 3a to 30 mol% slightly improved the yield of 4a to 39%, while decreasing the loading of catalyst 3a to 10 mol% reduced the vield to 10% (Table 1, entries 6 and 7). With the use of thiazolium salt 3a as an optimized NHC precatalyst, we then found that the action of the base employed was crucial to this reaction. For example, when the loading of Et₃N was increased to 2.5 equiv., the yield of 4a greatly improved to 71% (Table 1, entry 8). The replacement of Et₃N with Na₂CO₃ further increased the yield of 4a to 80%. However, DABCO led to the

formation of the product in a slightly lower yield (63%), while the use of NaOAc and Cs₂CO₃ dramatically diminished the yield of product 4a (Table 1, entries 9-12). After the screening of NHC catalysts and bases, the solvent effect was studied. It was found that the reactions of 1a with 2a catalyzed by thiazolium salt 3a and Na₂CO₃ provided the product in lower yields (14-61%) in dichloromethane, chloroform, DMF and THF, and the reaction was totally retarded in 1,4-dioxane (Table 1, entries 13-17). Finally, the influence of temperature on the reaction was examined. While the reaction at 40 °C gave a similar result to that at ambient temperature, either a higher temperature such as in refluxing CH₃CN or a lower temperature (0 °C) drastically decreased the chemical yield of product 4a (entries 18-20). Thus, the catalytic reaction using thiazolium salt 3a (30 mol%) as a precatalyst and Na₂CO₃ (2.5 equiv.) as a base in acetonitrile at room temperature appears to be





| Entry | Oxidant (equiv.) | Additive (equiv.) | Base | Solvent | Temp. (°C) | $\operatorname{Yield}^{b}(\%)$ | | |
|-------|------------------|-------------------|------------|----------------|------------|--------------------------------|----|----|
| | | | | | | 5a | 6a | 7a |
| 1 | TEMPO (2) | _ | _ | Dioxane | Reflux | 38 | 22 | 22 |
| 2 | TEMPO (3) | — | — | Dioxane | Reflux | 53 | 18 | 21 |
| 3 | TEMPO(4) | — | — | Dioxane | Reflux | 60 | 12 | 19 |
| 4 | | NIS (0.5) | Na_2CO_3 | Dioxane | Reflux | 31 | | _ |
| 5 | | NIS (2) | Na_2CO_3 | Dioxane | Reflux | 15 | | _ |
| 6 | TBHP (4) | _ | Na_2CO_3 | Dioxane | Reflux | | | _ |
| 7 | DTBP (4) | — | Na_2CO_3 | Dioxane | Reflux | | | _ |
| 8 | DCP (4) | — | Na_2CO_3 | Dioxane | Reflux | | | _ |
| 9 | TBPB (4) | — | Na_2CO_3 | Dioxane | Reflux | | | _ |
| 10 | BPO (4) | — | Na_2CO_3 | Dioxane | Reflux | | | _ |
| 11 | TBHP (4) | NIS (0.5) | Na_2CO_3 | Dioxane | Reflux | 38 | | _ |
| 12 | DTBP (4) | NIS (0.5) | Na_2CO_3 | Dioxane | Reflux | 24 | | _ |
| 13 | DCP (4) | NIS (0.5) | Na_2CO_3 | Dioxane | Reflux | 65 | | _ |
| 14 | BPO (4) | NIS (0.5) | Na_2CO_3 | Dioxane | Reflux | 37 | | _ |
| 15 | TBPB (4) | NIS (0.5) | Na_2CO_3 | Dioxane | Reflux | 86 | | _ |
| 16 | TBPB (4) | NIS (0.5) | — | Dioxane | Reflux | | | _ |
| 17 | TBPB (4) | $MnI_{2}(0.5)$ | Na_2CO_3 | Dioxane | Reflux | 82 | | _ |
| 18 | TBPB (4) | $FeI_2(0.5)$ | Na_2CO_3 | Dioxane | Reflux | 84 | | _ |
| 19 | TBPB (4) | NaI (0.5) | Na_2CO_3 | Dioxane | Reflux | 81 | | _ |
| 20 | TBPB (4) | NIS (0.5) | NaOAc | Dioxane | Reflux | 92 | | _ |
| 21 | TBPB (4) | NIS (0.5) | Et_3N | Dioxane | Reflux | 91 | | _ |
| 22 | TBPB (4) | NIS (0.5) | DABCO | Dioxane | Reflux | 70 | | _ |
| 23 | TBPB (4) | NIS (0.5) | NaOAc | MeCN | Reflux | 51 | | _ |
| 24 | TBPB (4) | NIS (0.5) | NaOAc | <i>n</i> -PrCN | 100^{c} | 79 | | _ |
| 25 | TBPB (4) | NIS (0.5) | NaOAc | DMF | 100^{c} | 75 | | _ |
| 26 | TBPB (4) | NIS (0.5) | NaOAc | Cl_2CHCH_2Cl | 100^{c} | 24 | — | — |

^{*a*} Reaction conditions: Under nitrogen protection, a mixture of the reactant **4a** (0.5 mmol), radical initiator, additive and base was stirred in a refluxing solvent (5 mL) or at 100 °C for 10 h. ^{*b*} Isolated yield. ^{*c*} Oil bath temperature.

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After the optimization of the reaction conditions for the formation of 2-benzamido-2-phenyl-1-(2-vinylphenyl)ethanone 4a from o-vinyl benzaldehyde 1a and N-(phenyl(tosyl)methyl) benzamide 2a, we studied the radical-mediated reaction of 4a. Initially, 2,2,6,6-tetramethylpiperidinooxy (TEMPO) was employed as a radical initiator. In refluxing dioxane, the reaction of 4a mediated by 2, 3 and 4 equiv. of TEMPO, respectively, produced an interesting bridged eight-membered heterocyclic compound, namely 3,5-diphenyl-1,5-methanobenzo [f][1,3]oxazocin-6-one 5a, in 38–60% yields, along with the formation of two minor products, 2-benzamido-2-phenylnaphthalen-1-one 6a (12-22%) and polysubstituted 2,3-dihydroinden-1one derivative 7a (19-22%) (Table 2, entries 1-3) (see the X-ray structures of 5a and 7a in Fig. 1). No other products proposed in Scheme 1 were isolated. To improve the selectivity in the formation of 1,5-methanobenzo[f][1,3]oxazocin-6-one 5a and naphthalen-1-one 6a, other radical initiators were investigated. It was found that in the presence of N-iodosuccinimide (NIS, 0.5 equiv.) and Na₂CO₃ (1.2 equiv.), the reaction of 4a produced bridged heterocycle 5a in 31% yield without the formation of naphthalen-1-one 6a. Increasing the loading of NIS was not beneficial because only 15% yield of 5a was isolated from the reaction using 2 equiv. of NIS as the radical precursor (Table 2, entries 4 and 5). When a series of peroxide oxidants including t-butyl hydroperoxide (TBHP), di-t-butylperoxide (DTBP), dicumyl peroxide (DCP), t-butyl peroxybenzoate (TBPB) and dibenzoyl peroxide (BPO) were applied as radical initiators, the reactions of 4a yielded very complex mixtures, in which product 5a or 6a was not observed (Table 2, entries 6-10). Intriguingly, however, when a peroxide including TBHP, DTBP, DCP, BPO or TBPB (4 equiv.) was used in combination with NIS (0.5 equiv.) and Na_2CO_3 (1.2 equiv.), the reactions of 4a gave 5a in 24-86% yields, with no naphthalen-1-one 6a being detected (Table 2, entries 11-15). The best yield of product 5a (86%) was achieved from the reaction promoted by a combination of TBPB (4 equiv.), NIS (0.5 equiv.) and Na₂CO₃ (1.2 equiv.). It should be noted that in the absence of Na_2CO_3 , the reaction of 4a with TBPB and NIS did not proceed to form 5a. To further improve the production of bridged heterocyclic product 5a, the base and iodide additives were screened while

using TBPB as the radical initiator. We discovered that MnI_2 , FeI_2 and NaI were also effective iodide sources, giving good yields of product **5a** (81–84%) (Table 2, entries 17–19). Pleasingly, the use of Et_3N and NaOAc instead of Na_2CO_3 improved the yield of **5a** to 91% and 92%, respectively (Table 2, entries 20 and 21). A lower yield of **5a** (70%) was obtained when DABCO was used as a base. Finally, the reactions of **4a** promoted by a combination of TBPB (4 equiv.), NIS (0.5 equiv.) and NaOAc (1.2 equiv.) were examined in different solvents at 80–100 °C. Except for the reaction in refluxing 1,4-dioxane, other reactions in refluxing acetonitrile, hot butyronitrile, DMF and 1,1,2-trichloroethane (100 °C oil bath temperature) produced product **5a** in lower yields (24–79%) (Table 2, entries 23–26).

After identifying the optimized conditions for the NHC-catalyzed reaction of o-vinyl benzaldehyde 1a with N-(phenyl(tosyl) methyl)benzamide 2a and for the radical-mediated reaction of 2-benzamido-2-phenyl-1-(2-vinylphenyl)ethanone 4a, we tried the one-pot NHC- and radical-mediated sequential reaction of o-vinyl benzaldehyde 1a and N-(phenyl(tosyl)methyl)benzamide 2a. The sequential reactions in a one-pot fashion were first performed using the same base and solvent. We have shown that the optimized solvents for the azabenzoin reaction and radical reaction were acetonitrile and 1,4-dioxane, respectively, and the NHC-catalyzed reaction did not take place in 1,4-dioxane. On the other hand, Na₂CO₃ and Et₃N appeared as the most suitable bases for the NHC catalysis, while in the radical reaction, NaOAc, Et_3N and Na_2CO_3 acted as beneficial additives, leading to the formation of product 5a in good to excellent yields (see Tables 1 and 2). Taking consideration of the optimized solvents, bases, and temperature and their compatibility in the two reactions, we performed the one-pot sequential reaction of 1a with 2a using Na₂CO₃ or Et₃N as the sole base in acetonitrile or butyronitrile. From these reactions, 1,5-methanobenzo [f][1,3] oxazocin-6-one 5a was isolated in 22-41% yields (Scheme 2). Great effort was made to improve the efficiency of the one-pot reaction. For instance, the one-pot sequential reaction was then conducted in acetonitrile or butyronitrile with the use of Na₂CO₃ or Et₃N in the first step, followed by the addition of 1,4dioxane or 1,4-dioxane and NaOAc, which were the optimal solvent and base in the radical cyclization reaction of 4a. Disappointingly, however, only 22-25% yields of product 5a

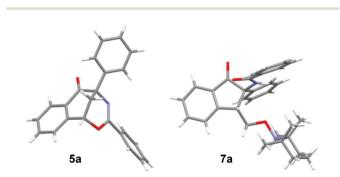
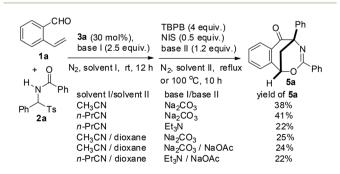


Fig. 1 X-ray structures of compounds 5a and 7a.

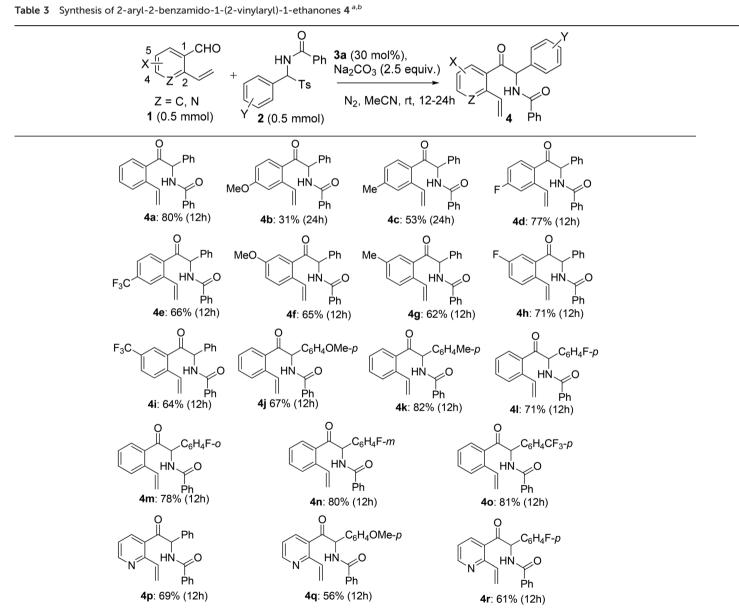


Scheme 2 One-pot NHC- and radical-mediated sequential reaction of o-vinyl benzaldehyde **1a** and *N*-(phenyl(tosyl)methyl)benzamide **2a**.

were isolated when different solvents and bases were used in two steps. The main reason for the low yields of **5a** from the one-pot operation was most probably the incompatibility of the conditions for the two individual steps.

Since the one-pot NHC- and radical-mediated sequential reaction of *o*-vinyl benzaldehyde **1a** and *N*-(phenyl(tosyl) methyl)benzamide **2a** did not provide high synthetic efficiency, and the bridged benzooxazocinone compounds **5** appeared to be important in terms of their unique structure and versatility in organic synthesis, we turned our attention to the synthesis of **5** by means of a stepwise method. Logically, we first examined the scope of the NHC-catalyzed azabenzoin reaction. Under the optimized conditions for the NHC-cata-

lyzed reaction, we investigated the reaction of *o*-vinyl aromatic aldehydes **1** with *N*-(aryl(tosyl)methyl)benzamides **2** which bear different substituents. As summarized in Table 3, the reaction displayed good tolerance toward both electron-donating and electron-withdrawing groups attached to both substrates, although the electronic nature and substitution pattern of the substituents influenced the reactivity of the reaction and chemical yields of 2-aryl-2-benzamido-1-(2-vinylaryl)-1-ethanone products **4**. For example, the introduction of an electron-withdrawing group to the *para*-position of the aldehyde group of substrates **1** had marginal influence on the reaction, as the reactions of 4-fluoro- and 4-trifluoromethyl-2-vinylbenzaldehydes **1d** and **1e** with **2a** produced products **4d** and

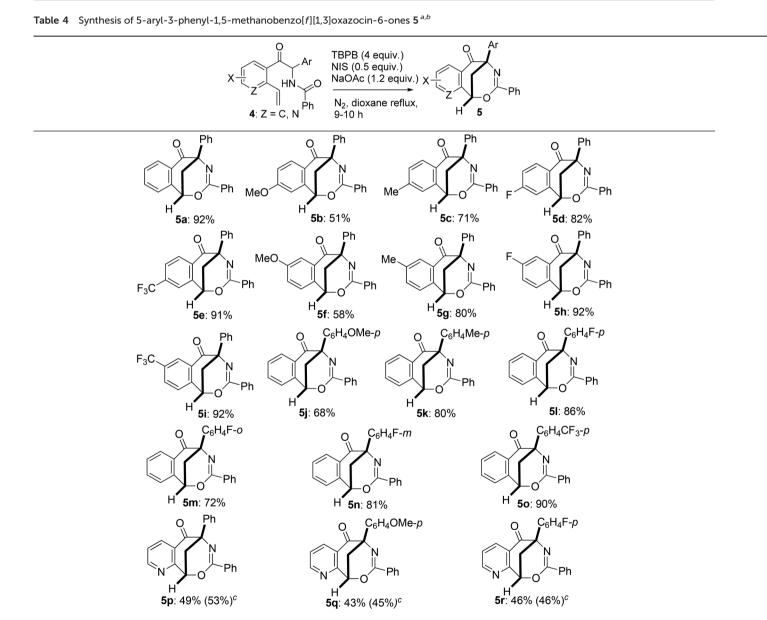


^{*a*} Reaction conditions: Under a nitrogen atmosphere and at room temperature, a mixture of *N*-(aryl(tosyl)methyl)benzamides **2** (0.5 mmol), thiazolium salt **3a** (0.15 mmol), Na₂CO₃ (1.25 mmol) and *o*-vinyl aromatic aldehydes **1** (0.5 mmol) in dry acetonitrile (5 mL) was stirred for 12–24 h at room temperature. ^{*b*} Isolated yield.

Organic Chemistry Frontiers

4e in 77% and 66% yields, respectively. However, an electrondonating group at the *para*-position of aldehyde decreased the reactivity of substrates **1**. This was evident for the reaction of 4-methoxy- and 4-methyl-2-vinylbenzaldehydes **1b** and **1c**, which produced **4b** and **4c** in lower yields (31% and 53%, respectively) even though the reaction time was prolonged from 12 h to 24 h. When the substituent was moved from the *para*-position to the *meta*-position of benzaldehydes **1**, no matter whether it was an electron-donating or electron-withdrawing group (5-OMe, 5-Me, 5-F and 5-CF₃), the reactions of **1f–1i** with **2a** proceeded equally well to give products **4f–4i** in 62%–71% yields. Being different from the substituent effect observed for *o*-vinyl benzaldehydes **1**, the electronic nature and substitution pattern of the groups attached to *N*-benzoylarylimines exerted much weaker influence on the reaction. All *N*-(aryl(tosyl)methyl)benzamides **2** substituted with a *p*-OMe, *p*-Me, *p*-F, *o*-F, *m*-F or *p*-CF₃ group reacted smoothly with *o*-vinyl benzaldehyde **1a** to afford products **4j**-**4o** in 67%–82% yields. Finally, a heteroaromatic substrate, 2-vinylnicotinaldehyde **1k**, was also found to react analogously with **2a**, **2b** and **2d**, producing 2-aryl-2-benzamido-1-(2-vinyl-3-pyridinyl)-1-ethanones **4p**–**4r** in 56–69% yields (Table 3).

With various 2-aryl-2-benzamido-1-(2-vinylaryl)-1-ethanones (also namely N-(1-aryl-1-(2-vinylaroyl)methyl)benzamides) 4 in hand, we then studied the generality of the radical-mediated intramolecular cyclization of 4 to the synthesis of bridged

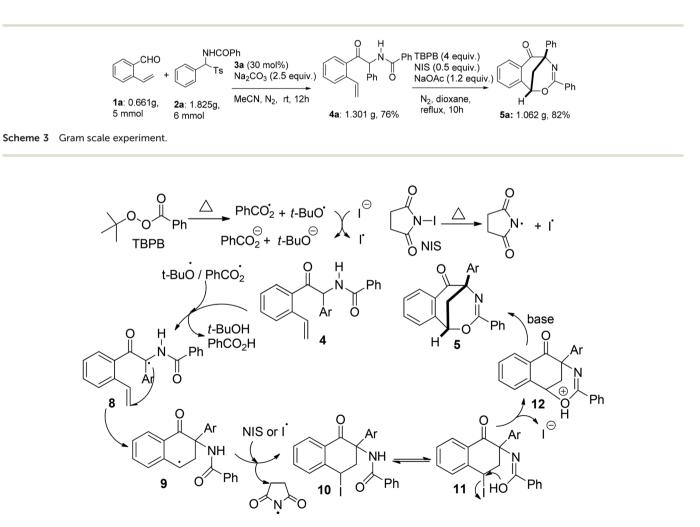


^{*a*} Reaction conditions: Under a nitrogen atmosphere and at room temperature, 2-aryl-2-benzamido-1-(*o*-vinylaryl)-1-ethanones 4 (0.5 mmol), NaOAc (0.6 mmol), NIS (0.25 mmol), TBPB (2 mmol) and dry 1,4-dioxane (5 mL) were added to a dry Schlenk tube. The reaction mixture was stirred in refluxing 1,4-dioxane for 9–10 h under the protection of nitrogen. ^{*b*} Isolated yield. ^{*c*} The yields in parentheses were obtained from the reaction using TBPB (2 equiv.), NIS (0.5 equiv.) and Et₃N (2 equiv.).

heterocyclic molecules. The reaction was found to tolerate a wide range of the substrates which contain different electrondonating and electron-withdrawing groups. As presented in Table 4, only reactants 4b, 4f and 4j, which bear a methoxy group on the 1- or 2-phenyl ring, gave moderate yields of 1,5methanobenzo [f] [1,3] oxazocin-6-ones 5b, 5f and 5j (51–68%) yields); all other substrates 4 containing a methyl, fluorine or trifluoromethyl group at different positions of each aryl moiety produced the corresponding products 5 in good to excellent yields (71-92%). Under the identical reaction conditions, 2-aryl-2-benzamido-1-(2-vinyl-3-pyridinyl)-1-ethanones 4p-4rproduced 6,10-methanopyrido[3,2-f][1,3]oxazocin-5-ones 5p-5r in lower yields (43-49%). The low chemical yields of 5p-5r were due to the formation of many inseparable by-products which were observed by TLC. Varying the reaction conditions, including bases, reaction temperature, and the loads of oxidants, bases and NIS, did not significantly improve the yields of bridged pyrido[3,2-f][1,3]oxazocine derivatives. For example, products 5p-5r were obtained in 45-53% yields from the reaction of 4p-4r initiated by TBPB (2 equiv.), NIS (0.5 equiv.) and Et_3N (2 equiv.) in refluxing 1,4-dioxane (see Table 4, the yields in parentheses).

It was worth addressing that the NHC- and radicalmediated two-step sequential reactions were scalable. The reaction of *o*-vinyl benzaldehyde **1a** with *N*-(phenyl(tosyl)methyl) benzamide **2a** was carried out readily on a gram scale under the optimized conditions, with the desired intermediate **4a** and product **5a** being synthesized in 76% and 82% yields, respectively (Scheme 3).

In this NHC- and radical-mediated reaction sequence, the formation of 2-aryl-2-benzamido-1-(2-vinylaryl)-1-ethanones **4** from *o*-vinyl aromatic aldehydes **1** and *N*-(aryl(tosyl)methyl) benzamides **2** proceeded *via* an azabenzoin reaction.⁷ On the other hand, the formation of 1,5-methanobenzo[*f*][1,3]oxazo-cin-6-ones **5** from 2-aryl-2-benzamido-1-(2-vinylaryl)-1-ethanones **4** in the presence of radical initiators TBPB and NIS is intriguing. To account for the unexpected formation of bridged heterocyclic compounds **5**, a radical-initiated cascade cyclization mechanism was proposed. As depicted in Scheme 4, the homolytic cleavage of peroxides TBPB and NIS under pyrolysis produces *tert*-butoxy and benzoate radicals and the iodine radical, respectively. These radicals would abstract the most vulnerable α -hydrogen atom from compounds **4** to generate radical intermediates **8**. An intramolecular radical

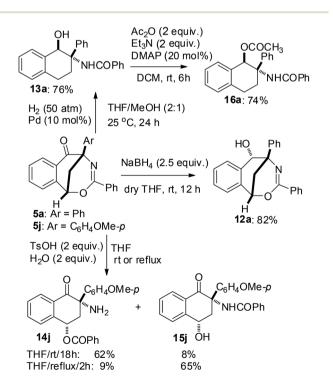


Scheme 4 Proposed mechanism for the radical-initiated intramolecular cyclization of 2-aryl-2-benzamido-1-(2-vinylaryl)-1-ethanones 4.

Organic Chemistry Frontiers

addition to the vinyl group of **8** leads to the formation of 3,4dihydronaphthalen-1-one radicals **9**. The radicals **8** are added predominately to the terminal carbon rather than the internal carbon of the vinyl group because the former reaction forms a more stable benzyl radical than the methyl radical in the latter one. Subsequently, the reaction of 3,4-dihydronaphthalen-1one radicals **9** with NIS or the iodine radical provides 2-aryl-4iodo-3,4-dihydronaphthalen-1-one-2-benzamides **10**, which tautomerize with 2-aryl-4-iodo-3,4-tetrahydronaphthalen-1-one-2-benzimidic acid **11**. Finally, a base-promoted intramolecular nucleophilic substitution reaction between benzyliodide and hydroxyl groups of intermediates **11** leads to the formation of 1,5-methanobenzo[*f*][1,3]oxazocin-6-one products **5**.

The synthetic value of this sequential reaction protocol was further demonstrated by investigating the transformation of 1,5-methanobenzo [f] 1,3] oxazocin-6-ones 5 (Scheme 5). For example, in dry THF and at ambient temperature, the selective reduction of the carbonyl group of compound 5a was achieved with NaBH₄ (2.5 equiv.) to furnish 1,5-methanobenzo[f][1,3] oxazocin-6-ol 12a in 82% yield. On the other hand, in a mixture of THF and MeOH (THF: MeOH = 2:1) at 25 °C, the Pd-C catalyzed hydrogenation reaction of 5a under 50 atm H₂ gas produced N-(1-hydroxy-2-phenyl-2-tetrahydronaphthalenyl) benzamide 13a in 76% yield. Furthermore, the acid hydrolysis of 5j led to the formation of two highly functional 1-tetralones 14j and 15j. The selective synthesis of 3-amino-3-(p-methoxyphenyl)-4-oxo-1-tetrahydronaphthalenyl benzoate 14j (62% yield) and N-(4-hydroxy-2-(p-methoxyphenyl)-1-oxo-2-tetrahydronaphthalenyl)benzamide 15j (65% yield) was achieved by the treatment of compound 5j with TsOH (2 equiv.) and H_2O



Scheme 5 Synthetic applications of 1,5-methanobenzo[*f*][1,3]oxazocin-6-ones **5**.

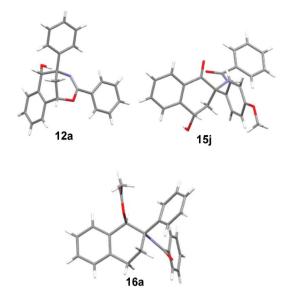


Fig. 2 X-ray structures of 12a, 15j and 16a.

(2 equiv.) in THF at room temperature and in refluxing THF, respectively. The structures of products 12a, 13a, 14j and 15j were elucidated on the basis of spectroscopic data. Both the reduction reactions of 5 by NaBH₄ and H₂ gas formed a new chiral carbon which was substituted by a hydroxy group, while the acid hydrolysis of 5 did not form a new chiral center. The polysubstituted tetrahydronaphthalen-1-ol 13a did not give satisfactory single crystals for X-ray analysis. Therefore, compound 13a was converted into 1-tetrahydronaphthalenyl acetate 16a by acylation with acetic anhydride in the presence of triethylamine and DMAP. Finally, the structures and relative configurations of compounds 12a, 15j and 16a were determined by single crystal X-ray diffraction analysis (see the X-ray structures of 12a, 15j and 16a in Fig. 2).

Both 1,5-methanobenzo[f][1,3]oxazocin-6-ones and 6,10methanopyrido[3,2-f][1,3]oxazocin-5-ones are new bridged heterocyclic compounds that no studies have been reported before. In contrast, a large number of 1-tetralone derivatives have been documented in the literature. 1-Tetralones not only are useful building blocks in organic synthesis,⁸ but also represent important scaffolds in a wide range of natural products and biologically active molecules of medicinal and agrochemical interest.⁹ This work provides a new method for the synthesis of highly functionalized 1-tetralone derivatives which would be further modified easily on the structures.

Conclusions

We have provided a two-step reaction method for the efficient synthesis of novel bridged heterocyclic compounds, namely 1,5-methanobenzo[f][1,3]oxazocin-6-ones, from simple and inexpensive starting materials. The method involved NHC-catalyzed azabenzoin condensation between o-vinyl aromatic aldehydes and N-benzoylarylimines and the radical-mediated

Research Article

cascade cyclizations of 2-aryl-2-benzamido-1-(2-vinylaryl)-1ethanones. The intramolecular regioselective addition of the 2-C radical of 2-aryl-2-benzamido-1-(2-vinylaryl)-1-ethanones to the terminal carbon rather than the internal carbon of the vinyl group forms 3,4-dihydronaphthalen-1-one rather than 2,3-dihydroinden-1-one intermediates. This method could also be used in the assembly of the novel 6,10-methanopyrido[3,2f][1,3]oxazocin-5-one framework from 2-vinylnicotinaldehyde and *N*-acylarylimines. The transformations of the resulting bridged heterocyclic compounds demonstrated the applications of this protocol not only in bridged aromatic ringfused 1,3-oxazocines, but also in highly functional tetralone derivatives.

Author contributions

Shuang-Shuo Niu performed the experiments. Ying Cheng conceived and supervised the work, analysed the data and wrote this manuscript. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- Some reviews on the radical cyclization reactions: (a) L. Yet, Free Radical in the Synthesis of Medium-Sized Ring, *Tetrahedron*, 1999, 55, 9349–9403; (b) M.-H. Huang, W.-J. Hao and B. Jiang, Recent Advances in Radical-Enabled Bicyclization and Annulation/1,n-Bifunctionalization Reactions, *Chem. – Asian J.*, 2018, 13, 2958–2977; (c) J. Xuan and A. Studer, Radical cascade cyclization of 1,n-enynes and diynes for the synthesis of carbocycles and heterocycles, *Chem. Soc. Rev.*, 2017, 46, 4329–4346; (d) A. J. McCarroll and J. C. Walton, Programming organic molecules: design and management of organic syntheses through free-radical cascade processes, *Angew. Chem., Int. Ed.*, 2001, 40, 2224–2248.
- 2 Examples for the construction of complex cyclic compounds via radical intramolecular cyclization reactions: (a) N. Zhou, M. Wu, M. Zhang, X. Zhou and W. Zhou, TBPB-initiated cascade cyclization of 3-arylethynyl-[1,1'-biphenyl]-2-carbonitriles with sulfinic acids: access to sulfone-containing cyclopenta[gh]phenanthridines, Org. Biomol. Chem., 2020, 18, 1733–1737; (b) H.-M. Huang and D. J. Procter, Radical-Radical Cyclization Cascades of Barbiturates Triggered by Electron-Transfer Reduction of Amide-Type Carbonyls,

J. Am. Chem. Soc., 2016, **138**, 7770–7775; (*c*) B. Jiang, J.-X. Liu, Y. Wei and M. Shi, Nickel-Catalyzed Synthesis of Benzo[*b*]naphtho[1,2-*d*]azepine via Intramolecular Radical Tandem Cyclization of Alkyl Bromide-Tethered Alkylidenecyclopropanes, *Org. Lett.*, 2018, **20**, 6229–6233; (*d*) P. S. Mahajan and S. B. Mhaske, Silver-Mediated Oxidative Decarboxylative Intramolecular Asymmetric Radical Cyclization (Csp³–Csp²) via Memory of Chirality: Access to Circumdatin Alkaloids, *Org. Lett.*, 2018, **20**, 2092– 2095.

- 3 Reviews on the synthesis of natural products via radical reactions: (a) U. Koert, Radical Reactions as Key Steps in Natural Product Synthesis, Angew. Chem., Int. Ed. Engl., 1996, 35, 405–407; (b) K. Hung, X. Hu and T. J. Maimone, Total synthesis of complex terpenoids employing radical cascade processes, Nat. Prod. Rep., 2018, 35, 174–202.
- 4 Examples for the synthesis of natural products *via* radical intramolecular cyclization reactions: (*a*) X. Wang, F. Liu, J. Yun, Z. Feng, J. Jiang, Y. Yang and P. Zhang, Iron-Catalyzed Synthesis of the Hexahydrocyclopenta[*c*]furan Core and Concise Total Synthesis of Polyflavanostilbene B, *Angew. Chem., Int. Ed.*, 2018, 57, 10127–10131; (*b*) Z. Yuan, X. Hu, H. Zhang, L. Liu, P. Chen, M. He, X. Xie, X. Wang and X. She, Total synthesis of conosilane A via a site-selective C–H functionalization strategy, *Chem. Commun.*, 2018, 54, 912–915; (*c*) W. Liu and B. Wang, Synthesis of (±)-Merrilactone A by a Desymmetrization Strategy, *Chem. Eur. J.*, 2018, 24, 16511–16515.
- 5 Reviews on the stereocontrol of radical reactions: (a) G. Bar and A. F. Parsons, Stereoselective radical reactions, *Chem. Soc. Rev.*, 2003, 32, 251–263; (b) T. V. RajanBabu, Stereochemistry of intramolecular free-radical cyclization reactions, *Acc. Chem. Res.*, 1991, 24, 139–145; (c) H. Miyabe and Y. Takemoto, Enantioselective radical cyclizations: a new approach to stereocontrol of cascade reactions, *Chem. – Eur. J.*, 2007, 13, 7280–7286.
- 6 (a) Y.-J. Liu, Y.-L. Ding, S.-S. Niu, J.-T. Ma and Y. Cheng, N-Heterocyclic, Carbene/Palladium Cascade Catalysis: Construction of 2,2-Disubstitiuted Benzofuranones from the Reaction of 3-(2-Formylphenoxy)propenoates with Allylic Esters, J. Org. Chem., 2018, 83, 1913-1923; (b) Z.-Y. Wang, Y.-L. Ding, S.-N. Li and Y. Cheng, N-Heterocyclic Carbene/ Lewis Acid Dual Catalysis for the Divergent Construction of Enantiopure Bridged Lactones and Fused Indenes, J. Org. Chem., 2016, 81, 11871-11881; (c) Z.-Y. Wang, Y.-L. Ding, G. Wang and Y. Cheng, Chiral N-Heterocyclic Carbene/Lewis Acid Cooperative Catalysis in the Reaction of 2-Aroylvinylcinnamaldehydes: A Switch of Reaction Pathway by Lewis Acid Activation, Chem. Commun., 2016, 52, 788-791; (d) H.-Y. Dang, Z.-T. Wang and Y. Cheng, Changing Reaction Pathways of the Dimerization of 2-Formylcinnamates by N-Heterocyclic Carbene/Lewis Acid Cooperative Catalysis: An Unusual Cleavage of Carbon-Carbon Bond, Org. Lett., 2014, 16, 5520-5523; (e) J.-T. Ma and Y. Cheng, Construction of Enantiopure Imine Bridged Benzo[c]azepinones by a Silver (I) and Chiral N-Heterocyclic

Carbene Multicatalytic Reaction Sequence of N'-(2-Alkynylbenzylidene)hydrazides and Cyclopropanecarbaldehydes, Org. Chem. Front., 2020, 7, 3459-3467; (f) Y.-f. Tong, J.-h. Mao, S. Wu, Y. Zhao and Y. Cheng, Changing the Reaction Pathway by NHC/Brønsted Base Cooperative Catalysis: Highly Stereoselective Synthesis of Multifunctional Dimerization Benzo[a]fluoren-11-ones from the of 2-(Aroylvinyl)arylaldehydes, J. Org. Chem., 2014, 79, 2075-2081; (g) Y. Zhao, Z.-T. Wang and Y. Cheng, N-Heterocyclic, Carbene/Brønsted Base Cascade Catalysis: Base-Controlled Selective Synthesis of Multifunctional Benzofuran-3-ones or Flavone Derivatives from the Reaction of 3-(2-Formylphenoxy)propenoates with Imines, Adv. Synth. Catal., 2014, 356, 2580-2590.

- 7 Examples of the NHC-catalyzed reactions between aldehydes and imines: (a) J. A. Murry, D. E. Frantz, A. Soheili, R. Tillyer, E. J. J. Grabowski and P. J. Reider, Synthesis of α-Amido Ketones via Organic Catalysis: Thiazolium-Catalyzed Cross-Coupling of Aldehydes with Acylimines, J. Am. Chem. Soc., 2001, 123, 9696–9697; (b) G.-Q. Li, L.-X. Dai and S.-L. You, Thiazolium-derived N-Heterocyclic Carbene-catalyzed Cross-coupling of Aldehydes with Unactivated Imines, Chem. Commun., 2007, 852–854; (c) S. M. Mennen, J. D. Gipson, Y. R. Kim and S. J. Miller, Thiazolylalanine-Derived Catalysts for Enantioselective Intermolecular Aldehyde-Imine Cross-Couplings, J. Am. Chem. Soc., 2005, 127, 1654–1655.
- 8 Some examples for the synthesis of bioactive compounds using 1-tetralone derivatives as reactants: (a) R.-Y. Yang, D. Kizer, H. Wu, E. Volckova, X.-S. Miao, S. M. Ali, M. Tandon, R. E. Savage, T. C. K. Chan and M. A. Ashwell, Synthetic methods for the preparation of ARQ 501 (β-Lapachone) human blood metabolites, *Bioorg. Med. Chem.*, 2008, 16, 5635–5643; (b) M. A. E. Pinto-Bazurco Mendieta, M. Negri, C. Jagusch, U. Müller-Vieira,

T. Lauterbach and R. W. Hartmann, Synthesis, Biological Evaluation, and Molecular Modeling of Abiraterone Analogues: Novel CYP17 Inhibitors for the Treatment of Prostate Cancer, J. Med. Chem., 2008, 51, 5009-5018; (c) R. Ortega, H. Hübner, P. Gmeiner and C. F. Masaguer, Aromatic ring functionalization of benzolactam derivatives: New potent dopamine D3 receptor ligands, Bioorg. Med. Chem. Lett., 2011, 21, 2670-2674; (d) M. Odagi, K. Furukori, K. Takayama, K. Noguchi and K. Nagasawa, Total Synthesis of Rishirilide B by Organocatalytic Oxidative Kinetic Resolution: Revision of Absolute Configuration (+)-Rishirilide B, Angew. Chem., Int. Ed., 2017, 56, 6609-6612. 9 Some examples for natural products and biologically active compounds containing a 1-tetralone scaffold: (a) J. G. Allen and S. J. Danishefsky, The Total Synthesis of (±)-Rishirilide B, J. Am. Chem. Soc., 2001, 123, 351-352; (b) S. Yao, C.-P. Tang, C.-Q. Ke and Y. Ye, Abietane Diterpenoids from the Bark of Cryptomeria fortunei, J. Nat. Prod., 2008, 71, 1242-1246; (c) K. P. Devkota, D. Covell, T. Ransom, J. B. McMahon and J. A. Beutler, Inhibition of Human Colon Carcinoma Cells by Sesquiterpenoids and Tetralones of Zygogynum calothyrsum, J. Nat. Prod., 2013, 76, 710-714; (d) J. M. Nyangulu, K. M. Nelson, P. A. Rose, Y. Gai, M. Loewen, B. Lougheed, J. W. Quail, A. J. Cutler and S. R. Abrams, Synthesis and biological activity of tetralone abscisic acid analogues, Org. Biomol. Chem., 2006, 4, 1400-1412; (e) J. Leng, H.-L. Oin, K. Zhu, I. Jantan, M. A. Hussain, M. Sher, M. W. Amjad, M. Naeem-ul-Hassan, W. Ahmad and S. N. A. Bukhari, Evaluation of multifunctional synthetic tetralone derivatives for treatment of Alzheimer's disease, Chem. Biol. Drug Des., 2016, 88, 889-898; (f) L. J. Legoabe, M. M. Van der Walt and G. Terre'Blanche, Evaluation of 2-benzylidene-1-tetralone derivatives as antagonists of A1 and A2 adenosine receptors, Chem. Biol. Drug Des., 2018, 91, 234-244.