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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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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 radical-radical 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.^{2c} 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.

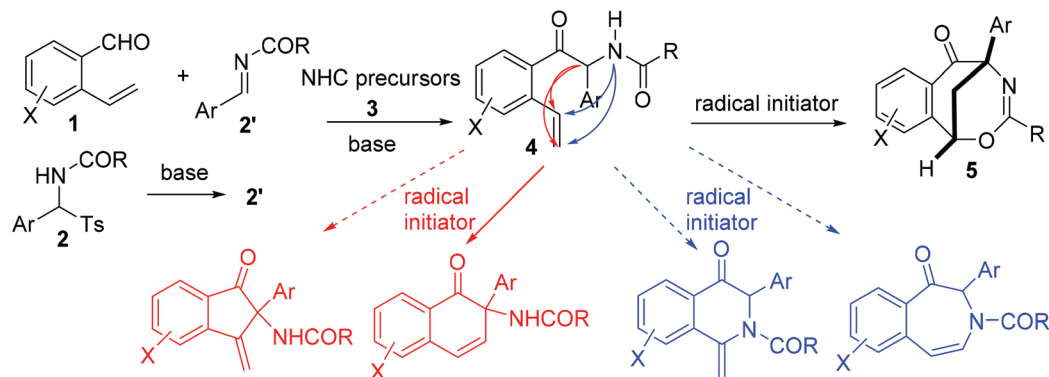
Furthermore, the radical cascade cyclizations are able to efficiently deliver unprecedented polycyclic molecular architectures from simple starting materials in a single synthetic operation.^{1,2} As a consequence, the development of novel radical-initiated cascade cyclization reactions is of great importance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

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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 1 Optimization 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 ₃ N (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 ₃ N (2.5)	MeCN	r.t.	71
9	3a (30)	DABCO (2.5)	MeCN	r.t.	63
10	3a (30)	Na ₂ CO ₃ (2.5)	MeCN	r.t.	80
11	3a (30)	NaOAc (2.5)	MeCN	r.t.	15
12	3a (30)	CS ₂ CO ₃ (2.5)	MeCN	r.t.	29
13	3a (30)	Na ₂ CO ₃ (2.5)	DCM	r.t.	61
14	3a (30)	Na ₂ CO ₃ (2.5)	CHCl ₃	r.t.	45
15	3a (30)	Na ₂ CO ₃ (2.5)	DMF	r.t.	51
16	3a (30)	Na ₂ CO ₃ (2.5)	THF	r.t.	14
17	3a (30)	Na ₂ CO ₃ (2.5)	Dioxane	r.t.	—
18	3a (30)	Na ₂ CO ₃ (2.5)	MeCN	40	75
19	3a (30)	Na ₂ CO ₃ (2.5)	MeCN	Reflux	43
20	3a (30)	Na ₂ CO 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.

Et₃N (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 yield 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

Table 2 Optimization of the reaction conditions for the radical-initiated cyclization reaction of 2-benzamido-2-phenyl-1-(2-vinylphenyl)ethanone **4a**^a

Entry	Oxidant (equiv.)	Additive (equiv.)	Base	Solvent	Temp. (°C)	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 ₂ CO ₃	Dioxane	Reflux	31	—	—
5		NIS (2)	Na ₂ CO ₃	Dioxane	Reflux	15	—	—
6		—	Na ₂ CO ₃	Dioxane	Reflux	—	—	—
7	DTBP (4)	—	Na ₂ CO ₃	Dioxane	Reflux	—	—	—
8	DCP (4)	—	Na ₂ CO ₃	Dioxane	Reflux	—	—	—
9	TBPB (4)	—	Na ₂ CO ₃	Dioxane	Reflux	—	—	—
10	BPO (4)	—	Na ₂ CO ₃	Dioxane	Reflux	—	—	—
11	TBHP (4)	NIS (0.5)	Na ₂ CO ₃	Dioxane	Reflux	38	—	—
12	DTBP (4)	NIS (0.5)	Na ₂ CO ₃	Dioxane	Reflux	24	—	—
13	DCP (4)	NIS (0.5)	Na ₂ CO ₃	Dioxane	Reflux	65	—	—
14	BPO (4)	NIS (0.5)	Na ₂ CO ₃	Dioxane	Reflux	37	—	—
15	TBPB (4)	NIS (0.5)	Na ₂ CO ₃	Dioxane	Reflux	86	—	—
16	TBPB (4)	NIS (0.5)	—	Dioxane	Reflux	—	—	—
17	TBPB (4)	MnI ₂ (0.5)	Na ₂ CO ₃	Dioxane	Reflux	82	—	—
18	TBPB (4)	FeI ₂ (0.5)	Na ₂ CO ₃	Dioxane	Reflux	84	—	—
19	TBPB (4)	NaI (0.5)	Na ₂ CO ₃	Dioxane	Reflux	81	—	—
20	TBPB (4)	NIS (0.5)	NaOAc	Dioxane	Reflux	92	—	—
21	TBPB (4)	NIS (0.5)	Et ₃ N	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 ₂ CHCH ₂ Cl	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.

optimal conditions for the azabenzoin reaction of *o*-vinyl benzaldehyde **1a** and *N*-(phenyl(tosyl)methyl)benzamide **2a**.

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-tetramethylpiperidinoxy (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-1-one 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 Na₂CO₃ (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 Na₂CO₃, 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 MnI₂, FeI₂ and NaI were also effective iodide sources, giving good yields of product **5a** (81–84%) (Table 2, entries 17–19). Pleasingly, the use of Et₃N and NaOAc instead of Na₂CO₃ 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, Et₃N and Na₂CO₃ 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 1,4-dioxane 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**

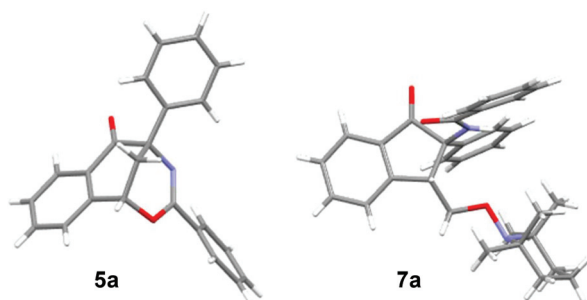
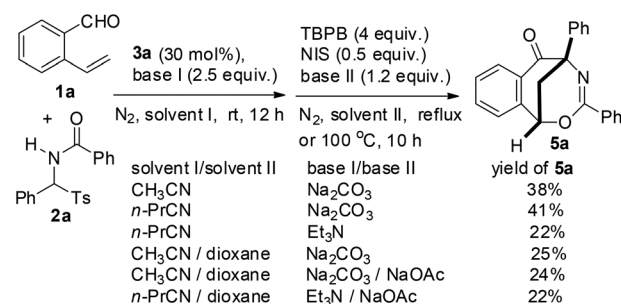


Fig. 1 X-ray structures of compounds **5a** and **7a**.



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

Table 3 Synthesis of 2-aryl-2-benzamido-1-(2-vinylaryl)-1-ethanones **4**^{a,b}

<p> X Z CHO 1 (0.5 mmol) $\text{Z} = \text{C}, \text{N}$ Y 2 (0.5 mmol) 3a (30 mol%), Na_2CO_3 (2.5 equiv.) N_2, MeCN, rt, 12-24h 4 </p>			
 4a : 80% (12h)	 4b : 31% (24h)	 4c : 53% (24h)	 4d : 77% (12h)
 4e : 66% (12h)	 4f : 65% (12h)	 4g : 62% (12h)	 4h : 71% (12h)
 4i : 64% (12h)	 4j : 67% (12h)	 4k : 82% (12h)	 4l : 71% (12h)
 4m : 78% (12h)	 4n : 80% (12h)	 4o : 81% (12h)	
 4p : 69% (12h)	 4q : 56% (12h)	 4r : 61% (12h)	

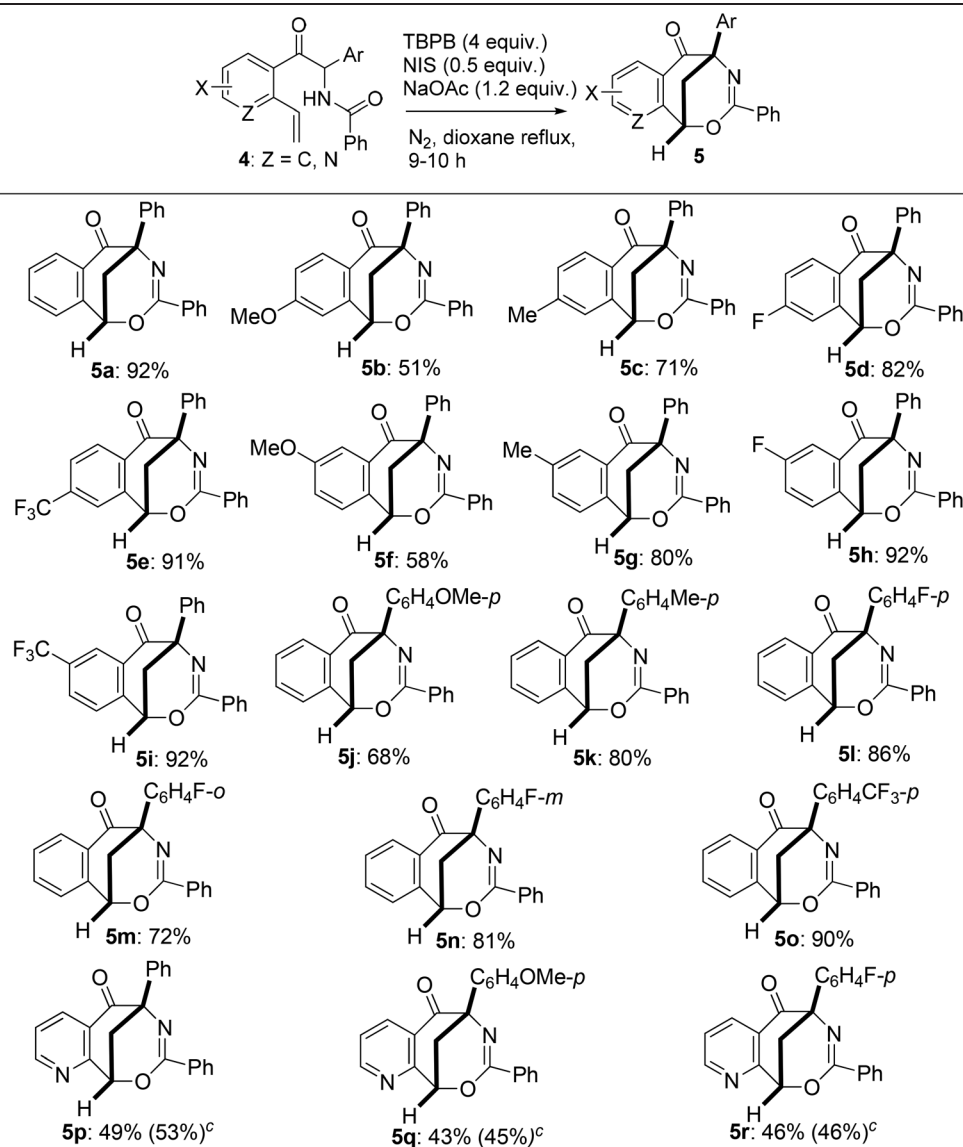
^a Reaction conditions: Under a nitrogen atmosphere and at room temperature, a mixture of *N*-(aryl(tosyl)methyl)benzamides **2** (0.5 mmol), thiazolium salt **3a** (0.15 mmol), Na_2CO_3 (1.25 mmol) and *o*-vinyl aromatic aldehydes **1** (0.5 mmol) in dry acetonitrile (5 mL) was stirred for 12–24 h at room temperature. ^b Isolated yield.

4e in 77% and 66% yields, respectively. However, an electron-donating 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-vinylaryl)methyl)benzamides) **4** in hand, we then studied the generality of the radical-mediated intramolecular cyclization of **4** to the synthesis of bridged

Table 4 Synthesis of 5-aryl-3-phenyl-1,5-methanobenzo[*f*][1,3]oxazocin-6-ones **5**^{a,b}



^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.).

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]oxazocin-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



addition to the vinyl group of **8** leads to the formation of 3,4-dihydronaphthalen-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-1-one radicals **9** with NIS or the iodine radical provides 2-aryl-4-iodo-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 benzyl iodide 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 H₂O

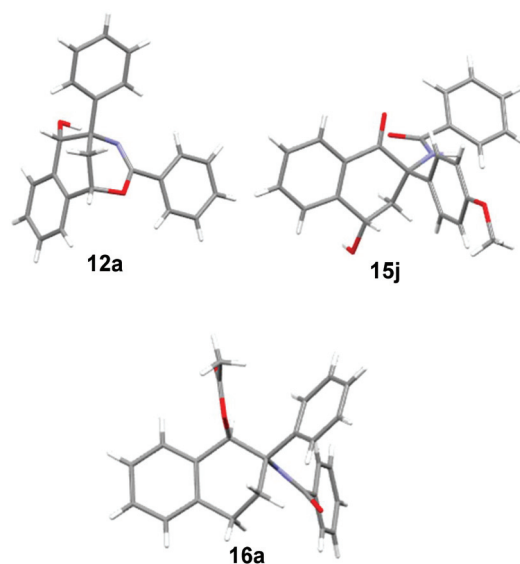


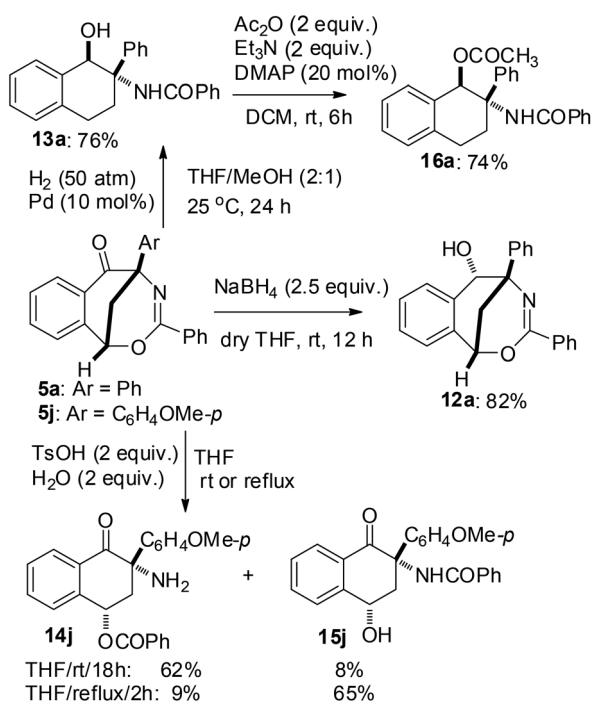
Fig. 2 X-ray structures of **12a**, **15j** and **16a**.

(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 6,10-methanopyrido[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



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

cascade cyclizations of 2-aryl-2-benzamido-1-(2-vinylaryl)-1-ethanones. 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[3,2-*f*][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 ring-fused 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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