

RESEARCH ARTICLE

Palladium-catalyzed, copper-mediated construction of benzene rings from the reactions of indoles with *in situ* generated enones†

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Construction of the benzene ring in carbazoles was efficiently realized through a domino dehydrochlorination/alkenylation/cycloaddition–oxidation sequence by means of palladium(II)-catalyzed, copper(II)-mediated reactions of *N*-protected 2,3-unsubstituted indoles with 3-chloropropiophenones in the presence of a base. 3-Alkenylated indole was confirmed to be formed as the reaction intermediate which then underwent Diels–Alder cycloaddition to the initially *in situ* generated enone from a 3-chloropropiophenones substrate, and the subsequent dehydrogenative aromatization yielded the carbazole product. The strategy to employ *in situ* generated enones as the reactive species avoided the use of a large excess of labile substrates and lessened the side reactions.

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Construction of benzene rings is usually the key step to establish important aromatic systems.¹ Functionalized aromatics are traditionally prepared through aromatic electrophilic substitution reactions or by transition-metal catalyzed multistep transformations generally involving alkynes.² Polycyclic (hetero)-arenes have demonstrated valuable utility in synthetic chemistry, and their concise synthesis is strongly desired from the reactions of readily available building blocks, among which formal oxidative cross-coupling of three alkenes seems to be a promising route to a benzene ring.³

Carbazoles are an important class of aromatic heterocyclic nuclei as structural motifs in many synthetic compounds and naturally occurring alkaloids.⁴ The cross-coupling reactions of C–H/C–X bonds (X = halo, N, O, C, *etc.*) have been employed for their synthesis.^{5–9} Oxidative intramolecular C–H/C–H cross-coupling of prefunctionalized diarylamines was realized for the same purpose.¹⁰ 2-Aryl and 2-heteroarylindoles were reported to react with alkynes to prepare carbazoles.^{11,12} Using a trimetallic system, *i.e.*, Pd(OAc)₂/Cu(OAc)₂/Ag(OCOCF₃), *N*-methylindoles reacted with 10 equiv. of methyl or phenyl vinyl ketone to form diacetyl- and dibenzoylcarbazoles,

respectively.¹³ Although indoles can react with α,β -unsaturated carbonyls,¹⁴ synthesis of carbazoles from their reactions with electron-deficient alkenes is still challenging because aryl vinyl ketones (enones) are usually not commercially available due to their susceptibility to heat, light and oxygen during preparation and storage. Palladium-catalyzed dehydrogenation of alkyl ketones was thus documented to prepare enones, but the synthesis generally requires high catalyst loading and relatively harsh conditions.¹⁵ As an alternative route, *in situ* generation of enones has recently attracted attention using saturated alkyl ketones and β -keto esters as the alkene sources.^{15c,16}

Recently, we found that β -chloroalkyl aryl ketones and their ester and amide derivatives can be utilized as precursors to α,β -unsaturated carbonyls in Rh(I)-catalyzed conjugate addition by arylboronic acids.¹⁷ Under an oxygen atmosphere, PdCl₂-catalyzed trimerization of phenyl vinyl ketone afforded 1,3,5-tribenzoylbenzene in 25% yield.^{3b} We thus envisioned that 3-chloropropiophenone might undergo the same reaction *via* the *in situ* generated enone intermediate. To our delight, such a reaction occurred to give the target trimerization product in 20% yield (Scheme 1a). Retrosynthetic analysis suggests that construction of a benzene ring is plausible from the reaction of a 3-chloroalkyl carbonyl (as the enone precursor) with indole (as an alkene building block) because palladium-catalyzed indole alkenylation with electron-deficient acrylates and alkenes has been well-known.¹⁸ Herein, we report the synthesis of functionalized carbazoles by the reactions of 3-chloroalkyl ketones with indoles through a domino sequence¹⁹ (Scheme 1b).

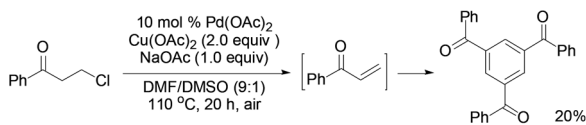
Initially, *N*-methylindole (**1a**) was reacted with 3-chloropropiophenone (**2a**) in dioxane at 100 °C under a nitrogen atmosphere using 10 mol% Pd(OAc)₂ as the catalyst, Cu(OAc)₂ as the

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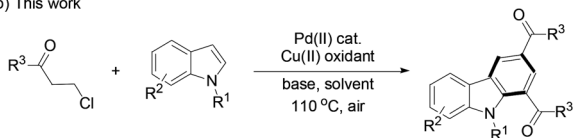
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(a) Construction of a benzene ring from 3-chloropropiophenone



(b) This work

Scheme 1 Synthesis of carbazoles via *in situ* generated enones.Table 1 Screening of conditions for the reaction of *N*-methylindole (1a) with 3-chloropropiophenone (2a)^a

Entry	Catalyst	Oxidant	Base	Temp (°C)	Yield ^b of 3a (%)
1 ^c	Pd(OAc) ₂	Cu(OAc) ₂	Na ₂ CO ₃	100	10
2 ^d	Pd(OAc) ₂	Cu(OAc) ₂	Na ₂ CO ₃	100	43
3 ^e	Pd(OAc) ₂	Cu(OAc) ₂	Na ₂ CO ₃	100	51
4	Pd(OAc) ₂	Cu(OAc) ₂	Na ₂ CO ₃	100	74
5	Pd(OAc) ₂	Na ₂ CO ₃	Na ₂ CO ₃	100	<1
6	Pd(OAc) ₂	CuOAc	Na ₂ CO ₃	100	<1
7	Pd(OAc) ₂	Cu(OAc) ₂	Na ₂ CO ₃	110	77
8	Pd(OAc) ₂	Cu(OAc) ₂	Na ₂ CO ₃	120	73
9		Cu(OAc) ₂	Na ₂ CO ₃	110	0
10	Pd(OAc) ₂	Cu(OAc) ₂	NaOAc	110	81
11 ^f	Pd(OAc) ₂	Cu(OAc) ₂	NaOAc	110	82
12 ^f	Pd(OAc) ₂	Air	NaOAc	110	<1
13 ^{f,g}	Pd(OAc) ₂	Cu(OAc) ₂	NaOAc	110	63
14 ^f	Pd(OAc) ₂	CuOAc	NaOAc	110	51
15 ^{f,h}	Pd(OAc) ₂	Cu(OAc) ₂	NaOAc	110	70

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), catalyst (0.02 mmol), base (0.8 mmol), oxidant (1.2 mmol), solvent (2.5 mL, DMF–DMSO, v/v = 9 : 1), 0.1 MPa N₂, 20 h. ^b Isolated yield. ^c In dioxane. ^d In DMSO. ^e In DMF. ^f In air. ^g Cu(OAc)₂ (1.0 mmol) was used. ^h Using 5 mol% catalyst.

oxidant, and Na₂CO₃ as the base, giving the desired product **3a** in 10% yield (Table 1, entry 1). Changing the solvent to DMSO or DMF improved the reaction efficiency, and a 9 : 1 mixture of DMF and DMSO promoted the reaction to form **3a** in 74% yield (Table 1, entries 2–4). Cu(OAc)₂ acted as the most effective oxidant among those screened, *i.e.*, Cu(OAc)₂, Cu(OAc)₂·H₂O, AgOAc, AgCO₃, benzoquinone (BQ), and *t*BuOO*t*Bu, while the reaction hardly occurred without an added oxidant or by using CuOAc as the sole oxidant (Table 1, entries 5 and 6). Elevating the temperature to 110 °C improved the reaction (Table 1, entry 7). A catalyst was necessary for the reaction, and Pd(OAc)₂ was shown to be the most efficient one among the screened Pd(II) and Pd(0) sources (see the ESI†). A base was required for the reaction, and NaOAc behaved better than Na₂CO₃. An air atmosphere slightly improved the yield of **3a** (82%), but oxygen as the sole oxidant did not facilitate the

Table 2 Reactions of **2a** with indoles **1**^{a,b}

Indole Derivative	Yield (%)
3a (R = Me)	82%
3b (R = Et)	70% ^c
4b (R = Et)	24% ^c
3c (R = <i>n</i> -Pr)	60%
4c (R = <i>n</i> -Pr)	35%
3d (R = Bn)	63% ^c
4d (R = Bn)	31% ^c
3e (R = Ph)	0%
4e (R = Ph)	91%
3f (R = allyl)	56%
3g (R = Me, 2-Me)	78%
3h (R = Me, 3-Me)	76%
3i (R = Me, 4-Me)	70%
3j (R = Me, 5-Me)	79%
3k (R = Me, 2-Me, 4-Me)	80%
3l (R = Me, 2-Me, 6-F)	70%
3m (R = Me, 2-Me, 4-Cl)	61%
3n (R = Me, 2-Me, 4-NO ₂)	60% ^c
3o (R = Me, 2-Me, 4-CN)	65%
3p (R = Me, 2-Me, 4-CO ₂ Me)	54%
3q (R = Me, 2-Me, 4-CO ₂ Me)	67%
3r (R = Me, 2-Me, 4-CO ₂ Me)	60%

^a Reaction conditions: **1** (0.2 mmol), **2a** (0.8 mmol), Pd(OAc)₂ (10 mol%), Cu(OAc)₂ (6 equiv.), NaOAc (4 equiv.), DMF–DMSO (2.5 mL, v/v = 9/1), 20 h. ^b Isolated yields. ^c 30 h.

reaction (Table 1, entry 12). Using less Cu(OAc)₂ reduced the yield of **3a** (Table 1, entry 13). Although both CuOAc and oxygen cannot be used as the sole oxidants, their combination worked well (Table 1, entry 14). A reduced loading of the catalyst (5 mol%) led to a lower yield of **3a** (70%) (Table 1, entry 15). It should be noted that only a trace amount of **4a** was detected during the reaction.

Next, the indole scope was explored to probe the protocol generality (Table 2). As the steric hindrance of the *N*-R moiety in indoles was increased from methyl to ethyl, *n*-propyl, benzyl, and phenyl, yields of the desired products were gradually decreased from 82% (R = Me for **3a**) to 0% (R = Ph for **3e**). 3-Alkenylated indoles **4b–4d** were formed as the minor products (24–35%), while in the case of *N*-phenylindole, **4e** was formed as the only product (91%). The reaction of *N*-allylindole with **2a** afforded **3f** (56%) with its allyl functional group unchanged. The electron-donating substituents on the aryl rings of the indole substrates did not obviously affect the reaction efficiency as **3g–3k** were obtained in 70–80% yields, whereas the electron-withdrawing fluoro, chloro, nitro, cyano, and CO₂Me groups lessened the formation of the desired products **3l–3q** (54–70%). *N*-Methyl-7-azaindole also underwent the reaction with **2a** to form **3r** (60%). The molecular

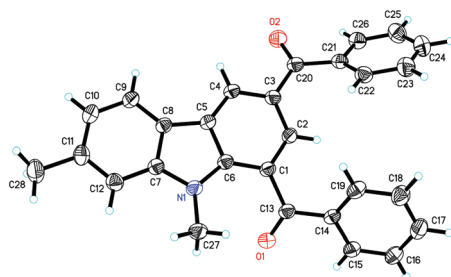


Fig. 1 Molecular structure of **3i**.

structures of compounds **3** were further confirmed by X-ray single crystal structural determination of **3i** (Fig. 1).

The protocol generality was then investigated by reacting indoles with various 3-chloroalkyl ketones (Table 3). Treatment of **1a** with substituted 3-chloroalkyl ketones (**2**) formed the desired products **5a–5e** in 74–85% yields. Increasing steric hindrance of the aryl moiety in **2** deteriorated the production of **5f–5i** (47–64%), and the reduced steric hindrance from 3,4-dimethyl groups only had a slight influence on the yield of **5j** (78%). Heteroaryl 3-chloropropiophenones underwent the same reactions to generate 1,3-diheteroarylcarbazoles **5k** (76%) and **5l** (75%), respectively. Substituted *N*-methylindoles also efficiently reacted with 3-chloroalkyl aryl ketones to afford products **5m–5r** (72%–80%). A 7-CO₂Me in **1** or thienyl in **2** led to reduced yields for **5s** (64%) and **5t** (66%), respectively. However, the reaction of 5-chloropentan-3-one with **1a** only gave **5u** in 26% yield with 3-alkenylated indole **4f** (59%) as the major product. Similar results were obtained in the case of 3-chloropropionic acid phenyl ester, forming **5v** (25%) and **4g** (70%). The β-methyl group in **2** completely inhibited the target reaction, resulting in **4h** (69%) as the only product.

To determine whether the 3-alkenylated indole of type **4** was an intermediate, the reaction of **1a** with **2a** was conducted at 80 °C using 4 mol% catalyst (eqn (1)). It was found that the reaction initially formed **4a**, which was then gradually converted to the desired product **3a**. Analysis of the reaction mixture at 3 h by GC revealed the presence of unreacted enone **6**.¹⁷ Reacting **1a** with **6** under the typical conditions afforded **3a** in 55% yield (eqn (2)), which is comparable with the 53% yield of the same reaction with 10 equiv. of **6** by means of the trimetallic system.¹³ These results have revealed that the present bimetallic system employing *in situ* generated enone **6** is efficient for carbazole synthesis.

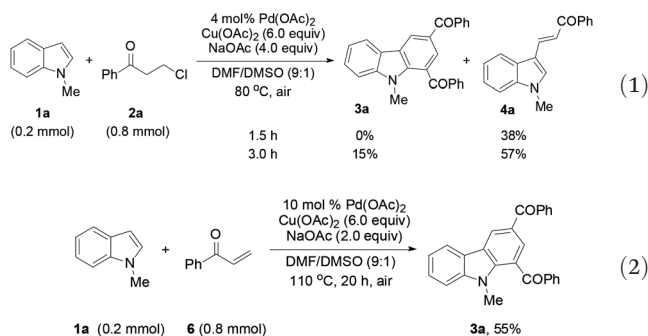
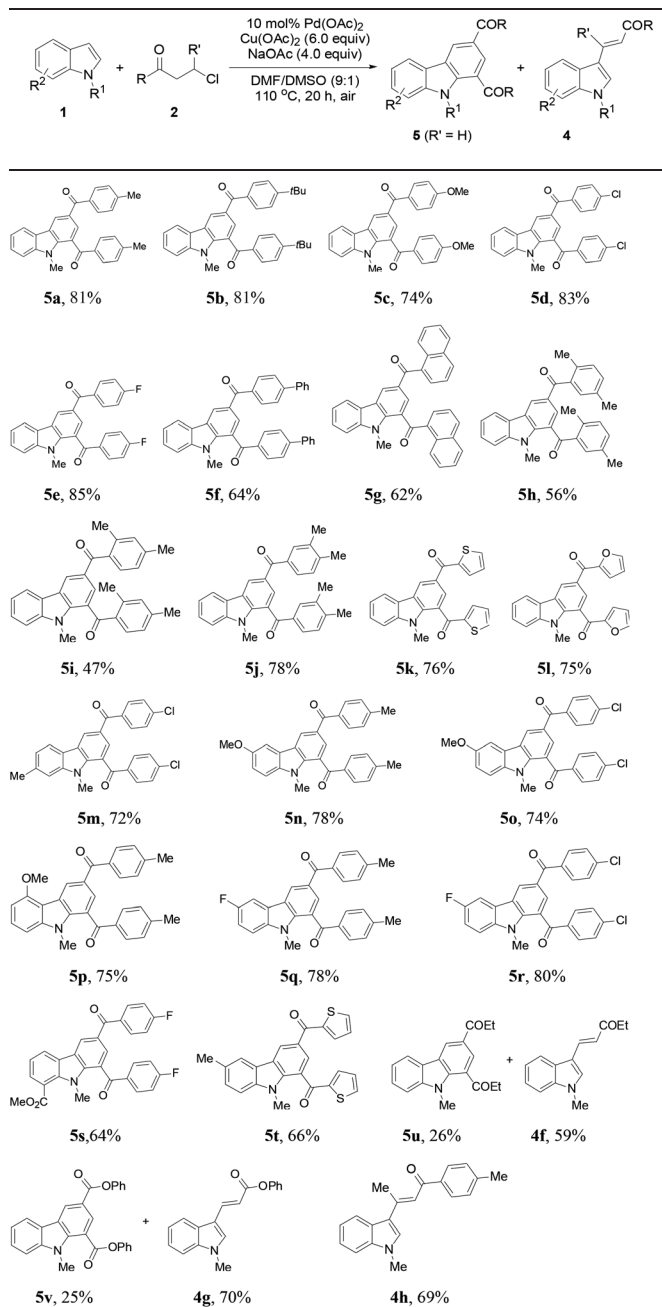


Table 3 Reactions of β-chloro ketones and their ester derivatives **2** with indoles **1**^{a,b}



^a Reaction conditions: **1** (0.2 mmol), **2a** (0.8 mmol), Pd(OAc)₂ (10 mol%), Cu(OAc)₂ (6 equiv.), NaOAc (4 equiv.), DMF–DMSO (2.5 mL, v/v = 9/1).
^b Isolated yields.

To probe further into the reaction pathway of the 3-alkenylated indole intermediate with the *in situ* generated enone species, the controlled reaction of **4a** with **2a** was investigated (Table 4). Deviation of the standard conditions by omitting one or two reaction parameters changed the formation of **3a**. Under the standard conditions as shown in eqn (3), **3a** was formed in 75% yield (Table 4, entry 1). Without Pd(OAc)₂ as the catalyst, the reaction was not affected much to give **3a** (78% yield in air,

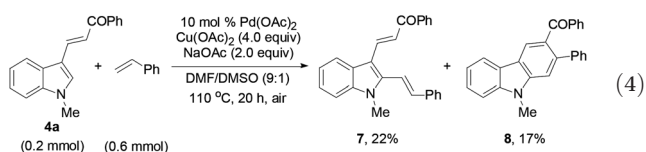
Table 4 Controlled reactions of **4a** with **2a**

Entry	Conditions	Yield ^a
1	Standard conditions	75%
2	Without Pd(OAc) ₂	78%
3	Without Pd(OAc) ₂ under 0.1 MPa N ₂	83%
4	Without Cu(OAc) ₂	51%
5	Without both Pd(OAc) ₂ and Cu(OAc) ₂	48%
6	Without both Pd(OAc) ₂ and Cu(OAc) ₂ under 0.1 MPa N ₂	Complicated

^a Isolated yield of **3a**.

83% yield under atmospheric nitrogen) (Table 4, entries 2 and 3). Without Cu(OAc)₂, or in the absence of both Pd(OAc)₂ and Cu(OAc)₂, **3a** was still obtained in 48–51% yields, whereas the same reaction became complicated under a nitrogen atmosphere (Table 4, entries 4–6), suggesting that an added oxidant or air should be used as the oxidant for the reaction to occur properly. These results have revealed that a palladium catalyst is not necessary for the reaction as shown in eqn (3), and the reaction can occur without Cu(OAc)₂ in air, but an added oxidant such as Cu(OAc)₂ promotes the reaction better than air.

Reacting **4a** with styrene under the standard conditions (eqn (4)) afforded 2,3-dialkenylated indole **7** (22%) and carbazole **8** (17%) through multiple C–H activation of the indole substrate. The X-ray single crystal structure of **8** was also confirmed (Fig. 2). No product of type **7** was obtained from the reaction of **4a** with **2a**, excluding a C–H activation pathway. These results led us to deduce that Diels–Alder cycloaddition and subsequent oxidation were involved in forming the benzene ring in the overall reaction.



A proposed mechanism is depicted by the reaction of **1a** with **2a** (Scheme 2). The indole substrate initially undergoes

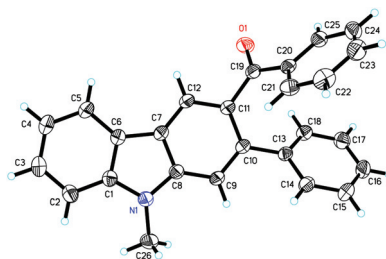
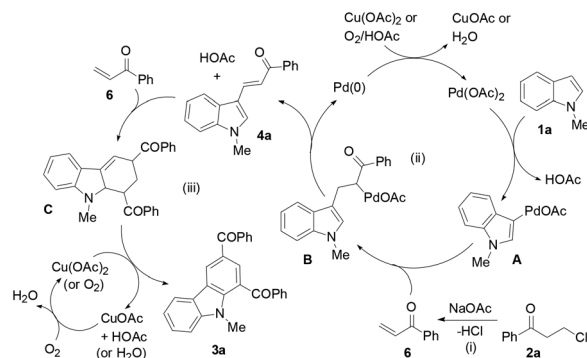


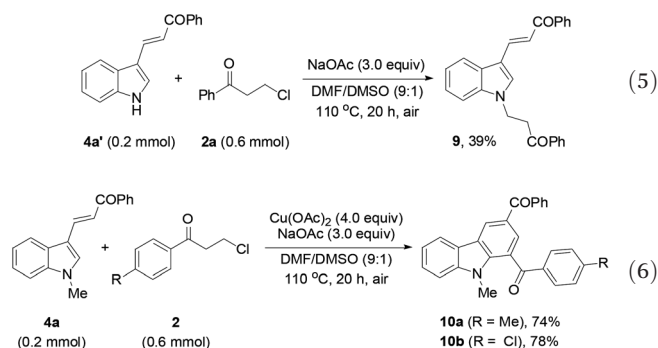
Fig. 2 Molecular structure of **8**.



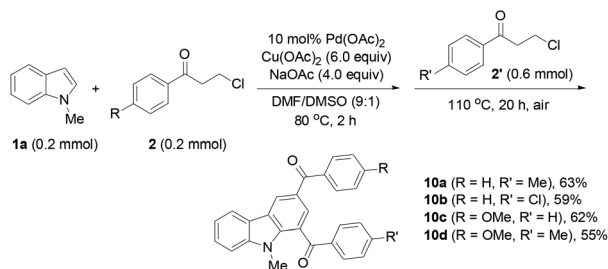
Scheme 2 Proposed mechanism.

palladation at its 3-position to form a palladated species **A** and HOAc. **A** reacts with the *in situ* generated enone **6** from **2a** to yield an alkene insertion species **B**, which undergoes reductive elimination to produce 3-alkenylated indole **4a** and a Pd(0) species. A Diels–Alder cycloaddition of **6** to **4a** forms tetrahydrocarbazole **C**, which is subsequently oxidized to form the desired product **3a**. Air facilitates regeneration of the Cu(II) oxidant and the Pd(II) catalyst.

Finally, the protocol was extended to the reactions of *N*-unprotected indoles. It was found that the *N*-unprotected analogue of **4a** reacted with **2a** in the presence of NaOAc to form the *N*-(3-oxo-3-phenylpropyl)-substituted product **9** (39%), affording no desired carbazole product (eqn (5)). For the versatile synthesis of carbazoles, the reactions of **4a** with 3-chloroalkyl aryl ketones were performed, producing carbazoles **10a** (74%) and **10b** (78%) bearing two different substituents (eqn (6)). A one-pot, two-step procedure was also established to synthesize the mixed aryl-substituted carbazoles **10a–10d** (55–63%) (Scheme 3), providing a potentially applicable route to functionalized carbazoles.



In summary, palladium(II)-catalyzed, copper(II)-mediated synthesis of carbazoles has been efficiently realized through a domino dehydrochlorination/alkenylation/cycloaddition–oxidation sequence by means of the reactions of *N*-protected indoles with 3-chloropropiophenones in the presence of a base. The strategy employed *in situ* generated α,β -unsaturated carbonyls to avoid using a large excess of labile substrates and to lessen side reactions. The present method provides a concise route to functionalized carbazoles.



Scheme 3 One-pot synthesis of functionalized carbazoles.

Experimental section

A typical procedure for the synthesis of carbazoles: synthesis of 3a

A mixture of *N*-methylindole (**1a**) (26 mg, 0.2 mmol), 3-chloropropiophenone (**2a**) (133 mg, 0.8 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol), Cu(OAc)₂ (218 mg, 1.2 mmol), and NaOAc (66 mg, 0.8 mmol) in 2.5 mL DMF–DMSO (v/v = 9:1) was stirred at 110 °C under an air atmosphere for 20 h. After cooling to ambient temperature, 10 mL CH₂Cl₂ was added and the resulting mixture was filtered through a short pad of silica gel, followed by rinsing with 20 mL CH₂Cl₂. The combined filtrate was washed with brine (15 mL) and separated. The organic phase was dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: petroleum ether (60–90 °C)–EtOAc–CH₂Cl₂ = 30:1:2, v/v/v) to afford **3a** as a white solid (64 mg, 82%).

Acknowledgements

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