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Three-Component Indium-Mediated Domino Allylation of 1*H*-Indole-3-carbaldehyde with Electron-Rich (Hetero)arenes: Highly Efficient Access to Variously Functionalized Indolylbutenes

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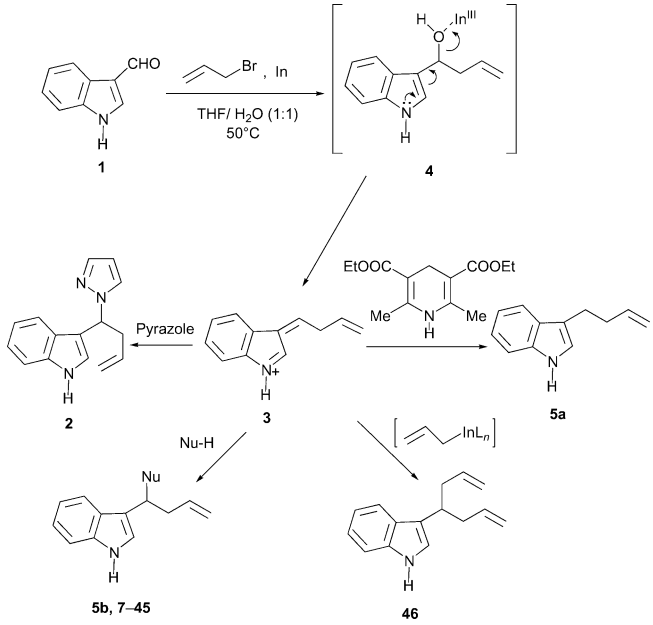
We have developed a three-component, one-pot domino reaction that combines the allylindation of 1*H*-indole-3-carbaldehyde with the dehydrative alkylation of stabilized C nucleophiles (e.g., electron-rich heteroarenes, electron-rich aromatics, and stabilized enols) or N nucleophiles (e.g., azoles).

Introduction

The ubiquitous presence of the indole skeleton in a large number of naturally occurring and biologically important compounds has elicited intense research aimed to facilitate its synthesis and functionalization. Moreover, the indole unit has been recognized as a component of highly specific information-transmitting molecules, a role it plays because it can bind to many receptors with a high degree of affinity. Consequently, much efforts is being devoted to develop efficient methods for the installation of a variety of functional groups on the indole scaffold.[1]

Following our interest in this area we revisited the Barbier-type indium-mediated allylation[2,3] (hereafter called allylindation) of 1*H*-indole-3-carbaldehyde (**1**) in the presence of azoles (e.g., pyrazole). At variance with results previously reported by others,[4] we anticipated that adduct **2** could be obtained by a three-component, one-pot domino process (as shown in the Scheme 1)[5,6]

Inspired by successful and ready reaction with N nucleophiles, we proceeded to develop a C–C bond-forming reaction by merging allylindation with a dehydrative Friedel–Crafts-type alkylation. If successful, this approach would facilitate the access (via common intermediate **3**) to a variety of structurally diverse products by simply changing the C nucleophile chosen to react with it. The present report describes the results of this study and their applications to the synthesis of nonsymmetrical bis(indolyl)-, heteroaryl(indolyl)-, and alkyl(indolyl)butenes.[6,7]



Scheme 1.

Results and Discussion

We started from the allylindation of **1** in the presence of indole (as a neutral C nucleophile, i.e. one possessing relatively high-lying HOMOs) to obtain the already-known indole **5**; standard conditions were used as described by Kumar et al.[4] Treatment of **1** with allyl bromide (1 equiv.) and indole (1 equiv.) in the presence of indium metal (0.7 equiv.)

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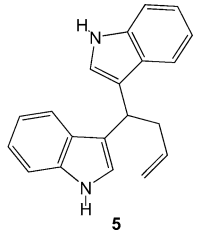
Table 1. Optimization of reaction conditions for allylindation of aldehyde **1** in the presence of indole.

Entry	Solvents	**1**/allyl bromide/In/indole	Temperature [°C]	*t* [h]	Yield [%][a]/[%][b]
1	THF/H_2O (2:1)	1:1:0.7:1	room temp.	3	40–55[c]/11–17[c]
2	THF/H_2O (1:1)	1:2:1.4:1	50	2	86/10
3	CH_2Cl_2	1:2:1.4:1	40	2	35/21
4[d]	DMF	1:2:1.4:1	50	2	33/25
5	MeOH	1:2:1.4:1	50	2	15/25
6[e]	MeCN/H_2O (1:1)	1:3.3:1.1:1	room temp.	4	73/12
7	MeCN/H_2O (1:1)	1:3.3:1.1:1	room temp.	4	25/20
8[e]	MeCN	1:3.3:1.1:1	50	6	49/16
9[e]	MeOH	1:3.3:1.1:1	50	6	57/21
10[f]	THF/H_2O (1:1)	1:2:1.4:1	50	2	61/11
11[f]	MeCN/H_2O (1:1)	1:3.3:1.1:1	50	6	65/13

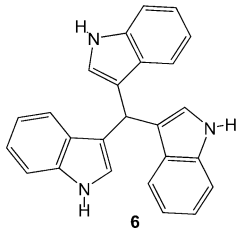
[a] Isolated yields based on aldehyde **1**. [b] Isolated yields of **6**. [c] Yield range over three runs. [d] KI (1 equiv.) was added. [e] HCOOH (0.1 equiv.) was added. [f] High-intensity ultrasonic irradiation (20 kHz, 250 W).

in THF/H_2O (2:1) at 30 °C for 3 h afforded the desired adduct **5**. In our hands, however, the reaction often failed to go to completion and its isolated yield varied from 40 to 55% (three runs; Table 1, Entry 1). As conversions were unsatisfactory, we undertook an investigation to find how they could be improved. We identified five main factors that influenced reaction efficiency and selectivity: (1) the solvent, (2) the stoichiometric ratio of reactants, (3) the temperature, (4) the presence of acid catalysts, and (5) ultrasonic irradiation. We experimented with a wide range of solvents (including THF, MeCN, CH_2Cl_2, DMF, and MeOH), either neat or mixed with H_2O, and found that the highest yield (86%) was achieved in THF/H_2O (1:1) and at 50 °C. Different temperatures for the allylindation reactions were investigated during our previous work on this subject.[2] A complete survey led us to carry out the three-component reactions at 50 °C in THF/H_2O (1:1). So, we report here the results with optimized experimental procedures.

Under these conditions, an excess amount of allyl bromide (2 equiv.) and indium (1.4 equiv.) was also required for the reaction to go to completion (Table 1, Entry 2). With other solvents (i.e., CH_2Cl_2 and DMF) the reaction was slower (Table 1, Entries 3 and 4, respectively), whereas MeOH gave very low conversions (Table 1, Entry 5).



5



6

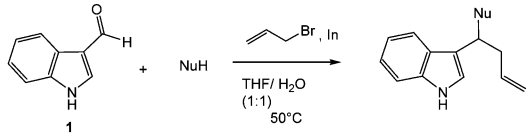
Under these conditions, however, the process was plagued by a side reaction, that is, the condensation of **1** with indole to give **6**[8] in yields ranging from 10 to 25%. By carrying out the reaction with the use of THF as solvent or cosolvent the formation of **6** was minimized. Other supplementary surveys regarding the effects of the single solvent or the solvent mixtures will be studied in the future. We then proceeded to screen three Brønsted acid catalysts (HCOOH,[9] AcOH,[10] and NH_4Cl[11]) that had previously worked well for indium-mediated reactions. HCOOH looked particularly promising on the basis of previous work by Whitesides.[9] In fact, treatment of **1** with this catalyst (0.1 equiv.) at room temperature cleanly afforded **5** (Table 1, Entry 6) in a pleasing 73% yield; no unreacted aldehyde remained (TLC). In the absence of HCOOH, the reaction was slower and led to a mixture of products (Table 1, Entry 7). In the presence of HCOOH (0.1 equiv.), MeCN or MeOH also performed well as solvent, and significantly increased conversions and yields were observed (Table 1, Entries 8 and 9, respectively). Finally, carrying out the reaction in an ultrasonic bath (20 kHz, 250 W) under the conditions detailed in Entries 2 and 6 (Table 1) had no significant effect on either conversions or overall yields (Table 1, Entries 10 and 11, respectively). Although the 1:1:1 adduct **5** was obtained in good yield at room temperature with the use of 1.1 equiv. of indium (Table 1, Entry 6), 1.4 equiv. of indium at 50 °C in THF/H_2O (1:1) worked even better (Table 1, Entry 2).

Having established an optimal set of conditions (Table 1, Entry 2) for the allylindation reaction, our procedure was tested on a range of nucleophilic probes (e.g., electron-rich heterocycles, electron-rich arenes, and stabilized enols).

As shown in Table 2, the use of skatole (3-methyl indole) as nucleophile did not significantly affect the yield but directed the alkylation at C-2 (Table 2, Entry 3) leading to **8**. Increasing the steric bulk at the 3-position decreased the selectivity. Thus, tryptophol (Table 2, Entry 4) gave both C- and N-alkylation products (**9** and **10**, respectively) in a 1.3:1 ratio, whereas tetrahydrocarbazole (Table 2, Entry 5) underwent N alkylation exclusively (to afford **11**).

The presence of an electron-withdrawing group at C-3 of the indole system had a detrimental effect on the reaction. Indeed, 3-bromo- and 3-phenylindole failed to give any derivatives, even under drastic conditions. On the contrary, under our conditions bis(alkylation) complicated the reaction of highly activated nucleophiles. In the case of pyrrole, some bis(adduct) **14** (7%) was obtained besides a mixture of **12** (56%) and **13** (17%). The most probable pathway for the formation of **13** appears to be an indium-mediated Barbier reaction of primary product **12**, as observed by Yadav[12] with pyrrole and indole. The 2:1 adduct **14** was found by ^1H and ^{13}C NMR spectra to be an inseparable diastereomeric mixture (*C_2*/*meso* ca. 1:1). Formation of **13**

Table 2. Domino allylindation–alkylation reaction[a] of aldehyde **1** with nucleophiles.



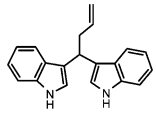
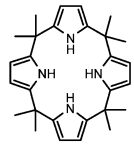
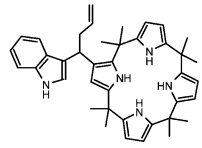
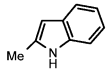
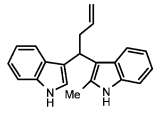
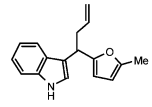
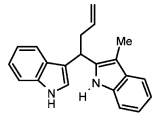
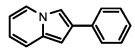
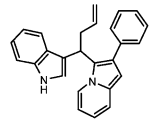
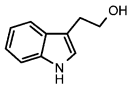
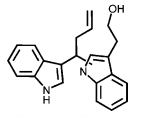
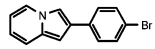
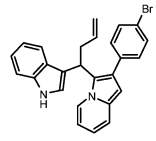
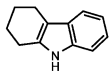
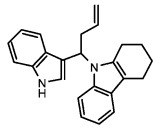
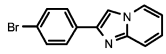
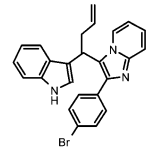
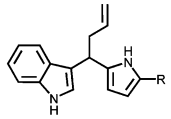
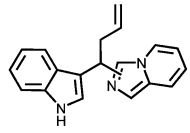
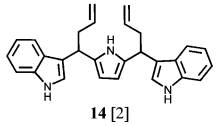
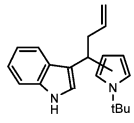
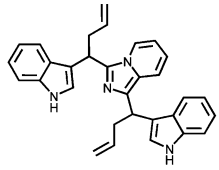
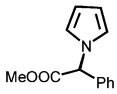
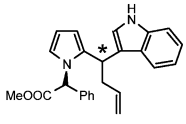
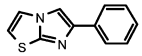
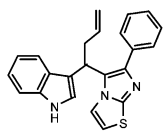
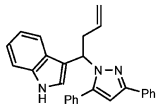
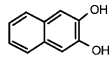
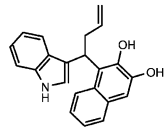
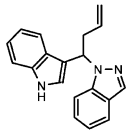
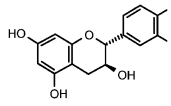
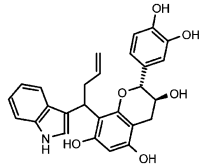
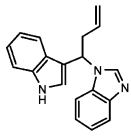
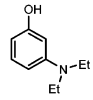
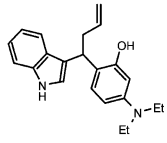
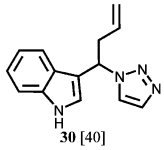
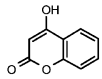
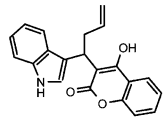
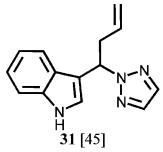
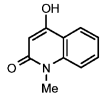
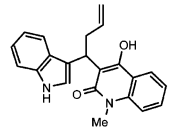
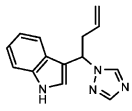
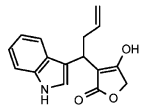
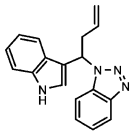
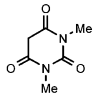
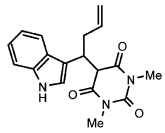
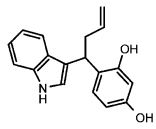
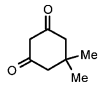
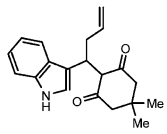
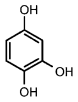
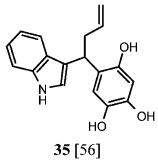
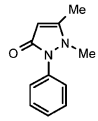
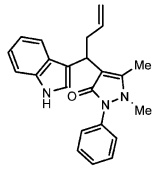
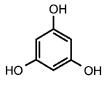
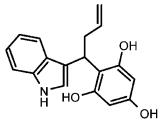
Entry	NuH	Product [%][b]	Entry	NuH	Product [%][b]
1		 **5b** [86]	9		 **18** [53]
2		 **7** [70]	10		 **19** [79]
3		 **8** [55]	11		 **20** [50]
4		 **9** (N-1), **10** (C-2) [40], [31]	12		 **21** [77]
5		 **11** [52]	13		 **22** [75]
6		 **12** (R:H), **13** (R: allyl)] [75], [8]	14		 **23** (C-3), **24** (C-1) [28], [6]
		 **14** [2]			
7		 **15** (C-3), **16** (C-2) [40], [17]			 **25** [36][c]
8		 **17** [60][c]	15		 **26** [90]

Table 2. *(Continued)*.

Entry	NuH	Product [%][b]	Entry	NuH	Product [%][b]
16		 **27** [41]	25		 **37** [55]
17		 **28** [56]	26		 **38** [86][c]
18		 **29** [32]	27		 **39** [33]
19		 **30** [40]	28		 **40** [91]
		 **31** [45]	29		 **41** [60]
20		 **32**[32]	30		 **42** [82]
21		 **33** [50]	31		 **43** [85]
22		 **34**[47]	32		 **44** [63]
23		 **35** [56]	33		 **45** [42]
24		 **36** [54]			

[a] Reaction conditions: aldehyde **1** (1 mmol), nucleophile (1 mmol), In (1.4 mmol), allyl bromide (2 mmol), THF/H_2O (1:1), 50 °C, 8 h (except for Entry 1). [b] Isolated yields based on aldehyde **1**. [c] Mixture of diastereomers.

and **14** could be partially (but not entirely) suppressed by using an excess amount of pyrrole, typically 5 equiv. (Table 2, Entry 6). Bulky substituents (e.g., *t*Bu) on the pyrrole system[13] caused an inversion of the inherent regiochemical preference, giving **15** and **16** in a 2.3:1 ratio (Table 2, Entry 7), although the 1-phenyl-1-carbomethoxymethyl group[14] directed the alkylation process on C-2 (to **17** as ca. 1:1 diastereomeric mixture) with complete regioselectivity (Table 2, Entry 8). Interestingly, *meso*-octamethylcalix[4]pyrrole,[15] which belongs to a well-known class of anion receptors,[16] afforded exclusively monoalkylated derivative **18** in good yields (Table 2, Entry 9). This finding paves the way to a new class of calixpyrroles, possibly endowed with interesting selective affinities for anions, to be obtained by varying the structures of functional groups.

When thiophene and its 2-methyl derivative were employed as nucleophiles, not even a trace amount of the three-component adducts could be detected. By comparing nucleophilicity parameters *N* (as defined by Mayr) of heteroarenes, we could rationalize these findings.[17,18] Whereas thiophene and its 2-Me derivative have $N = -1.01$ and $N = 1.26$,[19] respectively, indoles and pyrroles, which successfully behaved as π nucleophiles in the present work, had *N* values in the 4–7 range.[20] The *N* value of 2-methylfuran, 3.61,[18] may well mark the "threshold" of π-nucleophilic reactivity that is required for three-component adduct **19** (Table 2, Entry 10) to be formed from intermediates **3** or **4** in an aqueous solvent (see Scheme 1).

Pyrrolo[1,2-*a*]pyridines (or indolizines) and their aza-analogues (viz. imidazo[1,2-*a*]pyridines and imidazo[1,5-*a*]-pyridine) result from the juxtaposition of electron-rich and electron-poor heterocyclic rings; their electrophilic substitution reactions take place on the five-membered ring at C-3.[21] Thus, 2-phenyl- and 2-(4-bromophenyl)indolizine[22,23] gave, in good-to-excellent yields, the corresponding 3-alkylated compounds **20** and **21** (Table 2, Entries 11 and 12); likewise 2-(4-bromophenyl)imidazo[1,2-*a*]pyridine[24] (Table 2, Entry 13) yielded solely the 3-substituted derivative **22** in 75% yield. Imidazo[1,5-*a*]pyridine[25] (Table 2, Entry 14) proved less selective, giving a 4:1 mixture of 3- and 1-substituted compounds (**23** and **24**, respectively). In this instance, however, the 1,3-bis(alkylated) analogue **25** was the major product (isolated as an inseparable diastereomeric mixture), reflecting the enhanced reactivity of the five-membered ring. In the case of 6-phenylimidazo[2,1-*b*]thiazole[26] (Table 2, Entry 15), electrophilic attack occurred at the expected 5-position, leading to **26**.

Electron-poor azoles, for example, triazoles and benzo-fused analogues (Table 2, Entries 16–21), exhibited a similar reactivity towards **3**, affording the respective N-alkylated derivatives **27**–**33** in moderate-to-good yields; no trace amounts of C-alkylation products were detected.

These findings are consistent with the well-known chemistry of azoles. Accordingly, in free(NH) azole, where (neutral) pyrrole-like and (base/nucleophilic) pyridine-like N atoms occur in the same molecule, an electrophile will *always* react with the latter.[27] The structure of **28** and **33** was confirmed by single-crystal X-ray diffraction analysis.[28]

To assess the scope of our procedure, we examined the reactivity of **3** towards a number of electron-rich benzenoid compounds. A single alkyl substituent on the ring apparently did not suffice to promote Friedel–Crafts-type alkylation. Surprisingly, no reaction was observed with phenols and anilines, although these substrates are regarded as strongly activated arenes. Because electronic effects alone cannot account for such a dramatic lack of reactivity, other factors must be responsible (deactivation of the aromatic ring by coordination of In^{III} species arising from allylindation?). To address this issue, we turned to doubly activated aromatics (e.g., polyphenols, aminophenols). Under our conditions, polyphenols (Table 2, Entries 22–26) gave the corresponding monoalkylated derivatives **34**–**39** in moderate-to-good yields. Although 2-naphthol and 2,7-dihydroxynaphthalene were inert, the reaction of 2,3-dihydroxynaphthalene proceeded smoothly to afford compound **37** (Table 2, Entry 25) in 55% yield. Interestingly, the naturally occurring (+)-catechin[29] gave **38** (Table 2, Entry 26) in 86% yield. In recent years interest in polyphenolic compounds has been growing due to their wide-ranging biological activities. By our method, the 8-position of (+)-catechin can reliably be functionalized under mild conditions; the access is thus opened to a new class of derivatives, possibly susceptible of interesting pharmacologic applications. Needless to say, aromatics bearing electron-withdrawing groups proved inert under these reactions, which is consistent with the affirmed nucleophilic role of the aromatic ring.

Alkylation of enolates derived from 1,3-dicarbonyls has been widely employed in the synthesis of a variety of complex molecules.[30] These nucleophiles can undergo C and/or O alkylation; the conditions that enhance the ambidoselectivity of the reaction have been well established. Under our conditions, the putative 3-alkylidene-3*H*-indolium cation **3** was efficiently intercepted by 1,3-dicarbonyls to give C-alkylated derivatives **40**–**45** in fair-to-good yields, regardless of the nature of the two carbonyl groups (Table 2, Entries 28–33). The intermediacy of 3-alkylidene-3*H*-indolium cation **3** was further proven by carrying out the allylindation of **1** in the presence of a suitable reducing agent (e.g. Hantzsch ester) to lead to 3-but-3-enyl-1*H*-indole (**5a**).

It is interesting to note that no acid and/or base were required to promote substrate enolization. The formation of O-alkylation products was not observed. Gratifyingly, these results further expand the synthetic potential of our method for assembling variously functionalized alkyl(indolyl)butenes.

Taken together, the foregoing results leave little doubt that **4** is involved in this reaction. Under acid catalysis, indoles of this type are thought to generate 3-alkylidene-3*H*-indolium cations (viz. stabilized benzylic-type cations), which can be trapped by heteronucleophiles and stabilized C nucleophiles[31] in a three-component one-pot domino allylation–dehydrative Friedel–Crafts-type process. Notably, in all the examples listed in Table 2 the reaction proceeded well with 1.4 equiv. of indium. The metal plays a twofold role: to promote both the Barbier reaction [as In^0] and the

subsequent dehydrative alkylation step [as In^{III} species]. Indeed, In^{III} salts have been recently shown to be effective Lewis acids in many chemical transformations both in aqueous and organic media under mild conditions.[32] In particular, $InBr_3$ has attracted increasing attention as a green Lewis acid catalyst by virtue of its water stability, ease of recovery, operational simplicity, and good tolerance of oxygen- and nitrogen-containing substrates.[33]

Because of its electrophilic character, the exocyclic alkylidene carbon atom of **3** is a likely candidate for the intermolecular addition of C nucleophiles. To test this hypothesis, we treated it with $InBr_3$ (0.1 equiv.) homoallylic alcohol **4** (obtained from **1** by reaction with allylmagnesium bromide)[34] in the presence of indole (1 equiv.) in THF/H_2O (1:1) at 50 °C. Bis(indole) adduct **5** was isolated in 83% yield, which convincingly argues for the intermediacy of **3**. In an analogous vein, the catalytic activation of allylic and benzylic alcohols by In^{III} salts has been recently reported.[35] When no In^{III} salt was added, messy reaction mixtures were reported.

Homoallylic alcohol **4** was unstable when stored at room temperature for several days. Its lability extended to silica gel chromatography such that its purification was not possible. Under our optimized conditions and in the absence of competing nucleophiles, attempts to prepare **4** by allylindation of **1** were thwarted by its proclivity to undergo subsequent addition (via **3**) of allylIn^{I}[36] leading to **46** (42%)[2,4] as the major product, along with a plethora of byproducts (Scheme 1).

Conclusions

We developed a three-component one-pot domino reaction combining the allylindation of 1*H*-indole-3-carbaldehyde with the dehydrative alkylation of stabilized C nucleophiles (e.g., electron-rich heteroarenes, electron-rich aromatics, and stabilized enols) and N nucleophiles (e.g., azoles) to generate a library of variously functionalized indolylbutenes. Biological activities of some of these compounds are currently being evaluated.

The method meets the requirements of high-throughput parallel synthesis. As demonstrated above, product design is susceptible to numerous variations through the choice of C and N nucleophiles. An even greater synthetic flexibility can be achieved through the choice of other allylic and propargylic halides. Furthermore, the synthetic potential must be addressed of the C–C double bond ubiquitous in these substrates. Preliminary studies along these lines are encouraging and results will be reported in due course.

Experimental Section

Typical Experimental Procedure for the Synthesis of 5b–45: To a solution of 1*H*-indole-3-carbaldehyde (0.145 g, 1 mmol) in THF/H_2O (1:1, 12 mL) was added allylbromide (0.176 mL, 2 mmol), the chosen nucleophile (1 mmol), and indium powder (0.161 g, 1.4 mmol). The resulting mixture was stirred at 50 °C and stopped after 8 h. Distilled water (15 mL) was added to the flask, and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic extract was washed with water (2×15 mL) and dried with anhydrous sodium sulfate, and the solvents were evaporated under vacuum. Crude products **5b**–**45** were purified by flash silica gel chromatography.

Supporting Information (see footnote on the first page of this article): Experimental procedures, compound characterization, and analytical data (^{1}H NMR, ^{13}C NMR, MS, elemental analyses) for all new compounds.

Acknowledgments

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