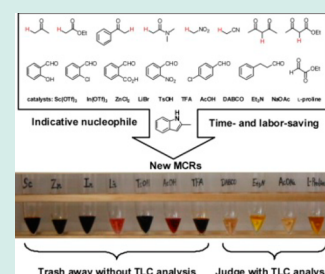


# 2-Methylindole as an Indicative Nucleophile for Developing a Three-Component Reaction of Aldehyde with Two Different Nucleophiles

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## S Supporting Information

**ABSTRACT:** 2-Methylindole was used as an indicative nucleophile for rapid screening of MCRs of aldehydes with two different nucleophiles. By removal of some samples that have characteristic color associated with the generation of di(indolyl)methane derivatives the difficulties encountered in the product analysis were alleviated significantly.



**KEYWORDS:** 2-methylindole, indicative nucleophile, three-component reaction

## INTRODUCTION

Multicomponent reactions (MCRs) not only enable the flexible assembly of three or more substrates in one-pot operation, but also generates products that contain substantial elements of all the reactants.<sup>1</sup> Electrophilic reaction of aldehydes with two different nucleophiles is known to be a common strategy for developing MCRs.<sup>2</sup> However, this strategy is often plagued by side reactions of the aldehyde with the same nucleophile. Therefore, in this area, most of the research efforts are paid to rational design of substrate and catalysts to control the reaction selectivity.<sup>3</sup> For instance, an assistance of an intramolecular cyclization or hydrogen bond has been well adopted in designing substrates.<sup>4</sup> Unfortunately, because of the intrinsic sensitivities of these MCRs to catalyst, solvent and some other parameters, exploration of this type three-component reaction is now a labor-intensive and time-consuming task for researchers. On this account, an effective method for rapid screening of substrate, catalyst and other parameters is needed.

Because many components were involved in the reaction mixture, the choke point for implementing the study of MCRs is, in the most cases, analysis of the product. An ideal method to solve this problem is to establish a convenient way to identify the formation of the target compound. However, it is not easy because in most cases the desired product is unknown and it is hard to predict its properties. As an alternative method, we can also use the generated byproduct, that is capable of indicating its formation in a practically simple way, as a probe to monitor whether side reactions occur extensively.

To establish this concept, the choice of the indicative nucleophile is the key. A suitable one should have the following properties: (i) side reaction of the indicative nucleophile with

aldehyde should be closely associated with a distinctive phenomenon that enabled us to realize its occurrence; (ii) the reactivity of the indicative nucleophile should be much higher than that of its partner nucleophile; this ensures the indicative nucleophile has the priority to react with aldehyde when the reaction conditions are inappropriate for the progress of the expected MCR; (iii) the indicative nucleophile should be representative of many other nucleophiles in terms of the reactivity and stability; thus the obtained catalytic/synthetic systems can be applied in developing other MCRs. All these things put together tend to narrow the possibility of finding a suitable indicative nucleophile. Thanks to the extensive studies on the electrophilic alkylation of aldehydes with indole,<sup>5</sup> we found one. Herein, we report for the first time the use of 2-methylindole as an indicative nucleophile for establishing the concept. The aim of this work is to show that the aforementioned difficulties associated with the analysis of reaction products can be alleviated by removing some reaction samples that have the characteristic color of the byproduct generated through electrophilic alkylation of aldehyde with 2-methylindole.

## RESULTS AND DISCUSSION

During the course of investigating the synthetic reactions of indole derivatives,<sup>6</sup> we became aware of an extraordinary color alteration in the electrophilic alkylation of aldehydes with indoles. Once the reaction is initiated, the color of the reaction

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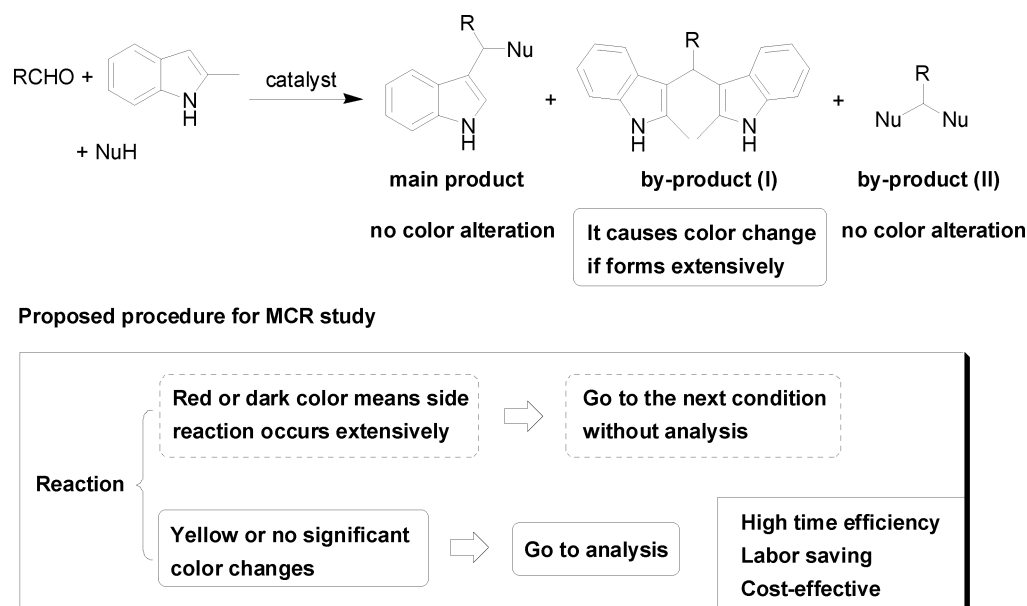


Figure 1. Schematic representation of our work.

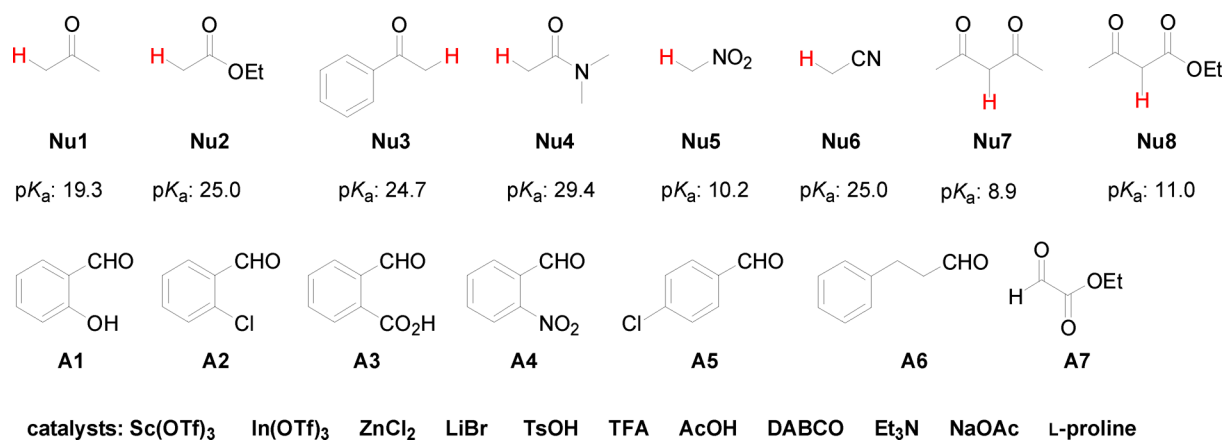


Figure 2. Libraries of the partner nucleophile, aldehyde, and catalyst.

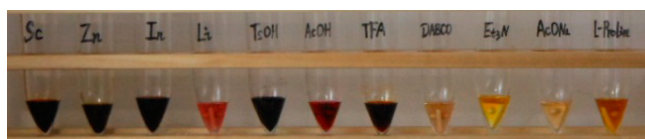
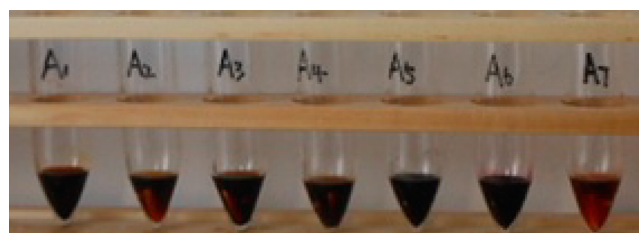


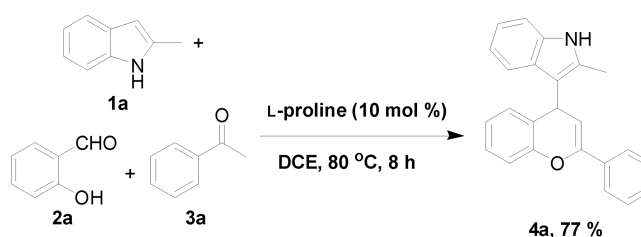
Figure 3. A photo of reaction of Nu3, A1, and 2-methylindole over different catalysts.

Figure 4. ZnCl<sub>2</sub>-catalyzed electrophilic reactions of A1 + 2-methylindole to A7 + 2-methylindole.

mixture becomes immediately red and, sometimes, even dark. Particularly, in the reaction of 2-methylindole, this behavior is acute and inevitable. Intriguingly, no significant color change was observed if a three-component reaction occurs exclusively

Figure 5. Sc(OTf)<sub>3</sub>-catalyzed reactions of Nu1 + A1 to Nu1 + A7 in the presence of 2-methylindole.

### Scheme 1. Three-Component Reaction of Nu3, A1, and 2-Methylindole



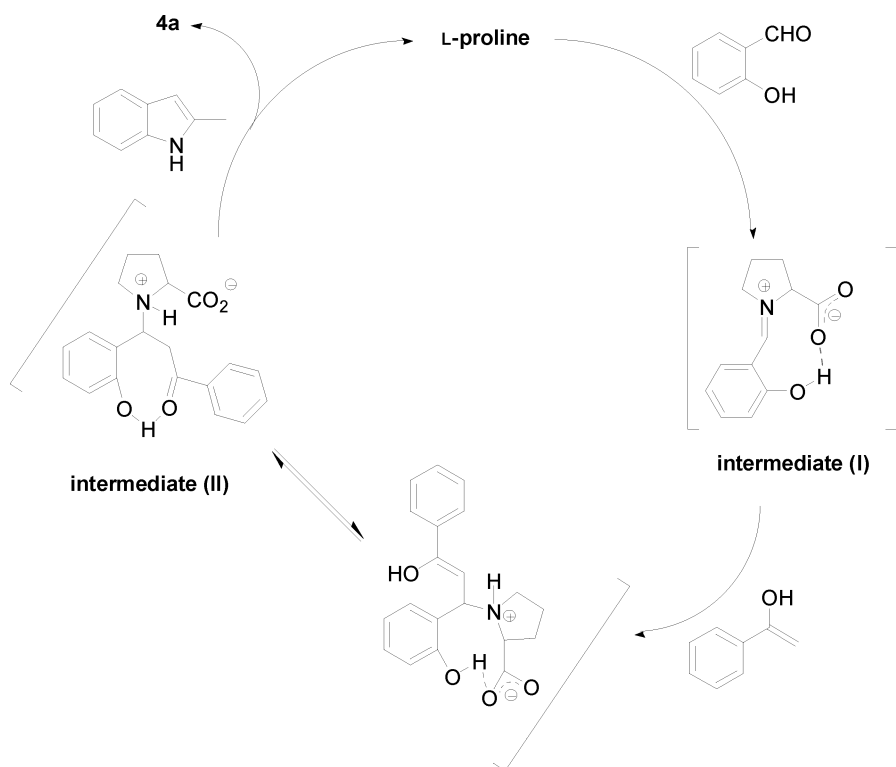


Figure 6. Proposed mechanism.

in the presence of a suitable nucleophile and an appropriate catalyst.<sup>7</sup> Similar tendencies were also observed in many other indole-participated MCRs.<sup>8</sup> This stimulated us to use it as an indicative nucleophile in this work. The  $pK_a$  value of 2-methylindole is  $-0.3$  at  $25\text{ }^\circ\text{C}$ .<sup>9</sup> To maximize the evaluation efficiency of our method, an overwhelming reactivity predominance should be arranged to be the indicative nucleophile. For this reason, some nucleophiles that have much lower reactivity toward aldehydes were selected as shown in Figure 2. To facilitate selective assembly of all these three types of substrates, first, some aldehydes that are able to assist the assembly with an intramolecular interaction were selected. A para-substituted aromatic aldehyde, an aliphatic aldehyde and ethyl glyoxalate were also involved in the library of aldehydes. It should be noted that aldehydes bearing dark colors cannot be employed here, for example 2-pyridinecarboxaldehyde and furfural. As for the catalysts, both strong and weak Lewis and Brønsted acids were all included. By the same token, some acids that can colorize the reaction solution, such as  $\text{FeCl}_3$  and  $\text{I}_2$ , were ruled out. Both organic and inorganic bases and an amphoteric catalyst, L-proline, were also involved in this library.

Initially, electrophilic alkylation of the aldehydes and 2-methylindole was examined in dichloroethane using  $\text{ZnCl}_2$  as catalyst and the results verified that the colors of the reaction mixtures changed to red or dark in all the cases (Figure 4). This implies that 2-methylindole should be able to act as an indicative nucleophile to cooperate with all the aldehydes in Figure 2. We then started to scrutinize the performance of each combination of the three components using  $\text{Sc}(\text{OTf})_3$  as a catalyst. To avoid the possible interference of over-reactions, which also resulted in dark solution, the reactions were stopped within 30 min at  $80\text{ }^\circ\text{C}$ . A significant color alteration was observed in  $\text{Sc}(\text{OTf})_3$ -catalyzed reactions of Nu1 + A1 to Nu1 + A8 in the presence of 2-methylindole. In these cases, the

combinations were considered as failure and eliminated without analysis (Figure 5). Similarly, all the nucleophile–aldehyde combinations associated with  $\text{In}(\text{OTf})_3$ ,  $\text{ZnCl}_2$ , TsOH, LiBr, TFA, and AcOH catalysts resulted in either red or dark solutions, implying the fact that all these reactions were detrimentally affected by the side reaction of aldehyde and 2-methylindole. To verify the reliability of our method, some samples were also subjected to TLC analysis, and the results were always in a good agreement with that the reaction color indicated. When basic and amphoteric catalysts were employed, the obtained solutions were generally yellow. In these cases, further analysis is needed in order to know whether the expected three-component reaction occurred. Although a tedious TLC analysis is still needed, this method removed more than 60% of the samples without TLC analysis, improving significantly the efficiency of substrate- and condition-screening. Incidentally, in many cases, the reaction solution becomes dark within only 5 min, allowing us to judge the reaction outcome more quickly. This improved further the screening efficiency.

With this method, a three-component reaction of salicylaldehyde (2a), acetophenone (3a) and 2-methylindole was successfully discovered with the aid of the L-proline catalyst (Scheme 1). A two-step method for the synthesis of 4a has been reported,<sup>10</sup> which involves (i) synthesis of 2-hydroxychalcone through condensation of 2a and 3a under basic conditions; (ii) tandem Michael addition/cyclization reaction of 2-methylindole with 2-hydroxychalcone using iodine as catalyst (the maximum yield is 69%). The MCR in Scheme 1 not only opened a straightforward route to access 4a-type 4H-chromenes, but also improved the synthesis in terms of enhancing the reaction yield and simplifying the operational procedure.

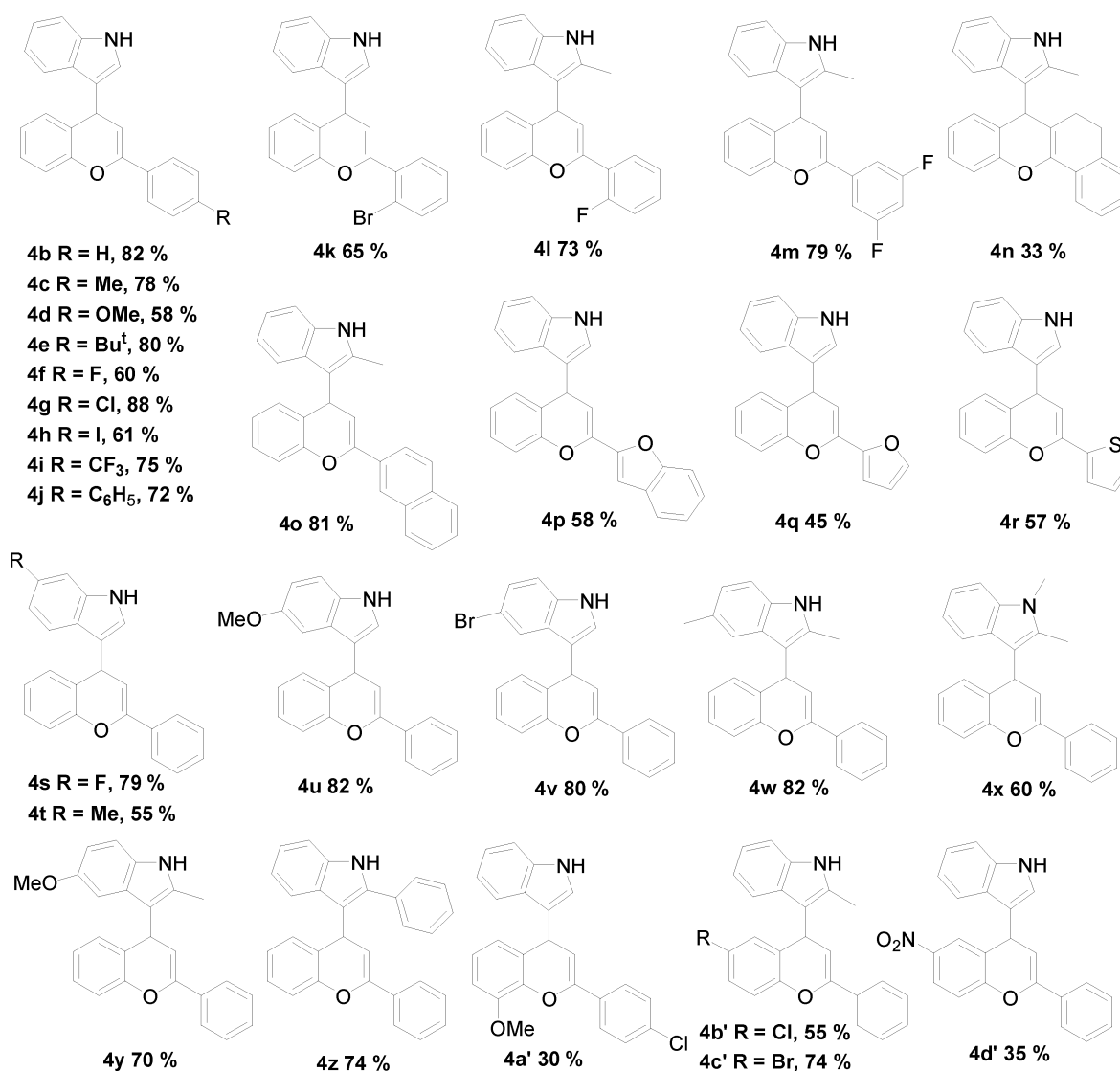
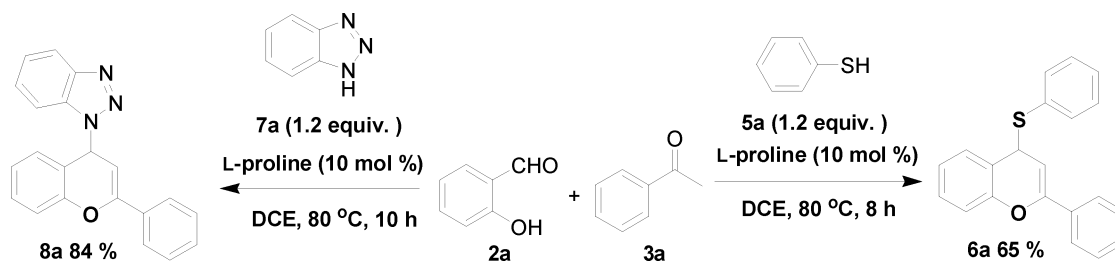


Figure 7. Substrate scope of the three-component reaction.

### Scheme 2. Utilization of L-Proline Catalyst in the Other MCRs



Initial event of the reaction might be the formation of imine (I),<sup>11</sup> which is followed by a nucleophilic attack of an enolize acetophenone with the aid of intermolecular hydrogen bond that produced a Mannich-type intermediate (II). A competition of both carboxylic and ketocarbonyl groups as a hydrogen bond acceptor allowed the proline fragment in the intermediate (II) to be a good leaving group (Figure 6).<sup>7b</sup> Finally, substitution of 2-methylindole to proline and the subsequent dehydration resulted in the formation of **4a**. Figure 7 shows substrate scope of the three-component reaction. Acetophenones with both electron-donating and electron-

withdrawing groups worked well. No significant steric effect was observed in acetophenone as both 2-fluoroacetophenone and 2-bromoacetophenone can be used uneventfully. 1-Tetralone and 2-acetonaphthone and some aryl methyl ketones with a heterocyclic fragment, such as furanyl, thienyl and benzofuranyl, also participated readily in this reaction. Substituted indoles with methyl, methoxy, fluoro, bromo and phenyl groups can all be used in this system, producing the desired products in fairly good yields. The scope of salicylaldehyde was proved to be good as well, and the

substrates possessing both electron-donating and electron-withdrawing groups participated readily in the reaction.

One of the main aims of utilizing the indicative nucleophile was to develop other new MCRs with the aid of the obtained catalytic/synthetic system. We then replaced 2-methylindole with other nucleophiles in the L-proline system. Both thiophenol and 1*H*-benzotriazole can be used as nucleophile to react with **2a** and **3a** (Scheme 2). These results not only offered an effective way for the synthesis of 4*H*-chromenes,<sup>12</sup> but also demonstrated that the use of an indicative nucleophile is indeed able to help the implementation of MCR study.

## CONCLUSIONS

A novel method for the rapid screening of MCRs was developed by using 2-methylindole as an indicative nucleophile. In electrophilic reaction of aldehydes with two different nucleophiles, this method improved the analytical efficiency by removing some samples that have red or dark color, which was ascribed to the extensive formation of “ABB” type byproduct. With this strategy, three-component reactions of salicylaldehyde, acetophenone and a carbon-, sulfur-, or nitrogen-based nucleophile were developed, opening an effective and a straightforward way for the synthesis of 4*H*-chromene derivatives.

## EXPERIMENTAL PROCEDURES

<sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR spectra were recorded on a Bruker AV-400. Chemical shifts are expressed in ppm relative to Me<sub>4</sub>Si in CDCl<sub>3</sub>. HRMS was recorded on a Bruker micrOTOF-Q II instrument. IR spectra were recorded on a FT-IR Bruker (VERTEX 70) using liquid film technology. All chemicals and reagents were purchased from standard commercial suppliers.

**Procedure of Screening Three-Component Reactions of Aldehyde, Nucleophile, and 2-Methylindole with the Aid of a Catalyst.** First, nucleophile Nu1 (3.0 mmol) was mixed with aldehyde A1 to A7 (3.0 mmol), respectively, in dichloroethane (12.0 mL). Then, 2-methylindole (6.0 mmol) was added into these seven solutions, respectively. Each of the obtained solution thereby was divided into eleven equal parts, and then subjected to evaluation with a catalyst in the library (10 mol %). The reaction was performed at 80 °C, and stopped at 30 min. Some of the reaction mixtures became red or dark within few minutes. In these cases, the mixtures were directly trashed away. TLC analysis is needed when yellow or colorless solution was obtained. The other nucleophiles, Nu2 to Nu8, were all submitted to the same procedure.

**Typical Procedure for Three-Component Reaction of Acetophenone, Salicylaldehyde, and Indole.** All reactions were conducted in a 10 mL of V-type flask equipped with triangle magnetic stirring. In a typical reaction, 1,2-dichloroethane (1.0 mL) was mixed with **1a** (98.3 mg, 0.75 mmol), **2a** (91.5 mg, 0.75 mmol), **3a** (60.0 mg, 0.5 mmol), and L-proline (5.8 mg, 10 mol %) under air. The mixture was stirred for 8 h at 80 °C. After reaction, the mixture was cooled to room temperature and the desired product **4a** was obtained by preparative TLC using a mixed solution of ethyl acetate and petroleum ether as eluting solvent (the ratio of ethyl acetate/petroleum ether is 1/8 v/v). Tests for substrate scope and the reaction of using other nucleophiles were all performed according to an analogous procedure.

## ASSOCIATED CONTENT

### Supporting Information

Spectroscopic data for the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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