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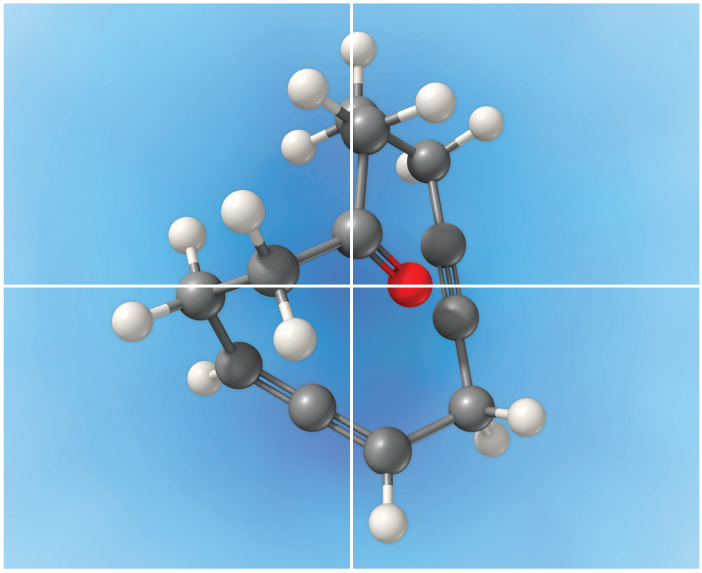

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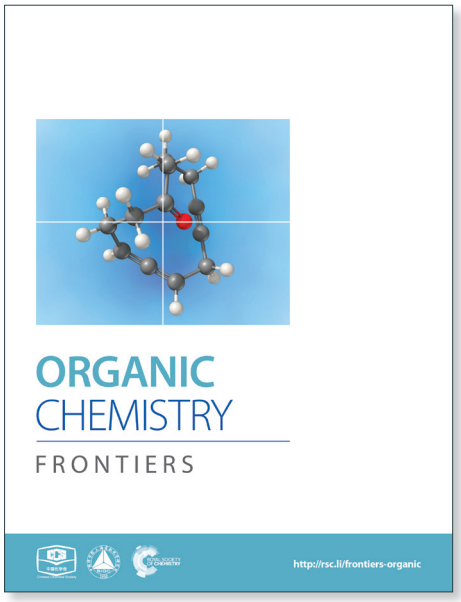


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ARTICLE

# $AlCl_3$-Catalyzed *O*-Alkylative Passerini Reaction of Isocyanides, Cinnamaldehydes and Various Aliphatic Alcohols for Accessing α-Alkoxy-β,γ-Enamides

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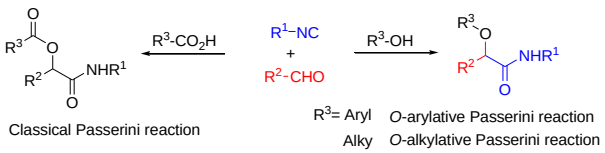
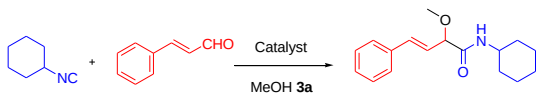
The inexpensive Lewis acid $AlCl_3$ was found to be an efficient catalyst for *O*-alkylative Passerini reaction of isocyanide, cinnamaldehyde and alcohol. Instead of carboxylic acid in classical Passerini reaction, alcohols performed both as solvent and substrate nicely to afford α-alkoxy-amide product in good yield (up to 91%). This method provide a practical accessing for functional α-alkoxy-β,γ-enamide derivatives.

The Passerini three-component reaction (P-3CR), discovered in 1921, is the known isocyanide-based multiconponent reactions to give α-acyloxy amide with isocyanide, aldehyde and carboxylic acid.[1] The Passerini three-component reaction (3CR) play important roles in combinatorial chemistry, for drug discovery as well as natural product synthesis.[2] Besides, the application of Passerini reaction in the preparation of polymers and peptides have also been reported.[3,4] Recently, several examples of enantioselective versions for Passerini reactions have been developed. [5] Although various modifications of this reaction have been already developed, the direct Passerini reaction use a phenol or an aliphatic alcohol instead of a carboxylic acid are still less developed. Only three examples using other components instead of carboxylic acid have been reported so far. In 2006, El Kaim and Grimaud reported the O-arylative Passerini-type reaction using nitrophenol derivatives, which have a more acidic proton compared to aliphatic alcohols.[6] In 2010, Soeta and Inomata used silanol instead of carboxylic acid component, giving the corresponding α-siloxyamides in moderate to good yields.[7] The only report using aliphatic alcohol was developed by Taguchi.[8] Catalyzed by $In(OTf)_3$ with $HC(OMe)_3$ as an additive, isocyanides, aldehydes and aliphatic alcohols afforded α-alkoxy amide derivatives in good yield, but there was only one example of unsubstituted cinnamaldehyde and one isocyanide were reported. Herein, we developed an inexpensive Lewis acid $AlCl_3$ catalyzed direct Passerini reaction for accessing α-alkoxy-β,γ-enamide derivatives. A large scope of commonly available alcohols, isocyanides, cinnamaldehydes are suitable substrates in this catalyst system. By this synthetic strategy, a polyfunctional molecular scafford, α-alkoxy-β,γ-enamides could be prepared in one step. α-Alkoxy-β,γ-enamides is the core part in many natural compounds, such as symbioramide, a type of bioactive ceramide with antileukemic activities and as inhibitors of the Dengue and West Nile virus proteases.[9]




**Scheme 1** Passerini reaction.

**Table 1** Optimization of the reaction conditions of *O*-Alkylative Passerini reaction of Cy-NC **1a**, cinnamaldehyde **2a** and MeOH **3a**.[a]




1a 2a 4aaa

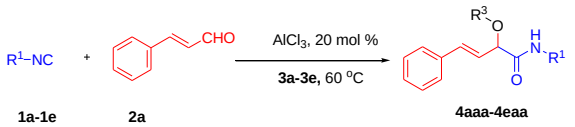
| Entry | **1a** (eq) | **2a** (eq) | Catalyst | Yield (%)[b] |
|---|---|---|---|---|
| 1 | 1 | 1.2 | None | trace |
| 2 | 1 | 1.2 | $Zn(OTf)_2$/ 0.2 | trace |
| 3 | 1 | 1.2 | AgOTf/ 0.2 | trace |
| 4 | 1 | 1.2 | $In(OTf)_3$/ 0.2 | 65 |
| 5 | 1 | 1.2 | $ZnCl_2$/ 0.2 | trace |
| 6 | 1 | 1.2 | $AlCl_3$/ 0.2 | 73 |
| 7 | 1 | 1.2 | $FeCl_3$/ 0.2 | 43 |
| 8 | 1 | 1.2 | $CuCl_2$/ 0.2 | trace |
| 9 | 1 | 1.2 | $CH_3COOH$/ 0.2 | trace |
| 10 | 1 | 1 | $AlCl_3$/ 0.2 | 76 |
| 11 | 1.2 | 1 | $AlCl_3$/ 0.2 | 79 |
| 12 | 1.5 | 1 | $AlCl_3$/ 0.2 | 85 |
| 13 | 1.8 | 1 | $AlCl_3$/ 0.2 | 80 |
| 14 | 1.5 | 1 | $AlCl_3$/0.1 | 63 |

[a] Reaction conditions: To a solution of catalyst (0.2 eq) in MeOH (1 mL) in a sealed vial were added cinnamaldehyde (0.2 mmol) and isocyanides (0.3 mmol) in sequence. The reaction mixtures were stirred at 60 °C for 12 h. [b] Isolated yield.

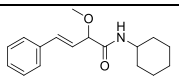
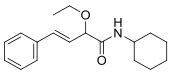
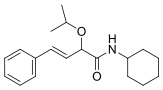
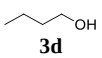
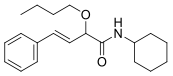
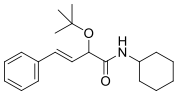
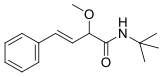
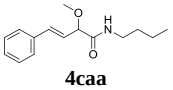
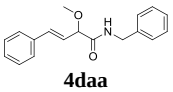
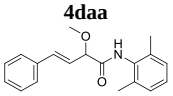
We initially started to optimize the reaction conditions using cyclohexyl isocyanide (Cy-NC) **1a** and cinnamaldehyde **2a** as the model substrates, MeOH **3a** as reagent as well as solvent. Selected results of Lewis acids are summarized in table 1. To

our delight, moderate to good yields were obtained catalyzed by several Lewis acids. Among them, $AlCl_3$ was the most efficient catalyst which gave the expected P-3CR product in 73% yield (entry 6, Table 1). The other two Lewis acid $In(OTf)_3$ and $FeCl_3$ were also effective in the reaction, while lower yields were resulted. The ratio of isocyanide **1a** and cinnamaldehyde **2a** were also investigated (entries 10-13), leaded to improvement of the yield from 73% to 85% (entry 12). 10 mol% $AlCl_3$ can make the reaction work, but relatively lower yield (63%) was obtained (entry 14).

**Table 2** *O*-Alkylative Passerini reaction of various isocyanides **1** and alcohols **3** with cinnamaldehyde **2a**.[a]



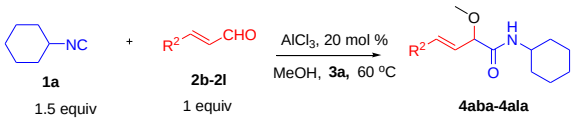

1a-1e 2a 4aaa-4eaa

| Entry | Isocyanides | Alcohols | Products | Yield (%)[d] |
|---|---|---|---|---|
| 1 |  **1a** | MeOH **3a** |  **4aaa** | 85 |
| 2 |  **1a** | EtOH **3b** |  **4aab** | 63 |
| 3 |  **1a** |  **3c** |  **4aac** | 64 |
| 4 |  **1a** |  **3d** |  **4aad** | 61 |
| 5[b] |  **1a** |  **3e** |  **4aae** | 53 |
| 6 |  **1b** | MeOH **3a** |  **4baa** | 81 |
| 7 |  **1c** | MeOH **3a** |  **4caa** | 82 |
| 8 |  **1d** | MeOH **3a** |  **4daa** | 75 |
| 9[c] |  **1e** | MeOH **3a** |  **4eaa** | 72 |

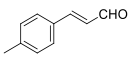
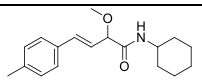
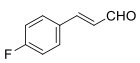
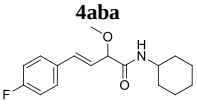
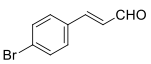
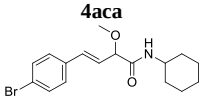
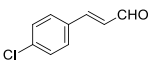
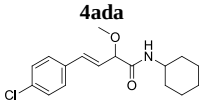
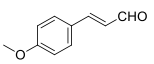
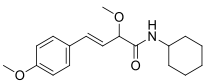
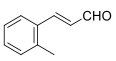
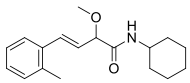
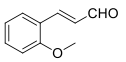
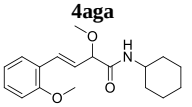
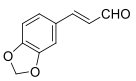
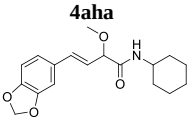
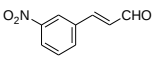
[a] To a solution of $AlCl_3$ (0.1 mmol, 0.20eq) in indicated alcohols (1 mL) in a sealed vial were added cinnamaldehyde **2a** (1mmol) and isocyanides **1** (1.5 mmol, 1.5 eq) in sequence. The reaction mixtures were stirred at 60 °C for 12h. [b] The reaction was carried out in *t*-BuOH in presence of 100 mol% $AlCl_3$, stirred at 80 °C for 36 h. [c] The reaction was carried out for 24 h. [d] Isolated yield.

With the optimized reaction conditions in hand, various α-alkoxy-β,γ-enamides were successfully synthesized via *O*-alkylative Passerini reaction of various isocyanide **1** and alcohols **3** with cinnamaldehyde **2a**. As shown in table 2, the reaction proceeded smoothly in many primary and secondary alcohols (entries 1-4). The corresponding α-alkoxy-β,γ-enamide were obtained in 61-85% yields. However, when the sterically hindered *tert*-butyl alcohol was used as substrate as well as solvent, only 53% yield was obtained even in presence of 100 mol% $AlCl_3$ stirring at 80 °C for 36 h (entry 5). The steric effect of isocyanides showed no obvious influence on the yields of products. 81% and 82% yields were obtained for *n*-butyl isocyanide and *tert*-butyl isocyanide separately (entries 6 and 7). Aromatic isocyanides **1e** also suitable substrate in this rection condition, affording corresponding product **4eaa** in 72% yield, but a longer reaction time (24h) was needed (entry 9).

**Table 3** *O*-Alkylative Passerini reaction of substituted cinnamaldehyde **2** with cyclohexyl isocyanide **1a** and methol **3a**.[a]



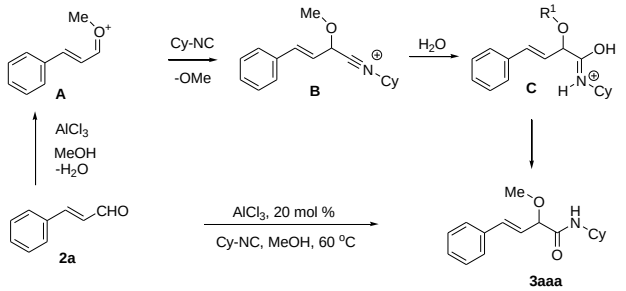

1a 2b-2l 4aba-4ala
1.5 equiv 1 equiv

| Entry | Cinnamaldehyde | Time(h) | Products | Yield (%)[d] |
|---|---|---|---|---|
| 1 |  **2b** | 12 |  **4aba** | 85 |
| 2 |  **2c** | 24 |  **4aca** | 64 |
| 3 |  **2d** | 24 |  **4ada** | 76 |
| 4 |  **2e** | 24 |  **4aea** | 73 |
| 5 |  **2f** | 12 |  **4afa** | 91 |
| 6 |  **2g** | 18 |  **4aga** | 80 |
| 7 |  **2h** | 24 |  **4aha** | 83 |
| 8 |  **2i** | 24 |  **4aia** | 75 |
| 9[b] |  **2j** | 48 |  **4aja** | 58 |
| 10[b] |  **2k** | 48 |  **4aka** | 56 |
| 11 |  **2l** | 24 |  **4ala** | 70 |

[a] To a solution of $AlCl_3$ (0.1 mmol, 0.20eq) in indicated alcohols (1 mL) in a sealed vial were added cinnamaldehyde **2a** (1mmol) and isocyanides **1** (1.5 mmol, 1.5 eq) in sequence. The reaction mixtures were stirred at 60 °C for indicated time. [b] 50 mol% $AlCl_3$ was added in two portion [c] Isolated yield.

To further investigate the substrate scope, a series of substituted cinnamaldehydes **2b-2l** were investigated as shown in Table 3. The results indicated that electronic effect of cinnamaldehyde **2** make a serious influence on this reaction. Cinnamaldehydes with electronic donating group provided the formation of α-alkoxy-β,γ-enamides in good yields (entries 1,5-8). Under the same optimized condition, substrates with weak electronic withdrawing group (F, Cl, Br) were also performed nicely to give corresponding products in moderate yields (entries 2-4). The reactions of cinnamaldehydes with strong electronic withdrawing group ($NO_2$, CN) were sluggish in this catalyst system. After further optimization, the desired products **4aja** and **4aka** were obtained in moderate yields when 50 mol% $AlCl_3$ was added in two portion (entries 9 and 10). In addition, 2-hydroxy-cinnamaldehyde with no protection at hydroxy group was also suitable for the reaction, indicating good substrate toleration for this synthetic methodology (entry 11). The influence of steric effect was also investigated. We found that *orth*-substitutes in phenyl ring showed no significant effects on the yields of products due to the distance from functional group of aldehyde. Therefore, it was not surprising that 2-methylcinnamaldehyde **2g** and 2-methoxycinnamaldehyde **2h** with electron-donating group but steric hindrance could still give the desired product **4aga** and **4aha** in 80% and 83% yield separately (entries 6-7).

On the basis of the result, a mechanism for the Lewis acid-catalyzed formation of α-alkoxy-β,γ-enamide derivatives via direct *O*-Alkylative Passerini reaction was shown in Scheme 2. In the presence of Lewis acid $AlCl_3$, cinnamaldehyde reacts with alcohol to generate oxocarbenium species **A**, which was isolated as shown in table 3 (entry 9 and 10) and lost a $H_2O$. Subsequently, **A** is attacked by isocyanide to give nitrilium intermediate **B**. Then, the hydrolysis of the intermediate **B** result the formation of **C** which is easy to isomerize to give α-alkoxy-β,γ-enamide **2**.




**Scheme 2** Proposed mechanism of the $AlCl_3$-catalyzed *O*-Alkylative Passerini reaction for accessing α-alkoxy-β,γ-enamides.

## Conclusions

In summary, we developed an efficient and practical *O*-alkylative Passerini reaction of isocyanides, cinnamaldehydes and alcohols catalyzed by inexpensive Lewis acid $AlCl_3$. This method offers a direct synthesis of α-alkoxy-β,γ-enamide derivatives in one step. A large scope of isocyanides, cinnamaldehydes and alcohols were suitable substrates in this catalyst system to afford the α-alkoxy-β,γ-enamide derivatives up to 91% yields. Further investigations on asymmetric synthesis methodology of α-alkoxy-β,γ-enamide derivatives and their biological activities evaluation are ongoing in our laboratory.

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## Notes and references

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