JOC Note

Direct Alkylative Passerini Reaction of Aldehydes, Isocyanides, and Free Aliphatic Alcohols Catalyzed by Indium(III) Triflate

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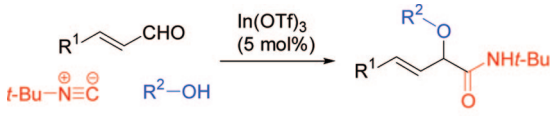

Direct use of free aliphatic alcohols

$In(OTf)_3$ was found to be a useful Lewis acid catalyst for direct alkylative Passerini reaction of aldehydes, isocyanides, and free aliphatic alcohols. In the present reaction, aromatic and α,β-unsaturated aldehydes performed as nice substrates to give the corresponding α-alkoxy amide products in good yield.

The Passerini three-component (P3C) reaction, which was discovered in 1921, is one of the most important multicomponent reactions.[1] This reaction is three-component condensation of aldehydes, isocyanides, and carboxylic acids to give α-acyloxy amides in one step. Various modifications of this reaction have already been developed,[2,3] while the use of phenol or aliphatic alcohol derivatives instead of a carboxylic acid component has not been realized until recently. In 2006, El Kaim and Grimaud reported the *O*-arylative Passerini-type reaction using nitrophenol derivatives,[4] which have a more acidic proton compared to aliphatic alcohols. On the other hand, Chatani and co-workers reported that the reaction of benzaldehyde, isocyanide, and silyl-protected aliphatic alcohol can be catalyzed by triflic acid to give α-alkoxy amide in moderate yield.[5] However, direct P3C-type reaction of aldehydes, isocyanides, and free aliphatic alcohols has not been achieved.

As one of our ongoing research projects, we have been exploring synthetic reactions catalyzed by indium(III) complexes such as indium halides and indium(III) triflate [$In(OTf)_3$].[6] Since In(III) complexes are known as mild, soft, and chemically stable Lewis acids,[7] we were interested in the application of In(III) Lewis acids to the Passerini-type reaction in protic media.[8,9] That is, In(III)-catalyzed formation of an oxocarbenium intermediate from carbonyl substrates in alcohol solvents followed by nucleophilic addition of isocyanides to the resultant oxocarbenium species should provide the direct procedure for *O*-alkylative P3C reaction using free alcohols.[10] In this paper, we disclose the first example for alkylative Passerini reaction of aldehydes, isocyanides, and free aliphatic alcohols.

To explore the effective Lewis acids for direct *O*-alkylative P3C reaction, we examined the reaction of benzaldehyde and *tert*-butyl isocyanide in 2-propanol in the presence of various Lewis acids. Selected results are summarized in Table 1. In the presence of 20 mol % of $In(OTf)_3$, the reaction of benzaldehyde **1a** with 1.0 molar equiv of *tert*-butyl isocyanide in 2-propanol at 80 °C for 24 h gave alkylative Passerini product **2a** in 38% yield along with the formation of a trace amount of nonalkylated adduct **3a** (entry 1). The increase in *tert*-butyl isocyanide to 2.0 molar equiv improved the product yield to 50% (entry 2). Moreover, we found that stepwise addition of $In(OTf)_3$ and *tert*-butyl isocyanide dramatically increases the product yield. For example, in the presence of 10 mol % of $In(OTf)_3$, benzaldehyde **1a** was reacted with 1.0 molar equiv of *tert*-butyl isocyanide at 80 °C for 12 h, then further treatment by additional both 10 mol % of $In(OTf)_3$ and 1.0 molar equiv of *tert*-butylisocyanide at the same temperature for 12 h gave **2a** and **3a** in 76 and 7% yield, respectively (entry 3). Employing this stepwise addition procedure, we examined the efficiency of other Lewis acids. The catalytic activity of other In(III) complexes, such as $InCl_3$, InF_3, and $InBr_3$, was significantly lower than that of $In(OTf)_3$ (entry 5). $FeCl_3$ and $Sc(OTf)_3$ were ineffective for the present reaction. $Bi(OTf)_3$ and certain lanthanoid(III) triflates, such as

(1) (a) Passerini, M. *Gazz. Chem. Ital.* **1921**, *51*, 126–181. (b) Ugi, I.; Lohberger, S.; Karl, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1083. (c) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (d) Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1–140. (e) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89.

(2) For recent examples for enantioselective Passerini-type reaction, see: (a) Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 388–391. (b) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7824–7825. (c) Denmark, S. E.; Fan, Y. *J. Org. Chem.* **2005**, *70*, 9667–9676. (d) Kusebauch, U.; Beck, B.; Messer, K.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2003**, *5*, 4021–4024. (e) Andreana, P. R.; Liu, C. C.; Schreiber, S. L. *Org. Lett.* **2004**, *6*, 4231–4233.

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(4) (a) El Kaim, L.; Gizolme, M.; Grimaud, L. *Org. Lett.* **2006**, *8*, 5021–5023. (b) El Kaim, L.; Gizolme, M.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, *72*, 4169–4180.

(5) (a) Tobisu, M.; Kitajima, A.; Yoshioka, S.; Hyodo, I.; Oshita, M.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 11431–11437. (b) Yoshioka, S.; Oshita, M.; Tobisu, M.; Chatani, N. *Org. Lett.* **2005**, *7*, 3697–3699.

(6) (a) Yanai, H.; Obara, S.; Taguchi, T. *Org. Biomol. Chem.* **2008**, *6*, 2679–2685. (b) Yanai, H.; Saito, A.; Taguchi, T. *Tetrahedron* **2005**, *61*, 7087–7093. (c) Yanai, H.; Taguchi, T. *Tetrahedron Lett.* **2005**, *46*, 8639–8643.

(7) (a) Chua, G.-L.; Loh, T.-P. In(III) Lewis Acids. In *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H., Ishihara, K., Eds.; Wiley-VCH: Weinheim, Germany, 2008; Vol. 1, pp 377−467. (b) Auge, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739–1764.

(8) For metal-triflate-catalyzed Passerini-type reactions, see: (a) Xia, Q.; Ganem, B. *Org. Lett.* **2002**, *4*, 1631–1634. (b) Wang, S.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Eur. J. Org. Chem.* **2007**, 4076–4080.

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(10) It is known that reaction of acetals and isocyanides in the presence of acid catalysts gives α-alkoxy amides. See: (a) Mukaiyama, T.; Watanabe, K.; Shiono, M. *Chem. Lett.* **1974**, 1457–1458. (b) Barrett, A. G. M.; Barton, D. H. R.; Falck, J. R.; Papaioannou, D.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 652–661.

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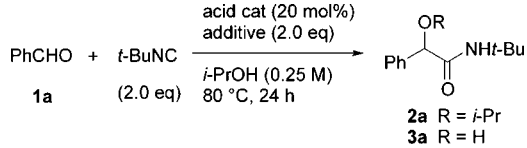
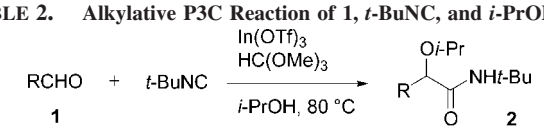
TABLE 1. Alkylative P3C Reaction of 1a, *t*-BuNC, and *i*-PrOH



			yield[a] (%)	
entry	acid cat	additive	**2a**	**3a**
1[b]	$In(OTf)_3$	none	38	trace
2	$In(OTf)_3$	none	50	trace
3[c]	$In(OTf)_3$	none	76	7
4[c]	$In(OTf)_3$	$HC(OMe)_3$	80	0
5[c]	$InCl_3$	none	28	2
6[c]	$Bi(OTf)_3$	none	59	7
7[c]	$FeCl_3$	none	15	trace
8[c]	$Sc(OTf)_3$	none	6	0
9[c]	$Y(OTf)_3$	none	61	6
10[c]	$Gd(OTf)_3$	none	64	11
11[c]	$Yb(OTf)_3$	none	59	8
12[c]	TFA	none	3	8

[a] Isolated yield. [b] One molar equiv of *t*-BuNC was used. [c] Acid catalyst, *t*-BuNC, and additive were added twice. See text.

TABLE 2. Alkylative P3C Reaction of 1, *t*-BuNC, and *i*-PrOH



entry	**1**	R	method[a]	time (h)	**2**	yield[b] (%)
1	**1b**	4-BrC_6H_4	A	24	**2b**	82
2	**1c**	4-ClC_6H_4	A	24	**2c**	83
3	**1d**	4-MeC_6H_4	A	24	**2d**	73
4	**1e**	4-$MeOC_6H_4$	A	24	**2e**	71
5	**1f**	2-naphthyl	A	24	**2f**	77
6	**1g**	2-furyl	B	5	**2g**	76
7	**1h**	PhCH=CH	B	5	**2h**	82
8	**1i**	MeCH=CH	B	5	**2i**	75

[a] Method A: 20 mol % of $In(OTf)_3$, 3.0 molar equiv of $HC(OMe)_3$, and 4.0 molar equiv of *t*-BuNC were added twice. Method B: 5 mol % of $In(OTf)_3$, 1.5 molar equiv of $HC(OMe)_3$, and 2.0 molar equiv of *t*-BuNC were added twice. [b] Isolated yield.

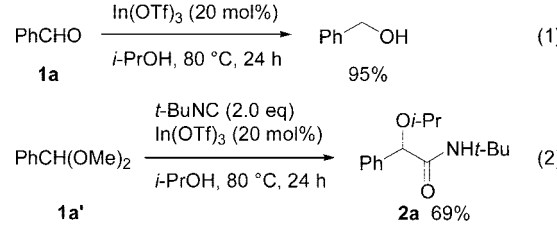
$Y(OTf)_3$, $Gd(OTf)_3$, and $Yb(OTf)_3$, were less effective due to slow formation of **2a** (entries 6−11). In addition, the use of trifluoroacetic acid (TFA) as a Brønsted acid was not effective to obtain **2a** in good yield (entry 12). We also found that the use of trimethyl orthoformate as an additive is effective to avoid the formation of α-hydroxy side product **3a** (entry 4).

Next, we examined the reaction with various aldehydes (Table 2). In the reaction of 4-substituted benzaldehyde derivatives under the optimized conditions (method A), electronic effect of the substituent on the product yield was found to be small to give the corresponding α-isopropoxy amides **2b**−**2e** in good yield (entries 1−4). Although, in the absence of trimethyl orthoformate, 2-naphtharenecarbaldehyde **1f** gave the product **2f** in low yield (36%) due to the rapid generation of 2-naphthylmethanol (33%), the addition of orthoester inhibited this reduction as a side reaction to result in clean formation of **2f** (entry 5, 77% yield). Interestingly, the reactivity of furfural **1g** and α,*β*-unsaturated aldehydes **1h**−**1i** was higher than that of benzaldehyde derivatives. For examples, the reaction of cinnamaldehyde, *tert*-butyl isocyanide, and 2-propanol in the presence of 1.5 molar equiv of trimethyl orthoformate was nicely catalyzed by only 5 mol % of $In(OTf)_3$ to give alkylative Passerini product **2h** in 82% yield (entry 7). In this case, the formation of the 1,4-adduct was not observed and short reaction time (within 5 h) was also realized (method B). Under the same conditions, furfural and crotonaldehyde gave the corresponding α-isopropoxy amides **2g** and **2i** in 76 and 75% yield, respectively (entries 6 and 8).[11]

Unfortunately, with aliphatic aldehydes, the yield of *O*-alkylated products was not so good. For example, according to method A, we conducted the reaction of cyclohexanecarbaldehyde **1j** with *tert*-butyl isocyanide in 2-propanol, and the desired product **2j** was obtained only in 47% yield due to the competitive formation of nonalkylated α-hydroxy amide **3j** in 14% yield (Scheme 1). To solve this problem, we planned an alkylative P3C reaction of α,*β*-unsaturated carbonyls followed by hydrogenation. In the presence of 5 mol % of $In(OTf)_3$, the reaction of **1k**, *tert*-butyl isocyanide (2.0 molar equiv), and trimethyl orthoformate (1.5 molar equiv) in 2-propanol gave the corresponding α-isopropoxy amide **2k** in 72% yield without formation of α-hydroxy side product. Following hydrogenation of this alkylative Passerini product using H_2 and palladium on carbon in MeOH gave **2j** in 98% yield.

As shown in Scheme 2, this reaction also proceeded in secondary or primary alcohol in place of 2-propanol. For example, according to method B, the reaction of cinnamaldehyde **1h** in cyclopentanol gave α-cyclopentyloxy-*β*,*γ*-enamide **2m** in 72% yield. Under the same conditions, the reaction in cyclohexanol gave **2n** in 68% yield. While, in general, the reactivity of primary alcohol such as 2-methylpropan-1-ol was lower than that of several secondary alcohols, **2o** was obtained in moderate yield without the formation of α-hydroxy product when the reaction was carried out under method A conditions.

Concerning these results, we conducted some controlled studies to reveal the reaction pathway of the present reaction. In the absence of *tert*-butyl isocyanide, the reaction of benzaldehyde **1a** in 2-propanol in the presence of 20 mol % of $In(OTf)_3$ gave benzyl alcohol in 95% yield, which was possibly generated by $In(OTf)_3$-catalyzed Meerwein−Ponndorf−Verley (MPV) reduction through the simultaneous coordination of both carbonyl oxygen of benzaldehyde and hydroxy oxygen of 2-propanol to the In(III) center (eq 1).[12] This finding indicated that further addition of isocyanide completely retards the MPV reduction, possibly via coordination of isocyanide to In complex.[13] Furthermore, the reaction of benzaldehyde dimethyl acetal **1a′** with *tert*-butyl isocyanide in the presence of $In(OTf)_3$ in 2-propanol provided the clean formation of α-isopropoxy amide **2a** in 69% yield (eq 2).



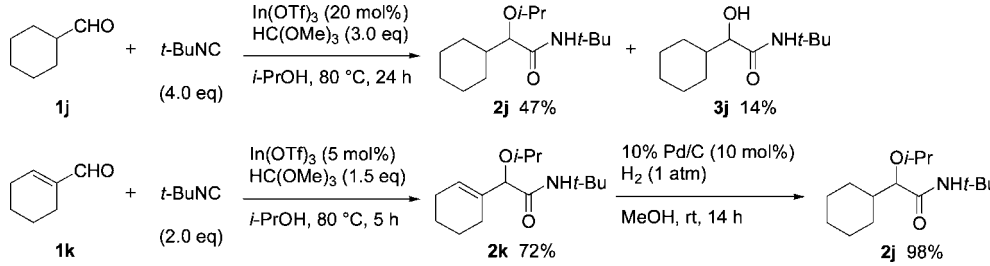
On the basis of these results, we propose the reaction pathway of the alkylative Passerini reaction as shown in Scheme 3.[14] That is, in the presence of $In(OTf)_3$, formation of oxocarbenium

(11) When the reaction of furfural **1g** was carried out under method A conditions, **2g** was obtained in 83% yield,

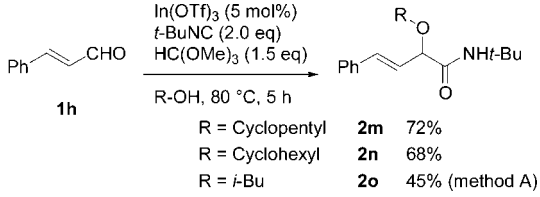
(12) To the best of our knowledge, this is the first example of MPV reduction catalyzed by In(III) Lewis acid.

(13) Bertani, R.; Crociani, L.; D'Arcangelo, G.; Rossetto, G.; Traldi, P.; Zanella, P. *J. Organomet. Chem.* **2001**, *626*, 11–15.

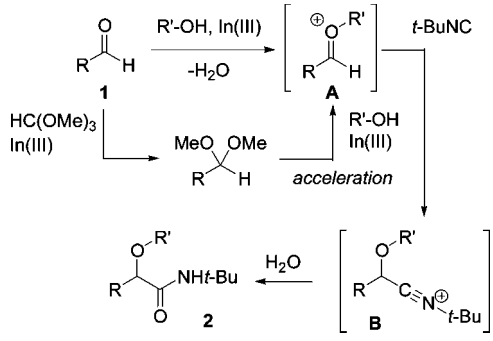
SCHEME 1. Direct and Stepwise Syntheses of 2j



SCHEME 2. Alkylative P3C Reaction in Various Alcohols



SCHEME 3. Proposed Reaction Pathway of the Present Reaction



species **A** by the reaction of aldehydes with alcohols initially occurs. The addition of orthoester possibly accelerates the formation of **A**. The nucleophilic attack of *tert*-butyl isocyanide to oxocarbenium species **A** and the following hydrolysis of the resultant nitrilium intermediate **B** by H_2O, which is generated in the oxocarbenium formation step, provide the alkylative Passerini products **2**. This mechanism would also be supported by the fact that benzaldehyde dimethyl acetal **1a′** in 2-propanol gave isopropylated Passerini product **2a**. Furthermore, in all examples shown here, the absence of some side products, such as enamines,[15] diimides,[5a] or α-alkoxy esters,[5b] which are potentially expected products by the addition of the second isocyanide to **B** or by alcoholysis of **B**, indicated that hydrolysis of nitrilium intermediate **B** is faster than the addition of sterically hindered isocyanide or alcohols.

In summary, we developed the direct alkylative P3C reaction of aldehydes, isocyanides, and free aliphatic alcohols. This is the first example of the Passerini-type reaction using free aliphatic alcohols instead of a carboxylic acid component. The present reaction is a highly useful method to construct the chemical library of α-alkoxy amide derivatives. Further studies on this reaction are in progress in our laboratory.

Experimental Section

General Procedure for Method A. To a solution of $In(OTf)_3$ (0.05 mmol, 10 mol %) in 2-propanol (2.0 mL) were added aromatic aldehyde (0.50 mmol), *t*-BuNC (1.0 mmol, 2.0 equiv), and $HC(OMe)_3$ (0.75 mmol, 1.5 equiv). After being stirred at 80 °C for 12 h, the reaction mixture was treated by additional $In(OTf)_3$ (0.05 mmol, 10 mol %), *t*-BuNC (1.0 mmol, 2.0 equiv), and $HC(OMe)_3$ (0.75 mmol, 1.5 equiv) at 80 °C for 12 h. The resultant mixture was concentrated under reduced pressure and purified by column chromatography on silica gel.

General Procedure for Method B. To a solution of $In(OTf)_3$ (12.5 μmol, 2.5 mol %) in 2-propanol (2.0 mL) were added α,β-unsaturated aldehyde (0.50 mmol), *t*-BuNC (0.5 mmol, 1.0 equiv), and $HC(OMe)_3$ (0.325 mmol, 0.75 equiv). After being stirred at 80 °C for 2.5 h, the reaction mixture was treated by additional $In(OTf)_3$ (2.5 μmol, 2.5 mol %), *t*-BuNC (0.5 mmol, 1.0 equiv), and $HC(OMe)_3$ (0.325 mmol, 0.75 equiv) at 80 °C for 2.5 h. After extractive workup and evaporation, the resultant residue was purified by column chromatography.

Supporting Information Available: Detailed experimental procedure, compound characterization data, ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The treatment of α-hydroxy amide **3a** by a catalytic amount of $In(OTf)_3$ in 2-propanol resulted in no reaction. This finding supports that the formation of **2a** does not proceed via $In(OTf)_3$-catalyzed nucleophilic substitution of hydroxy group of **3a** by 2-propanol. (a) Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1414–1416. (b) Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793–796.

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