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Indium(III) Chloride Promoted Highly Efficient Tandem Rearrangement–α-Addition Strategy towards the Synthesis of α-Hydroxyamides

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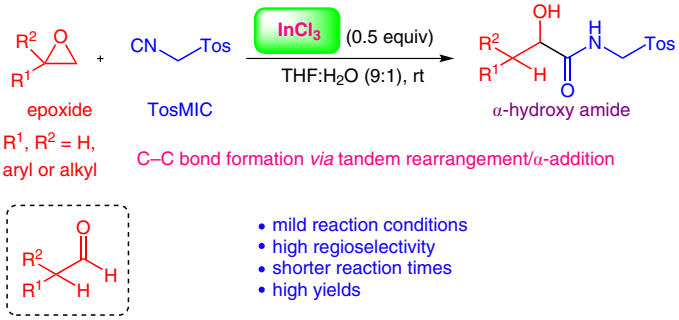

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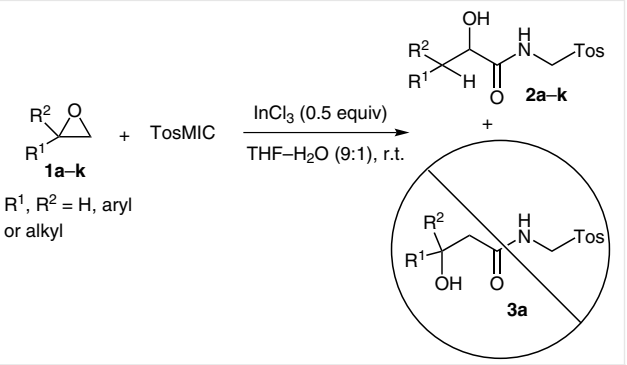
Abstract A new tandem process is reported that provides access to α-hydroxyamides from epoxides for the first time. Herein, we explore $InCl_3$-mediated tandem rearrangement of epoxides to aldehydes and α-addition of TosMIC to in situ derived aldehydes. An unprecedented C–C bond-forming reaction is disclosed that features mild conditions, high yields, and shorter reaction times.

Key words C–C bond formation, indium(III) chloride, epoxides, TosMIC, tandem rearrangement, α-addition

The α-hydroxyamides are useful building blocks for the synthesis of biologically active natural products,[1] especially depsipeptide compounds.[2] They have been identified as inhibitors of methionine aminopeptidase-2 and HIV protease, potent antitumor activity, and play an important role in medicinal chemistry.[3] Due to the significance of this core, the convenient formation of this moiety has attracted much attention in recent years. Classically, α-hydroxyamides have been synthesized by condensation of lactic acid with an amine and the most direct method is the Passerini-type reaction.[4–6] Since the early studies by Passerini,[7] Ugi, and coworkers[8] the power of α-addition reaction in constructing polyfunctional molecules has been well appreciated. The Passerini-type reaction, that is, reaction of aldehydes with isocyanides under acid-free conditions attracts chemists for wider applications. Although the Lewis acid mediated α-addition of isocyanides to aldehydes has been well studied,[9] most of these methods suffer from formation of undesired products and moreover, catalyst turnover for conventional Lewis acid catalysis requires the cleavage of the Lewis acid from the product.[10] Later on, dramatic improvement has been reported in the enantioselective α-addition of isocyanides to aldehydes.[11]

Bearing a formally divalent carbon, isocyanides are capable of engaging in carbon–carbon bond-forming reactions known as α-additions. *p*-Toluenesulfonylmethyl isocyanide (TosMIC), a unique isocyanide is widely used in the synthesis of heterocycles.[12] It is a densely functionalized building block with three functional groups that can engage in a multitude of reactions. In the course of our research aimed at expanding the TosMIC chemistry,[13,14] we attempted $InCl_3$-mediated nucleophilic ring-opening of epoxides with TosMIC. However, our results revealed the addition of TosMIC to epoxide does not form the expected product **3a** but affords instead the α-hydroxyamides **2a**–**k** through unprecedented tandem rearrangement of epoxides to aldehydes and subsequent α-addition of TosMIC to aldehydes (Scheme 1). To the best of our knowledge, this is the first example of synthesis of α-hydroxyamides directly from epoxides. Moreover, a full investigation on the literature reveals that TosMIC has not been used as an isonitrile component in most of the α-additions of isocyanides to aldehydes reported thus far. A few reported formation of byproducts along with the desired product when TosMIC was employed as a nucleophile in this reaction.[11b]

First, we examined the reaction of the styrene oxide (**1a**) with TosMIC using various Lewis acids (Table 1). Neither $BF_3{\cdot}OEt_2$ nor CuI gave the product (Table 1, entries 1 and 6). But the other Lewis acids like $Zn(OTf)_2$, $FeCl_3$, $Cu(OTf)_2$, and $RuCl_3$ gave lower yields (Table 1, entries 2, 4, 5, and 7). $InCl_3$ was found to be effective to furnish the product **2a** in less reaction time and high yield. It was also found that THF–H_2O (9:1) was the optimal solvent for this reaction. To determine the optimal catalyst loading the reaction using styrene oxide with TosMIC was conducted with varying amounts of $InCl_3$ (Table 2). A maximum yield of 90% was obtained with 50 mol% of catalyst (Table 2, entry 4). Increase in catalyst loading to 100 mol% did not have any



Scheme 1 $InCl_3$-mediated synthesis of α-hydroxyamides from epoxides

significant effect on the yield of the product (Table 2, entry 5). Particularly noteworthy was the dependence of reaction outcome on addition of water which facilitates easy hydrolysis. The reaction provided the α-substituted alcohol product **2a** instead of the expected β-substituted alcohol product **3a**, that is, the nucleophilic oxirane ring opening with isonitrile functionality of TosMIC. Although the nucleophilic ring opening of the epoxide is well established, the α-substituted alcohol synthesis remains typically limited.[15]

Table 1 Optimization of Reaction Conditions[a]

Entry	Catalyst	Solvent	Time (min)	Yield (%)[b]
1	$BF_3{\cdot}OEt_2$	THF	60	0
2	$Zn(OTf)_2$	THF	30	56
3	$InCl_3$	THF	30	80
4	$FeCl_3$	THF	60	50
5	$Cu(OTf)_2$	THF	20	55
6	CuI	THF	60	0
7	$RuCl_3$	THF	25	55
8	$InCl_3$	MeCN	30	75
9	$InCl_3$	THF–H_2O	30	90[c]
10	$InCl_3$	CH_2Cl_2	30	75

[a] Reaction conditions: epoxide (1.0 equiv), TosMIC (1.0 equiv), Lewis acid (0.5 equiv), and solvent.
[b] The yields refer to isolated products purified by column chromatography.
[c] The best yield was obtained in THF–H_2O (9:1).

The spectral analysis revealed **2a** as the predominant product. Thus, the ^1H NMR spectrum of product **2a** shows characteristic N–H as a broad singlet at δ = 7.55 ppm, methylene protons at δ = 4.65 ppm as a doublet (*J* = 6.97 Hz), CH–OH at δ = 4.21 ppm, two C–H protons as doublet of doublets at δ = 3.04 and 2.62 ppm, and all other protons resonated at their appropriate values. The possible formation of **3a** was discounted in view of the ^1H NMR analysis of

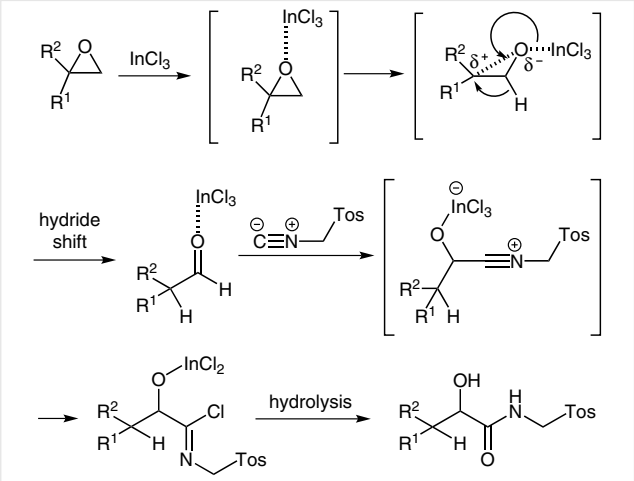
Table 2 Optimization of Catalyst Loading for the Synthesis of α-Hydroxyamides

Entry	$InCl_3$	Time (min)	Yield (%)[a]
1	0	60	–
2	10	60	71
3	30	60	82
4	50	30	90
5	100	30	90

[a] Yields refer to pure isolated products.

2a wherein CH–OH proton appeared at δ = 4.21 ppm. The same proton which otherwise would have appeared downfield shifted in **3a** than reported herein. Further, the formation of **2a** was unambiguously demonstrated by ^{13}C NMR analysis, and the IR spectrum revealed characteristic stretching frequencies at 3319 and 1675 cm^{-1} due to N–H and C=O functional groups. Observation of α-substituted alcohols in these reactions can be explained by tandem rearrangement of epoxide to aldehyde[16] followed by α-addition of TosMIC to aldehyde. While the rearrangement and α-additions are known separately, a simple method capable of effecting both elementary steps has not been identified. Indeed, the significance of this novel protocol is that it performs both operations in a single pot to afford α-hydroxyamides from easily accessed epoxides and TosMIC. To our delight, the test reaction between benzaldehyde **4** and TosMIC furnished the corresponding α-hydroxyamide **4a** in high yield, which itself has the ability to open a new era of $InCl_3$-mediated Passerini-type reaction under mild conditions. In Scheme 2, a plausible mechanism for $InCl_3$-mediated facile synthesis of α-hydroxyamides is outlined. Even though, the Lewis acid mediated rearrangement of epoxide to aldehyde is already known in the literature, in order to find the aldehyde formation, two parallel reactions of styrene oxide with and without addition of TosMIC were performed under standard conditions.[17a] Identification of aldehyde was done by comparing both the reaction sets, the reaction mixture without TosMIC showed the corresponding aldehyde,[17b] which was also seen in the reaction mixture wherein TosMIC was present which was further consumed (analysis by TLC) to give the α-hydroxyamide product. Moreover, the ^1H NMR analysis of the crude reaction mixture showed a triplet at δ = 9.73 ppm (*J* = 2.32 Hz) indicating the aldehyde formation as an intermediate (see Supporting Information).

Encouraged by these results, we next turned our attention to investigate the scope of the reaction. Generally, various epoxides (Table 3, entries **1a**–**k**) containing different substituents underwent the reaction under the standard conditions to give the corresponding α-hydroxyamides (**2a**–**k**) as the sole products. It indicates $InCl_3$-mediated isomerization of epoxides proceeded with complete regio-



Scheme 2 A plausible reaction pathway

selectivity. $InCl_3$ is a mild Lewis acid for complete regioselective transformation and has a great functional-group tolerance.

1-Aryl-, 1,1-diaryl-, 1,1-dialkyl-, and aryl-substituted epoxides underwent rearrangement to the corresponding aryl-substituted acetaldehydes by exclusive hydride shift (Table 3, entries 1 and 4–12). On the other hand, as observed in the rearrangement of stilbene oxide, that is, 1,2-diaryl epoxide, phenyl migration predominates the hydrogen shift (Table 3, entry 3). The formation of **2f** (Table 3, entry 7) can be explained by the rearrangement of α-pinene oxide to the expected aldehyde.[18] However, the reaction with **1l**, which is a nonaromatic epoxide has proven unsuccessful (Table 3, entry 13). Presumably, the incipient carbocation formed by the initial cleavage of epoxide is much less stabilized in alkyl-substituted epoxide compared to the aryl-substituted one. But in case of **2f** and **2k** the product formation can be explained by better stabilization of carbocation on the tertiary center. These reactions are usually fast and high-yielding. The spectral data of products **2b**–**k** further established the conclusive formation of the α-substituted alcohol product. However, the present protocol did not furnish the desired product when *tert*-butyl isonitrile and cyclohexyl isonitrile were used as isonitrile components. The reason for this may be attributed to the higher nucleophilicity of these compounds compared to TosMIC.[19]

Table 3 $InCl_3$-Promoted Synthesis of α-Hydroxyamides from Epoxides[a]

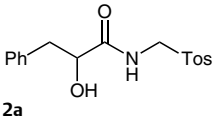
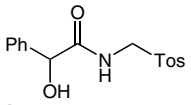
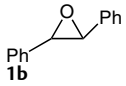
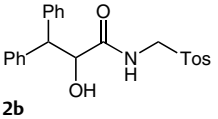
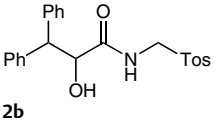
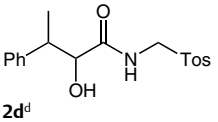
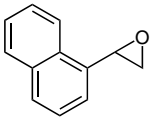
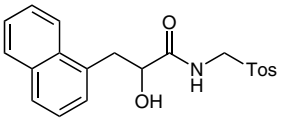
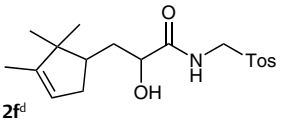
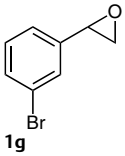
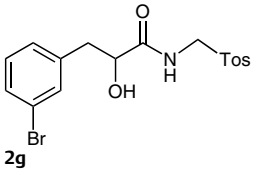
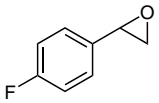
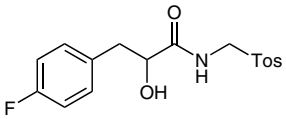
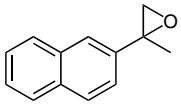
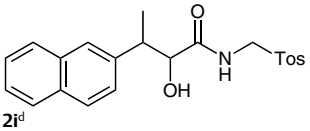
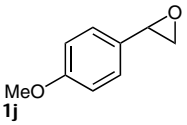
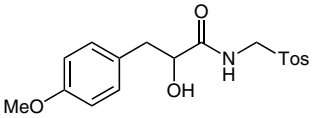
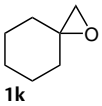
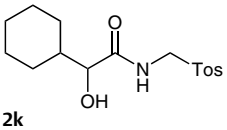
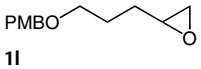
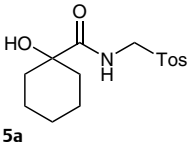
Entry	Substrate	Product[b]	Time (min)	Yield (%)[c]
1	 **1a**	 **2a**	30	90
2	Ph—CHO **4**	 **4a**	30	90
3	 **1b**	 **2b**	40	92
4	 **1c**	 **2b**	30	94
5	 **1d**	 **2d**[d]	30	92

Table 3 (continued)

Entry	Substrate	Product[b]	Time (min)	Yield (%)[c]
6	 **1e**	 **2e**	30	90
7	 **1f**	 **2f**[d]	60	85
8	 **1g**	 **2g**	45	89
9	 **1h**	 **2h**	40	90
10	 **1i**	 **2i**[d]	30	88
11	 **1j**	 **2j**	20	92
12	 **1k**	 **2k**	90	80
13	 **1l**	n.d.[f]	180	0[e]
14	 **5**	 **5a**	90	85

[a] Reaction conditions: epoxide (1.0 equiv), TosMIC (1.0 equiv), $InCl_3$ (0.5 equiv), and THF–H_2O (9:1).
[b] All the products were characterized from spectral data.
[c] Isolated yields after purification by column chromatography.
[d] The products **2d**,**f**,**i** were obtained as diastereomeric mixtures.
[e] Formation of unisolable products is observed.
[f] Not detected.

In general ketones are less reactive than aldehydes towards nucleophilic attack. A simple method for the α-addition of isocyanides to carbonyl compounds is still lacking. For instance, the susceptibility of the reaction with ketone, that is, cyclohexanone (Table 2, entry 14) under the same reaction conditions was next examined. It is noteworthy to mention that the reaction of TosMIC with **5** under the present conditions proceeded smoothly to afford **5a** in good yield. As far as we know, this is the first example of α-addition of TosMIC to ketone.

In conclusion, we have described for the first time a tandem protocol that provides efficient synthesis of α-hydroxyamides directly from epoxides.[20] A mechanistically novel reaction pathway for the construction of C–C bond formation was disclosed. Considering the mild reaction conditions, tolerance of various functional groups, easy availability of substrates, high regioselectivity, and shorter reaction times, the methodology described here undoubtedly will find new applications in future synthetic endeavors. The products obtained by the present protocol are densely functionalized and can act as unique building blocks.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561602.

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(20) **General Experimental Procedure (Table 3, Entry 1)**
A solution of styrene oxide (120 mg, 1.0 mmol), TosMIC (195 mg, 1.0 mmol), and $InCl_3$ (110 mg, 0.5 mmol) in THF–H_2O (9:1, 2 mL) was stirred at ambient temperature until completion (TLC). The resulting solution was partitioned between an equimolar ratio of Et_2O (2 × 20 mL), the combined organic layers were washed with brine (1 × 20 mL), dried (Na_2SO_4), evaporated under vacuum, and the residue thus obtained was purified by column chromatography (silica gel 60–120 mesh, EtOAc–*n*-hexane, 3.0:7.0) to afford **2a**.

2-Hydroxy-3-phenyl-*N*-(tosylmethyl)propanamide (2a)
Yellow solid (290 mg, 90% yield), mp 125–127 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.2 Hz, 2 H), 7.56 (br s, 1 H, NH), 7.39–7.15 (m, 7 H), 4.65 (d, *J* = 6.9 Hz, 1 H), 4.19 (dd, *J* = 9.4, 3.4 Hz, 1 H), 3.04 (dd, *J* = 13.9, 3.0 Hz, 1 H), 2.62 (dd, *J* = 14.0, 9.4 Hz, 1 H), 2.44 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.6, 145.5, 136.6, 133.7, 129.9, 129.4, 128.9, 128.7, 127.1, 72.8, 59.9, 40.5, 21.7. ESI-MS: *m/z* = 334 $[M + H]^+$. HRMS: *m/z* calcd for $C_{17}H_{19}O_4NNaS$ $[M + Na]^+$: 356.0927; found: 356.09226.