N-Boc-glycine-assisted indium-mediated allylation reaction: A sustainable approach

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ABSTRACT

An unprecedented improvement in the reaction rate (from hours to minutes) was observed during the In-mediated allylation of isatins with allyl bromide in the presence of *N*-Boc-glycine. The observed phenomena was generalized as a general protocol for the allylation of differently substituted isatins with excellent yields in a short time and with a wide range of functional group tolerance. Evidence suggests the unique role of the *N*-Boc-glycine additive was to increase the rate of formation and increase the nucleophilicity of the allylindium organometallic reagent.

The use of metallic indium (In) powder for the construction of C-C bonds was reported by Araki *et al* in 1988 and subsequently gained special interest in the synthetic organic community.¹ In particular, the Barbier-type allylation of carbonyl compounds and imines have shown distinct progress due to its unique properties such as low toxicity, tolerance towards air and moisture and low heterophilicity.

In our continuous effort to further explore the synthetic utility of organoindium reagents and improve their efficiency and applicability, we have developed several new avenues of indium-mediated allylation reactions including asymmetric versions.² During our investigation of the In-mediated cyclization of allyl bromide onto chiral hydrazones (Scheme 1), we discovered that the reaction would only proceed in the presence of carboxylic acid, namely, *N*-Boc-glycine (Boc-Gly-OH). Our observation that this additive had a pronounced effect on the successful indium-mediated intramolecular allylation of chiral hydrazones to form aminochromanes led us to further investigate the effect of Boc-Gly-OH and other *N*-Boc-protected amino acid additives (Boc-AAs) in these allylation reactions.

Scheme 1: Intramolecular indium-mediated allylation of hydrazones promoted by Boc-Gly-OH

To explore the application of Boc-AAs in the In-mediated allylation, we opted to utilize isatin as a model substrate due to the broad spectrum of biological activities associated with it and its derivatives.³ The study began with the model reaction involving treatment of isatin (**1a**) with allyl bromide (1 equiv) in the presence of In (1 equiv) and Boc-Gly-OH (2 equiv) using MeOH (2.5 mL) as solvent at rt. Results of our initial investigation are summarized in Table 1. To our delight, the product **2a** was produced in excellent yield in only 10 min (entry 2, table 1). In stark contrast, the reaction of isatin in the absence of Boc-Gly-OH only yielded 70% of **2a** even after 24 h (entry 1, table 1). The finding of rate acceleration in the In-mediated allylation of enamines in the presence of carboxylic acid⁴ influenced us to test different protic acids, including carboxylic acids. However, surprisingly, no reaction was observed upon treatment of **1a** with allyl bromide in presence of simple carboxylic acids or mineral acids (entry 4-8, table 1). The effect of amine additives was examined by performing the reaction in the presence of different bases (inorganic and organic. However, no product **2a** formation was observed (entry 9-12, table 1). The only observable product was the formation of *N*-allyl isatin, which suggested that the allyl bromide was reacting as an electrophile and allylindium reagents were not formed. To determine if there was a dual acid-base cooperative effect taking place with Boc-Gly-OH,⁵ the model reaction was carried out in the presence of pyrrole-2-carboxylic acid, to our disappointment, the reaction also failed affording only trace amounts of **2a** (entry 13, table 1). This essentially disqualified the role of Boc-Gly-OH as a cooperative acid-base agent. As the media in In-mediated allylation becomes increasingly more acidic as the reaction proceeds, we hypothesized that decomposition of the *N*-Boc protected amino acid could generate *t*-BuOH in the reaction. The

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role of *in situ* generated *t*-BuOH was tested by using *t*-BuOH (2 equiv) as an additive. The result was inferior suggesting the alcohol was not playing a role in the rate acceleration (entry 14, table 1). The effect of other Boc-AAs (Boc-Phe-Gly-OH, Boc-Phe-Ala-OH, Boc-Pro-OH, Boc-Val-OH, and Boc-Cys-OH) was evaluated for the model reaction, except for *N*-Boc-Cys-OH, a similar rate enhancement was observed (entry 15-18, table 1). However, compared to Boc-Gly-OH, the results were distinctly inferior. It was further noted that simple Gly-OH, without the *N*-protecting group, was found inferior compared to Boc-Gly-OH (entry 20, table 1). The free carboxylic acid of Boc-Gly-OH was necessary as demonstrated by application of the methyl ester derivative (entry 21, table 1). The reaction was significantly slower and the yield was markedly lower.

Table 1. Indium-mediated reaction of isatin (**1a**) with allyl bromide in presence of additives.^a

Entry	Additive (2 equiv)	Time (h)	Yield (%) ^b
1	None	24	70
2	Boc-Gly-OH	10 min	98
3	Boc-Gly-OH ^c	6	90
4	CH ₃ CO ₂ H	24	0 ^d
5	PhCO ₂ H	24	0 ^d
6	(CH ₃) ₃ CCO ₂ H	24	0 ^d
7	HCl (N)	24	0 ^d
8	HBr (N)	24	0 ^d
9	NH ₄ OH	24	0 ^e
10	DBU	24	0 ^e
11	Piperidine	24	0 ^e
12	Pyrrolidone	24	0 ^e
13	Pyrrole-2-carboxylic acid	24	0 ^d
14	^t BuOH	24	72
15	Boc-Phe-Gly-OH	2	94
16	Boc-Phe-Ala-OH	5	90
17	Boc-Pro-OH	6	87
18	Boc-Val-OH	2	93
19	Boc-Cys-OH	24	0 ^d
20	Gly-OH	12	70
21	Boc-Gly-OMe	5	78

^a**1a** (0.5 mmol) was treated with allyl bromide (0.5 mmol, 1 equiv) in presence of In (0.5 mmol, 1 equiv) using different additives (1 mmol, 2 equiv) in MeOH (2.5 mL) at rt for different time intervals. ^bIsolated yield of **2a**. ^cReaction was carried out using 1 equiv of Boc-Gly-OH. ^dStarting material **1a** was recovered intact. ^eThe isolated product was characterized as *N*-allyl isatin

The use of MeOH as solvent for the model reaction was selected based on the results of initial screening of different solvents (protic polar, aprotic polar, hydrocarbon, halogenated hydrocarbon, etheral) for the reaction of **1a** (1 equiv) with allyl bromide (1 equiv) in presence of In (1 equiv) at rt.⁶ We performed the reaction in a variety of solvents and found MeOH to be optimal (table 2).

The effect of Boc-Gly-OH on the other main group metals (Bi, Zn and Sn) known for their ability to form nucleophilic allylmetal reagents, and subsequent allylation of carbonyl compounds and imines,⁷ were investigated (table 3). A similar rate enhancement for Bi, Zn and Sn was observed. The extent of the effect of Boc-Gly-OH may be roughly ranked as

In > Zn > Sn > Bi. No effect of Boc-Gly-OH was noted in case of Mg, probably due to rapid protonation and destruction of the allylmagnesium bromide in methanol.

To demonstrate the synthetic utility of this methodology, under the established reaction conditions with the Boc-Gly-OH additive (Method A), a variety of isatins were efficiently converted into the corresponding homoallylic alcohols (Table 4). A variety of substitutions on the ring and the nitrogen were well tolerated. Substrates **1b**, **1c**, **1d** having *N*-Me, *N*-Ph, and *N*-Bn groups respectively were converted smoothly into corresponding alcohols with excellent yield (entry 1-3, table 4). Isatins having an electron-donating groups such as 5-Me (**1e**; entry 5, table 4) and 5-OMe (**1f**; entry 6, table 4), electron-withdrawing groups such as 7-CF₃ (**1g**; entry 7, table 4) and halogen functionalities **1i-1k** (entry 9-11, table 4) also performed well in the reaction providing the products in excellent yield and short reaction times (5-30 min).

Table 2. Indium-mediated reaction of isatin (**1a**) with allyl bromide in presence of Boc-Gly-OH as an additive in different solvent.^a

Entry	Solvent	Time	Yield (%) ^b
1	H ₂ O	10 min	trace
2	H ₂ O	12 h	85
3	MeOH	10 min	98
4	EtOH	10 min	32
5	EtOH	12 h	86
6	DMF	10 min	trace
7	DMF	12 h	81
8	Toluene	10 min	0 ^c
9	Toluene	24 h	0 ^c
10	CH ₂ Cl ₂	10 min	0 ^c
11	CH ₂ Cl ₂	24	10

^a**1a** (0.5 mmol) was treated with allyl bromide (0.5 mmol, 1 equiv) in presence of In (0.5 mmol, 1 equiv) using Boc-Gly-OH (1 mmol, 2 equiv) in different solvents (2.5 mL) at rt for different time intervals. ^bIsolated yield of **2a**. ^cStarting material **1a** was recovered intact.

Table 3: Effect of Boc-Gly-OH on the metal-mediated reaction of isatin (**1a**) with allyl bromide.^a

Entry	Metal	Time	Yield (%) ^b
1	In	10 min	98
2	Bi	4.5 h	97
3	Bi ^c	24 h	trace
4	Zn	1 h	95
5	Zn ^c	24 h	trace
6	Sn	4 h	81
7	Sn ^c	12 h	trace
8	Mg	24 h	trace
9	Mg ^c	24 h	trace

^a**1a** (0.5 mmol) was treated with allyl bromide (0.5 mmol, 1 equiv) in presence of different metal (0.5 mmol, 1 equiv) using Boc-Gly-OH (1 mmol, 2 equiv) in MeOH (2.5 mL) at rt for different time intervals. ^bIsolated yield of **2a**. ^cReaction was carried out using in absence of Boc-Gly-OH.

To demonstrate the advantage of Boc-Gly-OH additive, the allylations in the absence of Boc-Gly-OH and their results compared (Method B, table 4). The results clearly demonstrated the synthetic utility and superiority of the present protocol and demonstrated a sustainable development towards the allylation of isatins that may be further extended to other carbonyl and imine substrates. Further, the present protocol offers an advantage over other reported methods⁸ in terms of the amount of In and allyl bromide required to achieve nearly quantitative yield. Most of the reported methods required at least 50% excess allyl halide (halide/In 3:2) for complete reaction whereas the present method proceeds efficiently with only a 1:1 ratio of allyl bromide and In with respect to substrate **1a**. Clearly the additive increased the nucleophilicity of the allyl organometallic reagent and assisted in transferring more allyl moieties to the product as compared to the reaction without it.

Table 4: Boc-Gly-OH assisted In-mediated allylation of isatin.

Entry	1a-k	Method ^a	Time	Yield (%) ^b
1	1a ; R ¹ = R ² = H	A	10 min	98
		B	6 h	70
2	1b ; R ¹ = Me; R ² = H	A	10 min	97
		B	4 h	76
3	1c ; R ¹ = Ph; R ² = H	A	20 min	98
		B	6 h	83
4	1d ; R ¹ = Bn; R ² = H	A	10 min	96
		B	3 h	72
5	1e ; R ¹ = H; R ² = 5-Me	A	10 min	94
		B	3.5 h	70
6	1f ; R ¹ = H; R ² = 5-OMe	A	10 min	96
		B	4 h	79
7	1g ; R ¹ = H; R ² = 7-CF ₃	A	15 min	93
		B	3.5 h	68
8	1h ; R ¹ = H; R ² = 7-F	A	10 min	96
		B	2.5 h	69
9	1i ; R ¹ = H; R ² = 5-I	A	30 min	95
		B	8.5 h	78
10	1j ; R ¹ = H; R ² = 5-F	A	5 min	94
		B	4.5 h	74
11	1k ; R ¹ = H; R ² = 4-Br	A	10 min	99
		B	6 h	78

^aMethod A: Isatin (0.5 mmol) was treated with allyl bromide (0.5 mmol, 1 equiv) in presence of In (0.5 mmol, 1 equiv) and Boc-Gly-OH (1 mmol, 2 equiv) in MeOH (2.5 mL) at rt for stipulated time; Method B: same as Method A without the Boc-Gly-OH. ^bIsolated yield of **2**.

We have determined that the Boc-Gly-OH was assisting the nucleophilic transfer of allyl moieties from the In organometallic to the carbonyl increasing the efficiency and yield with only stoichiometric allyl bromide. Presumably the additive interacts with the reagent to increase electron density on the metal or change the aggregation state. The nature of this interaction is not clear and further investigation is being undertaken to elucidate how the additive may bind. In addition to modulating the reagent reactivity, we wondered if the additive played any role in the formation of the allyl indium reagent itself. To confirm this hypothesis, we performed NMR studies to observe the formation of allylindium species in the presence of Boc-Gly-

OH. When present, the formation of allyl indium species was rapidly detected (appearance of allylic protons at 1.75 and 1.93 ppm)^{1b} within 5 min (figure 1, **C** and **D**). In stark contrast, virtually no allyl indium was observed after 10 minutes in the absence of the additive (figure 1, **A**). And, only a trace of the reagent appeared after 30 min (figure 1, **B**). This strongly suggested that the rate acceleration observed in the Boc-Gly-OH assisted allylation was due to an increase in the rate of formation of the nucleophilic reagent.

Figure 1: ¹H NMR spectra showing the formation of allylindium species with and without Boc-Gly-OH respectively. **A:** In(0) + allyl bromide, 10 min; **B:** In(0) + allyl bromide, 30 min; **C:** In(0) + allyl bromide + Boc-Gly-OH, 5 min; **D:** In(0) + allyl bromide + Boc-Gly-OH, 10 min

In conclusion, we report that Boc-Gly-OH significantly enhanced the rate and efficiency of the In-mediated allylation of isatins. Further, the reaction could be carried out successfully in minutes in renewable solvents (MeOH) and represent an advance in sustainable synthetic methods requiring less indium metal and less allyl bromide. Investigation into the role of the additive in the formation of allyl indium and the reactivity of this reagent has led to greater understanding of these processes. Further studies are underway to understand the nature of the interactions and specific function of the additive in the allylation step. It is anticipated that this strategy can be further extended to other carbonyl compounds and imines thereby increasing the practical utility of In-mediated allylation methodology.

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Supplementary Material

Experimental procedures and characterization data for all homoallylic alcohols are contained in the supplementary material.

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