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Unprecedented One-Pot, Domino Tertiary Alcohol Protection–Michael Type Addition of Halides to Morita–Baylis–Hillman Adduct of Isatin with RCOX/K_2CO_3: Diastereoselective Synthesis of Oxindole Appended β-Halo Esters

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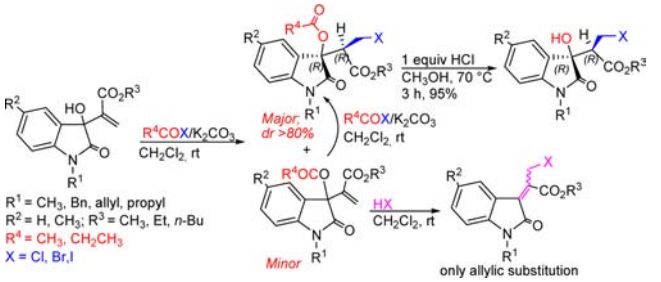
ABSTRACT



A facile method utilizing RCOX/K_2CO_3 as a novel reagent for conjugate addition of hydrogen halide, in addition to tertiary (3°)-hydroxyl protection that leads to the synthesis of functionalized β-halo Morita–Baylis–Hillman ester appended oxindoles, has been developed. The diastereoselective one-pot O-acylation–hydrohalogenation observed cannot otherwise be performed by treatment with hydrohalide. Deprotection of a 3°-hydroxyl protecting group has also been demonstrated by treatment with hydrochloric acid.

Development of novel methods to functionalize an oxindole nucleus has attracted much attention, since oxindole is an integral structural unit in alkaloid natural products and is widely found in heterocyclic compounds with biological and medicinal applications.[1,2] The Morita–Baylis–Hillman (MBH) adducts[3] and their acetate derivatives are useful precursors for the synthesis of diverse and multifunctional molecules,[4] and the MBH adduct of isatin has been utilized for functionalization of an oxindole

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(1) (a) Galliford, C. V.; Scheidt, K. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (c) Castaldi, M. P.; Troast, D. M.; Porco, J. A. *Org. Lett.* **2009**, *11*, 3362. (d) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967. (e) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007.

(2) For selected examples, see: (a) Zhang, Y.; Panek, J. S. *Org. Lett.* **2009**, *11*, 3366. (b) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477. (c) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666. (d) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135. (e) Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzinol, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147. (f) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186. (g) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Tetrahedron* **2004**, *60*, 9503.

(3) (a) Baylis, A. B.; Hillman M. E. D. German Patent 2155113, 1972. *Chem. Abstr.* **1972**, *77*, 34174q. (b) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.

(4) (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1. (c) Batra, S.; Singh, V. *Tetrahedron* **2008**, *64*, 4511. (d) Ciganek, E. *Organic Reactions*; Paquette, L., Ed.; Wiley: New York, 1997; Vol. 51, p 201. (e) Ma, G. N.; Jiang, J. J.; Shi, M.; Wei, Y. *Chem. Commun.* **2009**, 5496. (f) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447.

(5) (a) Garden, S. J.; Skakle, J. M. S. *Tetrahedron Lett.* **2002**, *43*, 1969. (b) Viswambharan, B.; Selvakumar, K.; Suchithra, M.; Shanmugam, P. *Org. Lett.* **2010**, *12*, 2108. (c) Selvakumar, K.; Vaithiyanathan, V.; Shanmugam, P. *Chem. Commun.* **2010**, *46*, 2826.

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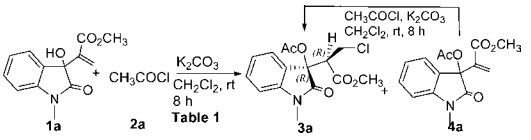
Scheme 1. 3°-Hydroxyl Protection and Michael Type HCl Addition to **1a** with $RCOCl/K_2CO_3$



nucleus.[5] β-Halo MBH esters[6] are vital intermediates to synthesize β-branched MBH esters.[7] Nucleophilic substitution of MBH adducts with various nucleophiles provided functionalized trisubstituted alkenes via an allylic nucleophilic substitution reaction.[8,9] In contrast to the previous reports,[10] we have observed conjugate addition of hydrogen halide along with tertiary alcohol protection by reaction with acyl halides (RCOX) in the presence of alkali carbonates, forming β-halo MBH esters of oxindole.

The protection−deprotection sequences of hydroxyl groups, particularly tertiary alcohol, is one of the essential transformations for selective reactions.[11] Hence, several studies have been directed toward developing efficient, simple methods to protect the hydroxyl group using a variety of protecting reagents and catalytic conditions.[12] However, many of them suffer from stringent experimental conditions, usage of expensive chemicals, and/or preparation of catalysts.[13] Against this background, and also in continuation of our interest in the functionalization of oxindole *via* Baylis−Hillman chemistry,[5b,c,8c] we report here a facile one-pot tertiary alcohol protection and diastereoselective hydrohalogenation (dr $<95\%$) of MBH adduct acrylates of isatin.

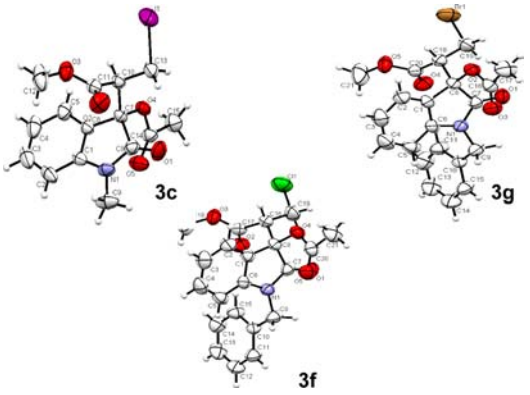


Figure 1. ORTEP diagram of compounds **3c**, **3g**, and **3f**.[14]

To avoid pyridine as a base, we examined the tertiary (3°) alcohol protection of MBH adduct **1a** with other alkali metal carbonate bases. Thus, adduct **1a** in acetonitrile was treated with acetyl chloride and potassium carbonate at rt. We were gratified to observe that the 3°-hydroxyl protection took place with a 52% yield of **4a** (Scheme 1).

To increase the yield of **4a**, the above reaction was monitored with increased amounts of acetyl chloride to 1.5 equiv. To our surprise, in addition to the formation of **4a** in 75% yield, the 3°-OH protected, hydrochlorinated MBH acetate **3a** was found to be forming in the reaction mixture in 20% yield. Compound **4a** can be converted to **3a** under similar reagent conditions.

The structure of **3a** was unambiguously assigned by spectroscopic data analyses (IR, ^1H, ^{13}C NMR, and mass), and the relative stereochemistry was confirmed as (*R*,*R*) by single crystal X-ray analysis of **3f** (Figure 1).

With this promising result in hand, we then undertook further optimization experiments, and the results are summarized in Table 1. The conditions were optimized for choice of base, solvent, and equivalents of acid halide and base used. The yield of compound **3a** increased with 1 equiv of base, and in 8 h, compound **3a** and acetate **4a** were formed in 75% and 12% yield, respectively (Table 1, entries 1−3), conferring high diastereoselectivity (95%) for **3a**. Although both K_2CO_3 and Na_2CO_3 lead to the high diastereoselectivity of product, potassium carbonate gave a higher yield of **4a** in a given reaction time. However, reaction with organic bases such as pyridine, Et_3N, and DABCO lead to the formation of acetate **4a** in good yield. From the results it is clear that the reaction conditions could be tuned for either the 3°-alcohol protected adduct or 3°-alcohol protected conjugate addition product, and the ideal conditions for the latter were found to include 1.5 equiv of acid halide and 1 equiv of potassium carbonate in dichloromethane (Table 1, entry 5).

The surprising Michael type conjugate addition of HX took place only under basic conditions. The reactions of

(6) (a) Senapati, B. K.; Hwang, G. S.; Lee, S.; Ryu, D. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 4398. (b) Li, Q.; Shi, M.; Lyte, J. M.; Li, G. *Tetrahedron Lett.* **2006**, *47*, 7699. (c) Lee, S.; Hwang, G. S.; Shin, S. C.; Lee, T. G.; Jo, R. H.; Ryu, D. H. *Org. Lett.* **2007**, *9*, 5087.

(7) (a) Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T.; Watanabe, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2358. (b) Ramachandran, P.; Rudd, M. T.; Burghardt, T. E.; Reddy, M. V. R. *J. Org. Chem.* **2003**, *68*, 9310. (c) Reynolds, T. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 15382. (d) Reynolds, T. E.; Scheidt, K. A. *Angew. Chem.* **2007**, *119*, 7952. *Angew. Chem., Int. Ed.* **2007**, *46*, 7806. (e) Tarsis, E.; Gromova, A.; Lim, D.; Zhou, G.; Guoqiang, C.; Coltart, D. M. *Org. Lett.* **2008**, *10*, 4819. (f) Mueller, A. J.; Jennings, M. P. *Org. Lett.* **2008**, *10*, 1649.

(8) (a) Basavaiah, D.; Kumaragurubaran, N.; Padmaja, K. *Synlett* **1999**, 713. (b) Kim, H. S.; Kim, T. Y.; Lee, K. Y.; Chung, Y. M.; Lee, H. J.; Kim, J. N. *Tetrahedron Lett.* **2000**, *41*, 2613. (c) Shanmugam, P.; Rajasingh, P. *Tetrahedron* **2004**, *60*, 9283.

(9) (a) Beltaïef, I.; Hbaïeb, S.; Besbes, R.; Amri, H.; Villiéras, M.; Villiéras, J. *Synthesis* **1998**, 1765. (b) Ying, T. K.; Bao, W. L.; Wang, Z. H.; Zhang, Y. M. *J. Chem. Res. (S)* **2005**, 96. (c) Yadav, J. S.; Reddy, B. V. S.; Madan, C. *New J. Chem.* **2001**, *25*, 1114.

(10) (a) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94. (b) Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213. (c) Basavaiah, D.; Bakthadoss, M.; Pandiaraju, S. *J. Chem. Soc., Chem. Commun.* **1998**, 1639.

(11) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991.

(12) (a) Schelhaas, M.; Waldmann, H. *Angew. Chem., Int. Ed.* **1996**, *35*, 2056. (b) Ramesh, R.; Bhat, R. G.; Chandrasekaran, S. *J. Org. Chem.* **2005**, *70*, 837. (c) Karimi, B.; Golshani, B. *J. Org. Chem.* **2000**, *65*, 7228. (d) Paleo, M. R.; Aurrecoechea, N.; Jung, K.-Y.; Rapoport, H. *J. Org. Chem.* **2003**, *68*, 130.

(13) (a) Poon, K. W. C.; Albiniak, P. A.; Dudley, G. B.; Berliner, M. A.; Ragan, J. A. *Org. Synth.* **2007**, *84*, 295. (b) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kobayashi, T.; Tokuyama, H.; Fukuyama, T. *Pure Appl. Chem.* **2003**, *75*, 29. (c) Shirakawa, E.; Hayashi, T. *Chem. Commun.* **2006**, 3927.

Table 1. Optimization for the Synthesis of **3a**

entry	equiv of MeCOCl	base	equiv of base	solvent	time (h)	products **3a/4a** (yield %)[a]
1	1	K_2CO_3	0.5	CH_3CN	4	0/52
2	1.5	K_2CO_3	0.5	CH_3CN	4	20/75
3	1.5	K_2CO_3	0.5	CH_3CN	8	30/56
4	1.5	K_2CO_3	1	CH_3CN	8	75[c]/12
5	**1.5**	**K_2CO_3**	**1**	**CH_2Cl_2**	**8**	**82[c]/5**
6	1.5	Cs_2CO_3	1	CH_2Cl_2	8	80[d]/3
7	1.5	Na_2CO_3	1	CH_2Cl_2	8	74[c]/8
8	1.5	K_2CO_3	1	PhMe	8	12/30
9	1.5	pyridine	1	CH_2Cl_2	8	5/55
10	1.5	Et_3N	1	CH_2Cl_2	8	8/56
11	1.5	DABCO	1	CH_2Cl_2	8	8/50
12[b]	**1.5**	**K_2CO_3**	**1**	**CH_2Cl_2**	**3**	**86/5**

[a] Isolated yield. [b] Acetyl bromide yielded the corresponding β-bromo MBH ester. [c] Dr of **4a** determined by ^{1}H NMR of the crude product was 95%. [d] Dr of **4a** was 80%.

both the adduct **1a** and the hydroxyl protected MBH adduct of isatin **4a**, with hydrogen halides, yielded only the allylic substituted product.[15] The hydrohalogenated MBH acetate could not be accomplished by a stepwise –OH protection and reaction with a hydrogen halide which yields only allylic halo substituted product **5** (Scheme 2).

The formation of the unexpected product with acetyl chloride prompted us to generalize with other acyl halides such as acetyl bromide for conjugate HBr addition with **1a** under optimal conditions. The reaction took place rapidly and afforded the β-bromo MBH ester **3b** (86%) in 3 h with a trace of **4a**. The diastereoselectivity for bromo compound **3b** was found to be 87% with the similar relative configuration (*R*, *R*) (Table 2, entry 2). Similarly, with acetyl iodide generated in situ from treating acetyl chloride with potassium iodide, the reaction proceeded smoothly to provide the desired iodo compound **3c** in 80% yield with 90% (*R*, *R*) diastereoselectivity (Table 2, entry 3). The versatility of the method developed was evaluated by screening other acyl halides. Propionyl chloride provided the hydrochlorinated propionate product **3d** in 60% yield along with the tertiary hydroxyl protected product **4b** in 29% yield, generalizing the method for acyl halides (Table 2, entry 4). The relative stereochemistry of iodo derivative **3c** and bromo derivative **3g** was confirmed as (*R*, *R*) by single crystal X-ray analysis (Figure 1). The synthesis of the β-halo product was unsuccessful with the acrylonitrile derived MBH adduct of isatin. When treated, only the protected adduct was formed up to 87% yield and no hydrogen

Scheme 2. Reaction of MBH Ester of Isatin with Halides under Acidic and Basic Conditions

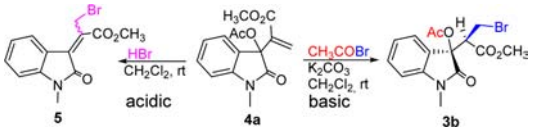
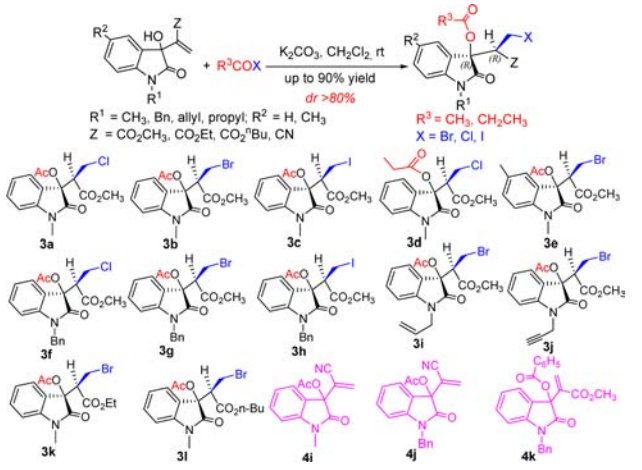


Table 2. Synthesis of Tertiary Alcohol Protected β-Halo MBH Esters **3a**–**j** and Acetate Adducts **4a**–**j** from MBH Adducts **1a**–**h**[a]



	MBH adduct				product[b]	
entry	R^1	Z	**1**	R^3COX	**3/4** (%)[d]	dr (%)[e]
1	Me	CO_2Me	**1a**	**2a**	**3a** (82)	95:05
2	Me	CO_2Me	**1a**	**2b**	**3b** (80)	87:13
3	Me	CO_2Me	**1a**	**2c**[f]	**3c** (80)	90:10
4[c]	Me	CO_2Me	**1a**	**2d**	**3d** (60)	90:10
5	Me	CO_2Me	**1b**[g]	**2b**	**3e** (75)	80:20
6	Bn	CO_2Me	**1c**	**2a**	**3f** (80)	95:05
7	Bn	CO_2Me	**1c**	**2b**	**3g** (75)	85:15
8	Bn	CO_2Me	**1c**	**2c**[f]	**3h** (74)	85:15
9	allyl	CO_2Me	**1d**	**2b**	**3i** (74)	84:16
10	propargyl	CO_2Me	**1e**	**2b**	**3j** (74)	80:20
11	Me	CO_2Et	**1f**	**2b**	**3k** (80)	88:12
12	Me	$CO_2{}^nBu$	**1g**	**2b**	**3l** (81)	88:12
13[h]	Me	CN	**1h**	**2a**	**4i** (91)	–
14[h]	Me	CN	**1h**	**2b**	**4i** (90)	–
15[h]	Bn	CN	**1i**	**2b**	**4j** (90)	–
16[h]	Bn	CO_2Me	**1c**	**2e**	**4k** (82)	–

[a] All reactions were performed with 1.5 equiv of RCOX and 1 equiv of K_2CO_3 in CH_2Cl_2. [b] Unless stated otherwise the corresponding 3°-hydroxyl protected MBH adduct was isolated in < 5% yield. [c] The corresponding 3°-hydroxyl protected MBH adduct was isolated in 29% yield. [d] Isolated yield of the major diastereomer. [e] Diastereomeric ratio was determined using ^{1}H NMR of the crude product. [f] In situ generation of acetyl iodide by treating acetyl chloride with KI. [g] R^2 = Me. [h] Only 3°-OH protected MBH adduct was obtained.

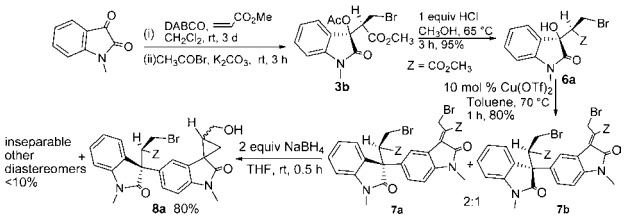
halide addition was noticed (Table 2, entries 13–15). The method has been found to be versatile with acyl halides. However, under optimized conditions, experiments with an aromatic acid halide, for example benzoyl chloride, led only to the tertiary hydroxyl protection (Table 2, entry 16).

To demonstrate the scope and limitation of the reaction, experiments with an MBH adduct of *N*-substituted and 5-substituted isatins **1b**–**e** were carried out, and they furnished the hydrohalogenated MBH acetate as the major product (Table 2, entries 5–10). To show the method is general for

(14) CCDC 915450, 911325, and 911324 contains the supplementary crystallographic data of compounds **3c**, **3g**, and **3f**, respectively. A copy of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).

(15) Shanmugam, P.; Vaithiyanathan, V.; Viswambharan, B. *Tetrahedron* **2006**, *62*, 4342.

Scheme 3. Synthesis of **3b** in a One-Pot Sequential Manner, 3°-Hydroxyl Deprotection and Synthetic Transformation of **3b**



acrylate derived MBH adducts, under optimized conditions, the reaction of ethyl acrylate and the *n*-butyl acrylate adduct of *N*-methyl isatin gave the *β*-bromo compound in 80% and 81% yields, respectively (Table 2, entries 11, 12).

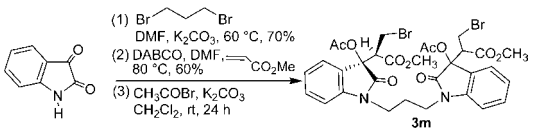
The formation of an MBH adduct of isatin and the reaction with acyl halide could also be achieved in a one-pot sequential manner, however, in a lower yield of **3b** (75%) (Scheme 3).

Compound **3b** with mineral acids such as H_2SO_4 or HCl in methanol at 65 °C for 3 h yielded deprotected product **6a** in 95% yield. Further synthetic transformation of **6a** with 10 mol % of $Cu(OTf)_2$ afforded unexpected, functionalized bis-isatin compounds **7a** and **7b**, where the hydroxyl group in **6a** has been substituted with another molecule of **6a** that became dehydrated to **7a** and **7b**. Reductive cyclization of **7a** with sodium borohydride at rt led to the formation of cyclopropane appended functionalized bis isatin **8a** in 80% yield in a diastereoselective manner along with a 10% yield of other inseparable diastereomers (Scheme 3).

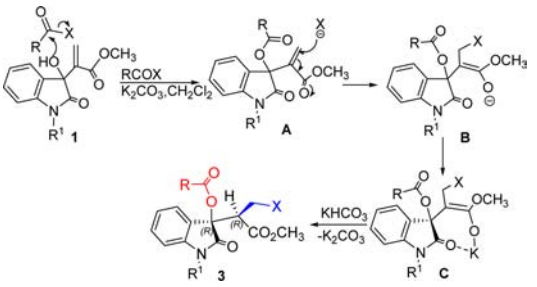
To widen the substrate scope, a methyl acrylate derived MBH adduct of N-bridged isatin **1j** was treated with acetyl bromide and furnished the bis-tertiary alcohol protected hydrogen halide addition product **3m** in 50% yield (Scheme 4). Thus, the method has versatility over the substituents of acyl halides, isatins, and acrylates. Experiments with the acrylate MBH adduct of ninhydrin and that of benzaldehyde resulted only in the hydroxyl protected compounds in 82 and 90% yields, respectively.

A mechanistic proposal for the diastereoselective formation of the *β*-halo ester appended oxindole is outlined in Scheme 5. The mechanism can be explained by invoking a diastereoselective domino acylation/Michael type addition pathway. In the initial step, the base triggers the alkoxide ion resulting from adduct **1**, to obtain acylated intermediate **A** followed by the attack of the halide on the activated double bond of the Michael acceptor, producing the enolate ion **B**. A possible coordination of the partially negative amide oxygen of oxindole with a metal enolate probably stabilizes

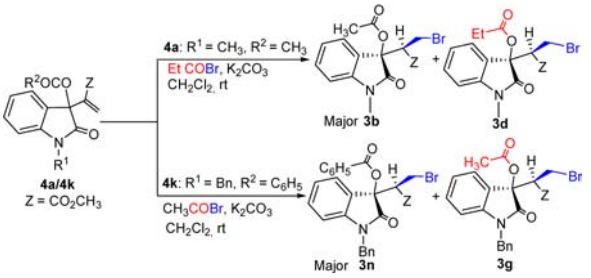
Scheme 4. Synthesis of 3°-OH Protected *β*-Halo MBH-Ester of N-Bridged Isatin **3m**



Scheme 5. Plausible Mechanism of the Reaction



Scheme 6. Experimental Support for the Mechanism



the intermediate and orients the path of protonation, explaining the observed acyclic stereocontrol in the product **3**.

The acylation and the attack of the halide ion on the activated double bond are consecutive under basic conditions, as inference from the experimental support (Scheme 6) that a reaction of the hydroxyl acetylated MBH adduct **4a** with propionyl bromide resulted in the formation of acetyl protected product **3b** in 70% yield along with a 5% yield of corresponding propionyl protected compound **3d**. Similarly, the hydroxyl benzoylated adduct **4k** with acetyl bromide under optimized conditions led to the formation of benzoate protected compound **3n** as a major product and acetyl protected product **3g** in 8% yield, sustaining the above presumption.

In conclusion, we have demonstrated a facile and efficient method that utilizes acyl halide for halogenation in addition to 3°-hydroxyl protection that leads to the synthesis of functionalized, *β*-halo MBH ester appended oxindoles. The reaction itself features a simple experimental procedure under benign conditions with acyclic stereocontrol and atom economy. Further studies with utilization of these *β*-halo MBH esters for functionalization of an oxindole core are underway.

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Supporting Information Available. Detailed experimental procedure, compiled spectroscopic data of new compounds, and scanned copies of spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.