

Indium-Promoted Chemo- and Diastereoselective Allylation of α,β -Epoxy Ketones with Potassium Allyltrifluoroborate

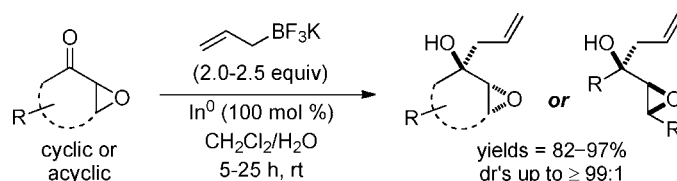
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ABSTRACT



A practical method for the chemo- and diastereoselective allylation of α,β -epoxy ketones has been developed by using the convenient air and moisture stable reagent potassium allyltrifluoroborate. Indium metal was found to promote addition in stoichiometric or catalytic amounts, to afford α,β -epoxyhomoallylic tertiary alcohols in high yields and diastereoselectivities, without competing ring-scission of the epoxide.

The formation of C–C bonds via the allylation of carbonyl compounds is an important method for the synthesis of homoallylic alcohols¹ and has been widely applied in the synthesis of natural products and other complex targets.² Classical allylation methods include the in situ reactions of allylic halides with stoichiometric metals (e.g., Mg, Cr, Zn, In) under Barbier-type³ conditions (type III^{1d} reagents), or the use of allyl or crotylmetaloids.^{4,5} The

addition of type II^{1d} allyl or crotylmetaloids (e.g., Sn, Si) to carbonyl groups requires Lewis acid activation, while type I^{1d} reagents, exemplified by allylboranes or boronates, undergo direct addition. Generally, additions to ketones are slower than for aldehydes thus requiring more vigorous conditions.

Given the well-known synthetic versatility of epoxy alcohols,⁶ there has been surprisingly little attention devoted to the addition of organometallic or metalloid reagents to epoxy ketones.⁷ Nucleophilic additions to epoxy ketones

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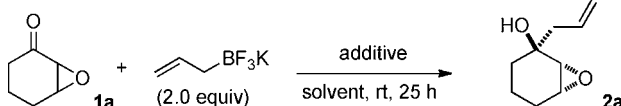
(5) See for example: (a) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481–8490. (b) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701–2704. (c) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160–10161.

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constitute a problem for many of the aforementioned allylation conditions, since epoxide ring-opening occurs in the presence of more nucleophilic reagents or Lewis acids,^{8,9} and deoxygenation in the presence of reducing metals. Reaction of α,β -epoxy ketones has been achieved diastereoselectively with allylstannanes using $\text{BF}_3\cdot\text{OEt}_2$ ^{10a} or PbI_2 activation,^{10b} or with Grignard reagents.^{10c–e} Unfortunately, these methods utilize toxic reagents, show limited substrate scope, and occur with diminished yields for cyclic substrates.¹⁰ An alternative one-pot sequential asymmetric allylation/directed epoxidation affords *syn*-epoxy homoallylic alcohols; however, it only works well for cyclic enones, with α -substitution necessary to obtain high selectivity.¹¹ We now report a general and selective organoboron-based method¹² for the allylation of α,β -epoxy ketones using indium metal as a catalyst,¹³ and demonstrate how the stereoselectivity of addition depends upon substrate class.

Organotrifluoroborate salts¹⁴ are well established as air and moisture stable reagents, acting as synthetic equivalents to boronic acids.¹⁵ Potassium allyl and crotyltrifluoroborate salts undergo addition reactions to carbonyl derivatives under Lewis acidic, phase-transfer catalyzed, or Montmorillonite K10 promoted conditions.¹⁶ Initial attempts to apply previously developed protocols for in situ activation of potassium allyltrifluoroborate using the model epoxy ketone **1a** gave only moderate yields of epoxy alcohol **2a** due to competing side reactions of **1a** (Table 1, entries 1 and 2). Alternative conditions using a variety of Lewis acids, fluorophiles, and

Table 1. Allylation of α,β -Epoxycyclohexanone (**1a**) with Potassium Allyltrifluoroborate



entry	additive (equiv)	solvent (mL)	yield ^a (dr) ^b
1	Mont. K10 (0.1 g) ^d	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (1.4:0.1)	62 (98:2)
2	$\text{BF}_3\cdot\text{OEt}_2$ (0.1) ^e	CH_2Cl_2 (1.5)	64 (98:2)
3	$\text{In}(\text{OTf})_3$ (0.1)	CH_2Cl_2 (1.5)	23 (82:18)
4	$\text{Cu}(\text{OTf})_2$ (0.1)	CH_2Cl_2 (1.5)	48 (91:9)
5	$\text{B}(\text{O}^i\text{Pr})_3$ (0.1)	CH_2Cl_2 (1.5)	43 (98:2)
6	$\text{B}(\text{O}^i\text{Pr})_3$ (1.0)	CH_2Cl_2 (1.5)	72 (76:24)
7	In (1.0)	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (1.4:0.1)	77 (93:7)
8	In (1.0)	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (1.45:0.05)	83 (95:5)
9	In (1.0)	CH_2Cl_2 (1.5)	N.R.
10	In (1.0)	$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (1.4:0.1)	N.R.
11	In (1.0)	$\text{MeCN}/\text{H}_2\text{O}$ (1.45:0.05)	33 (91:9)
12	In (1.0)	$\text{THF}/\text{H}_2\text{O}$ (1.45:0.05)	76 (94:6)
13	In (0.1)	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (1.45:0.05)	41 (95:5)
14	In (1.0)	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (1.45:0.05)	73 ^c (92:8)

^a Yield of product isolated after silica gel chromatography. ^b dr was determined by the integration of the α -epoxide C–H signal in the ¹H NMR of the crude reaction mixture. ^c Allylboronic acid pinacol ester (2.0 equiv) was used. ^d Mont. K10 is Montmorillonite K10. ^e Use of 1.0 equiv of $\text{BF}_3\cdot\text{OEt}_2$ led to decomposition.

solid additives were examined.¹⁷ Several Lewis acids were capable of promoting addition to **1a**, but product yields were disappointing (Table 1, entries 3–5). While the use of 0.1 equiv of $\text{B}(\text{O}^i\text{Pr})_3$ led to poor product yields, the use of a stoichiometric quantity led to an erosion of diastereoselectivity of **2a** (Table 1, entries 5 and 6). Intriguingly, metallic indium (1.0 equiv) was an effective promoter for the reaction,^{18,19} giving a good yield and dr of **2a** without leading to side-product formation (Table 1, entry 7). Further optimization revealed that reducing the amount of water improves yields of **2a**, but that poor reaction conversions were obtained in the absence of water (ca. 5%) (Table 1, entries 8 and 9). Reaction of **1a** with MeOH as a protic additive was unsuccessful, while the use of other solvents such as acetonitrile or THF resulted in lower yields (Table 1, entries 10–12). It is noteworthy that while potassium allyltrifluoroborate is stable in water, showing less than 5% decomposition over 24 h in the absence of the ketone, the presence of indium leads to formation of propene gas,²⁰ necessitating the use of 2.0 equiv to achieve full conversion of **1a**. The use of In in catalytic quantities was successful although a lower yield of **2a** was obtained with a similar reaction time (Table 1, entry 13). Reaction in the absence of In using water/ CH_2Cl_2 is ineffective. Stoichiometric quantities of In were therefore used for subsequent studies. Use of the pinacol ester

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Table 2. Stereoselective Synthesis of Epoxy Alcohols 2

$\text{1} \xrightarrow[\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}, 5-25 \text{ h, rt}]{\text{K}^+\text{BF}_3\text{K}^- (2.0-2.5 \text{ equiv}), \text{In} (1.0 \text{ equiv})} \text{2}$

entry	substrate	product	yield ^a (dr) ^b	entry	substrate	product	yield ^a (dr) ^b
1			83 (95:5) 79 ^c (94:6)	8			83 (88:12)
2			85 (93:7)	9			91 (95:5)
3			97 ^{d,e} ($\geq 99:1$)	10			82 (71:29)
4			90 ($\geq 99:1$)	11	1k R ¹ = Ph, R ² = Ph	2k	92 (97:3)
5			91 ($\geq 99:1$)	12	1l R ¹ = Me, R ² = Ph	2l	95 ($\geq 99:1$)
6			96 ($\geq 99:1$)	13	1m R ¹ = H, R ² = Ph	2m	96 (97:3)
7			91 (96:4)	14	1m R ¹ = H, R ² = Ph	2m	60 ^f (16:84)
				15	1n R ¹ = Ph, R ² = Me	2n	85 (86:14)
				16	1o R ¹ = Ph, R ² = H	2o	59 (54:46)
				17	1p R ¹ = Ph, R ² = Et	2p	93 ^d (95:5)
				18	1q R ¹ = Ph, R ² = <i>iso</i> -Pr	2q	83 ^d ($\geq 99:1$)
				19			94 ^e (97:3)

^a Isolated yield of the major diastereomer after silica gel chromatography, except for entries 10, 15, and 16 which were isolated as inseparable mixtures of diastereomers. ^b dr values were determined by ¹H NMR integration of the α -epoxide C–H's in the crude reaction mixture and/or GC analysis. ^c Reaction performed on 6.0 mmol of substrate scale. ^d 2.5 equiv of potassium allyltrifluoroborate was used to ensure full conversion. ^e The starting material was used as a mixture of epoxide diastereomers in a 93:7 ratio favoring the shown compound. The corresponding product was isolated in an identical ratio. ^f The diastereomeric product was obtained when Montmorillonite K10 is used instead of metallic indium. ^g The starting material was used as a mixture of enantiomers (er = 93:7, as determined by HPLC). The respective product was isolated with the same optical purity as determined by chiral HPLC.

of allylboronic acid under otherwise identical conditions failed to achieve full conversion to the desired product (Table 1, entry 14).²¹ Direct application of the protocol reported by Kobayashi occurred with diminished yield and selectivity (54%, crude dr 86:14).²⁰

The optimized conditions were then applied to a range of α,β -epoxy ketones to establish the generality of the protocol. In most cases examined the products **2** were obtained in excellent yields and good diastereoselectivity (Table 2). The reaction could be readily scaled with negligible effect on yield and dr (Table 2, entry 1). α -, β -, and γ -substitution on the epoxy ketones **1** was well tolerated (Table 2, entries 2–7). The steric constraints of the α -methyl group in **1c** did not result in a loss in dr,^{4e,11} but did necessitate a modest increase in the amount of allyltrifluoroborate salt required

to achieve full conversion within 24 h (Table 2, entry 3). Chemoselective allylation of the less sterically encumbered carbonyl group of **1f** occurred (Table 2, entry 6). The mild nature of the protocol is apparent from the good functional group tolerance achieved, such as with hydroxyl and acid labile dimethyl ketal groups previously shown to result in several side products using other organometallic reagents (Table 2, entries 7 and 8).²² Reaction of seven- and five-membered ring α,β -epoxy ketones **1i** and **1j** occurred in good yields (Table 2, entries 9 and 10), although the dr of **2j** was modest, favoring the *cis*-stereoisomer. For additions to cyclic six-membered ring α,β -epoxy ketones, the observed diastereoselectivity can be rationalized through attack of the nucleophile via a pseudoequatorial trajectory *syn* to the epoxide ring, matching well with conformational analy-

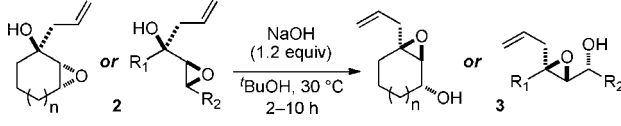
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ses,^{23,24} and steric and electronic factors previously examined.²⁵ The higher dr values observed for the formation of **2d** and **2f** are also consistent with this notion as well as reactions of the more conformationally rigid steroidal system **1g**. The reactions of **1h** and the cyclopentanone oxide **1j** occur through addition *anti* to the epoxide ring, presumably as a result of steric factors.²² Acyclic α,β -epoxy ketones could also be allylated by using the In protocol. Variation of the β -substituent in **1k–m** was found to have little effect upon the reaction (Table 2, entries 11–13). Interestingly, while the use of the Montmorillonite K10 promoted conditions^{16c} with epoxy ketones generally occurred with lower yields, a reversal of diastereoselectivity was observed for the reaction of **1m** (Table 2, entry 14). This result suggests that reaction occurs via a different allylation species under the In promoted conditions than the tricoordinate allylboron species that is postulated for the Montmorillonite K10 based protocol. Reaction via an allylindium species^{26,27} in a chelation-controlled manner may account for the selectivity difference, since chelation control does not for the direct addition of tricoordinate allylboron species. An increase in dr was observed as the steric bulk of the carbonyl substituent R² on **1k–q** increased (Table 2, entries 11 and 15–18). Reaction of enantiomerically enriched **1k**²⁸ occurred without loss of stereochemical fidelity (Table 2, entry 19). It is noteworthy that although a stoichiometric amount of indium was employed, it can be recovered and reused for further reactions.²⁰

The epoxy alcohols are useful intermediates for further transformations.⁶ For example, Payne rearrangement²⁹ of **2** afforded the more substituted epoxides **3** in excellent yields (Table 3). This also served to verify the *anti*-selectivity observed between the hydroxyl and oxirane moiety in both acyclic and cyclic substrates.³⁰ Overall, the two-step allylation–Payne rearrangement sequence allows for access to various structurally diverse *anti*-allylic epoxy alcohols which were, prior to this work, only accessible through limited means.³¹ Another useful demonstration of the utility of **2** is the semi-pinacol-type rearrangement³² of **2i** under

Table 3. Conversion of Compounds **2** to Substituted *anti*-Allylic Epoxy Alcohols **3**



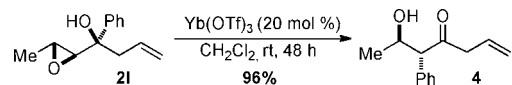
entry	substrate	product	yield (%) ^a
1	2a	3a	90
2	2c	3c	89 ^b
3	2i	3i	85
4	2l	3l	88
5	2m	3m	94

^a Isolated yield of the major compound after silica gel chromatography.

^b The starting material was used as a mixture of epoxide diastereomers in a 93:7 ratio favoring the shown compound. The corresponding product was isolated in an identical ratio.

Lewis acidic conditions to diastereoselectively afford the aldol-like ketone **4** (Scheme 1). Conventional aldol conditions

Scheme 1. Semi-Pinacol Rearrangement of Alcohol **2i**



would not be suitable for the synthesis of **4** due to the base lability of the β,γ -unsaturated ketone functionality.

In summary, an operationally straightforward procedure for the allylation of α,β -epoxy ketones using the stable potassium allyltrifluoroborate salt and In metal catalysis has been developed. The protocol shows good functional group tolerance, is readily scalable, and avoids the use of toxic reagents which have been required for the synthesis of **2**.¹⁰ The mild protocol solves the problems of chemoselective addition to α,β -epoxy ketones with reaction occurring in a highly diastereoselective fashion. Further studies on related diastereoselective transformations of **1–3** will be reported in due course.

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Supporting Information Available: Full experimental procedures, analytical data, and spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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