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Aryl λ³-Iodane-Mediated 6-*exo*-*trig* Cyclization to Synthesize Highly Substituted Chiral Morpholines

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Abstract: A mild and efficient transition metal-free approach has been developed for the synthesis of highly substituted chiral morpholines from alkenols by amino acid-derived iodine(III) reagents *via* a 6-*exo*-*trig* cyclization. The key features of this work include the formation of three chiral centers with a high diastereomeric ratio, broad functional group compatibility, and atom/time economic methodology.

Keywords: alkenes; 6-*exo*-trig cyclization; haloetherification; λ³-iodanes; morpholines

Over the past decades, hypervalent iodine has emerged as a powerful tool for several applications in organic chemistry.[1] It is mainly used as an oxidant or electrophilic reagent for the functionalization of alkenes in halolactonizations,[2] dioxytosylations,[3] α-functionalization of ketones,[4,5] and oxidative dearomatization of phenols.[6] In this context, the development of new and efficient hypervalent iodine reagents for organic transformations has emerged as an interesting area of research.[7] Zhdankin et al. synthesized amino acid-derived iodobenzene dicarboxylates from phenyliodonium diacetate (PIDA) and studied their application for the first time in the *anti* stereoselective α-iodocarboxylation of alkenes leading to amino acid esters (Figure 1a).[8] Thus far, this has been the only report on the application of amino acid-derived iodobenzene dicarboxylates. In the present study, we use amino acid-derived iodobenzene dicarboxylates for a new synthetic approach to construct 2,3,6-trisubsituted chiral morpholines *via* 6-*exo*-*trig* cyclization.

In particular, the synthesis of 2,3,6-trisubstituted chiral morpholines is highly desired owing to their

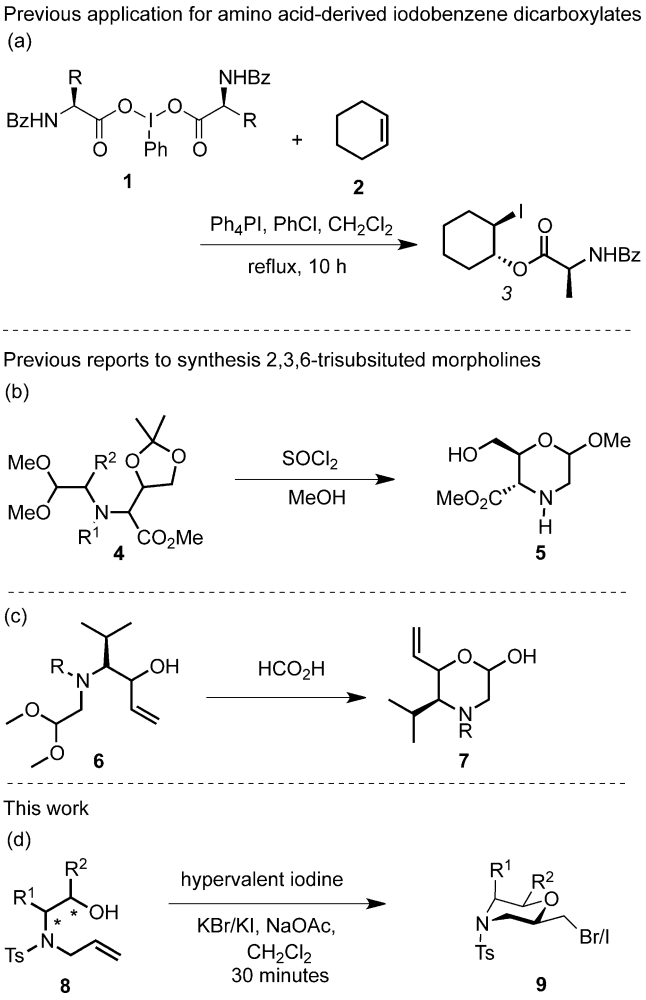


Figure 1. Synthesis of 2,3,6-trisubstituted morpholines and applications of hypervalent iodine reagents.

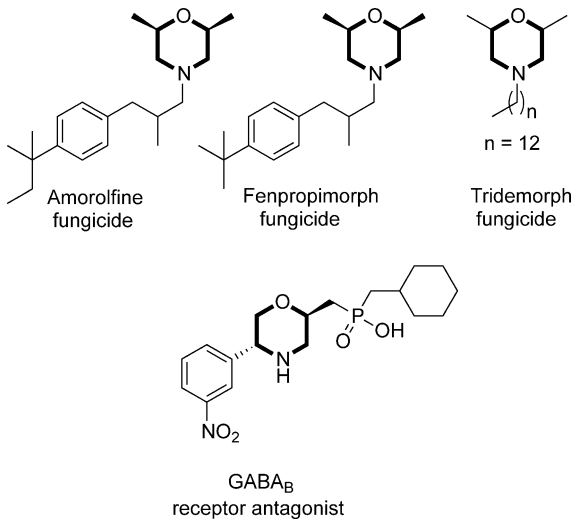


Figure 2. Biologically potent molecules.

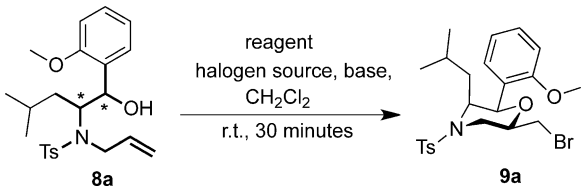
presence in a variety of pharmaceutical drugs and natural products;[9] moreover, they are used as key intermediates in organic synthesis.[10] Although many methods have been developed for the synthesis of morpholines (Figure 1b and c),[11,12] the exploitation of highly substituted chiral morpholines remains a challenging task. These scaffolds have a wide range of biological properties such as fungicidal and GABAB receptor antagonist properties (Figure 2).[13]

The amino-oxygenation or oxyamination process involves the simultaneous addition of oxygen and nitrogen across the double bond; this process has been studied extensively.[14] In contrast, the addition of oxygen and halogen across alkenes was less explored.[12b] Therefore, in this paper, we report a metal-free, mild, efficient, and time-economic method for the synthesis of 2,3,6-trisubstituted chiral morpholines promoted by amino acid-derived iodobenzene dicarboxylates from alkenols (Figure 1d).

The compound **8a** was synthesized from the respective chiral amino acid[15] and the stereochemistry was confirmed by 2D NMR and supported with DFT studies.[16] Synthesis of the starting material **8** from *N*-Boc and *N*-Cbz was not successful. The initial optimization studies were investigated with compound **8a** as a model substrate. After extensive optimization studies,[17] the reaction with PIDA, $CuBr_2$, and NaOAC afforded **9a** with 81% yield (Table 1, entry 1). The reaction with I_2 as a catalyst yielded a complex mixture (entry 2). Without PIDA or NaOAc, the reaction was not successful (entries 3 and 4). The reaction was efficient with other bromide sources such as $NiBr_2$ and KBr (entries 5 and 6). Finally, KBr was selected as the optimal bromide source owing to its economic and environmentally benign properties.

To improve the diastereomeric ratio, we used some chiral hyperiodine reagents identified in the literature.[8] Thus, the L-amino acid-derived iodine(III) reagents (Figure 3, **A**–**F**) were synthesized by the reported method,[8] and they were examined instead of PIDA. Interestingly, as compared to PIDA, the reactions worked well in good yields with increasing the diastereomeric ratios (entries 7, 8, and 12). In particu-

Table 1. Optimization reactions for synthesizing chiral morpholine derivatives.[a]



Entry	Reagent	Halide source	Base	Yield [%]	*dr*[b]
1	PIDA	$CuBr_2$	NaOAc	81	2:1
2[c]	I_2	–	–	–	–
3	–	$CuBr_2$	NaOAc	N.R	–
4	PIDA	$CuBr_2$	–	N.R	–
5	PIDA	$NiBr_2$	NaOAc	82	2:1
6	PIDA	KBr	NaOAc	84	2:1
7	**A**	KBr	NaOAc	87	10:1
8	**B**	KBr	NaOAc	92	16:1
9	**C**	KBr	NaOAc	90	2:1
10	**D**	KBr	NaOAc	88	2:1
11	**E**	KBr	NaOAc	86	2:1
12	**F**	KBr	NaOAc	89	16:1

[a] Compound **8a** (1 mmol), halide source (1 equiv.), reagent (1 equiv.), base (1 equiv.), and solvent (5 mL).
[b] Diastereomeric ratios were confirmed by ^{1}H NMR.
[c] Complex mixture.

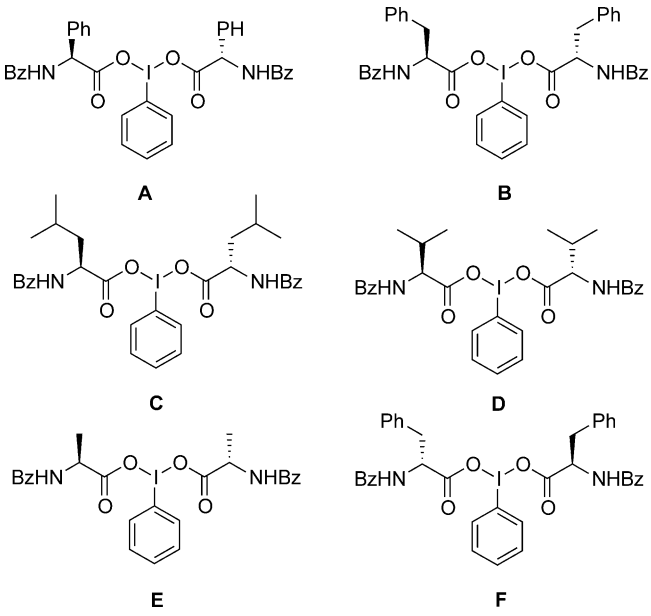
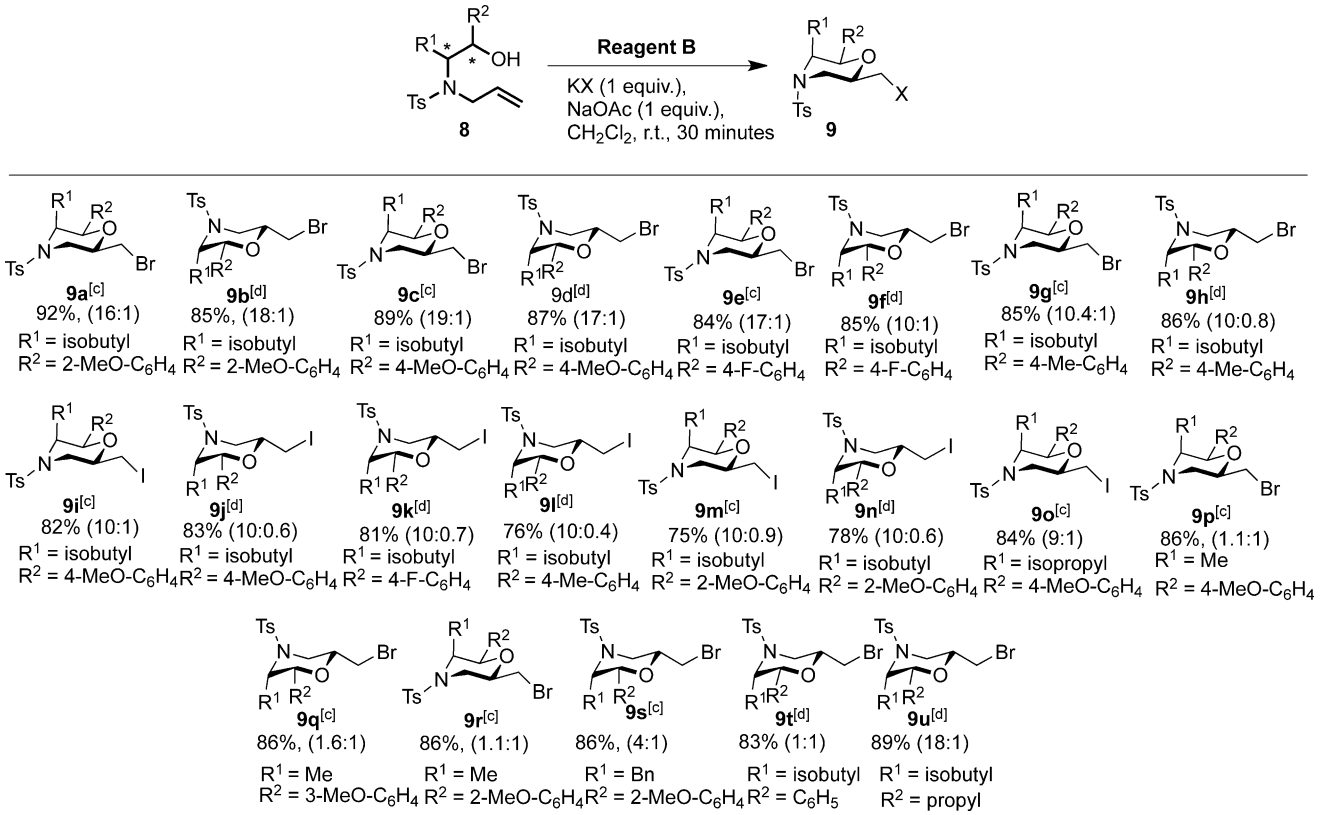


Figure 3. Amino acid-derived iodobenzene dicarboxylates.[8]

Table 2. Scope of the reaction.[a,b]



[a] Compound **8** (1 mmol), reagent **B** (1 equiv.), KX (X = Br or I) (1 equiv.), NaOAc (1 equiv.), and CH_2Cl_2 (5 mL).
[b] The *dr* values were determined by ^{1}H NMR.
[c] From the L-form of the amino acid starting material.
[d] From the D-form of the amino acid starting material.
[e] Starting material **8t** used as two isomers (1:1) asconfirmed by HPLC.

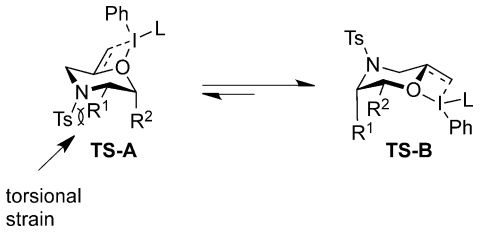
lar, the L-phenylalanine-derived iodine(III) reagent **B** produced 92% yield with a high diastereomeric ratio of 16:1 (entry 8). Other chiral PIDA reagents with aliphatic linkages were not efficient in providing high diastereomeric ratios (entries 9–11). Reagent **F** (entry 12) from D-phenylalanine also showed a high diastereomeric ratio, similar to reagent **B**.

The optimized conditions are shown in Table 1 (entry 8), and the scope of the reaction was studied in Table 2. The reactions worked well with various aryl and alkyl substituents at the C-2 position. Alkenols bearing electron-donating groups such as OMe and Me at the *ortho*, *meta*, and *para* positions on the phenyl ring produced the final compounds with good to high yields (**9a–9d** and **9g–9s**). The reactions of compound **8** with the electron-withdrawing group F at the *para* position of the phenyl ring gave the desired compounds with good yields (**9e**, **9f**, and **9k**). The reaction with a simple phenyl ring proceeded smoothly (**9t**). The propyl chain as alkyl substituent was successful with high yield (**9u**). The reaction worked well with halide sources such as bromo (**9a–9h** and **9p–9s**) and iodo (**9i–9o**) substituents.

The substituent at C-3 position influenced the diastereoselectivity ratio of the desired compounds. With the isobutyl chain, the diastereomeric ratios were high (**9a–9n**), whereas with the isopropyl chain, the ratios were relatively low (**9o**). The ratios were further decreased with the benzyl and methyl groups at the C-3 position (**9p** and **9s**).

The stereochemical outcome of morpholine formation was considered to proceed *via* a chair-like transition state in which the C-3 (R^1) substituent can be placed in a pseudoequatorial (**TS-A**) or pseudoaxial (**TS-B**) position.[18] However, the C-3 substituent adopts the energetically favored pseudoaxial position due to less torsional strain. The observed results were consistent with the above hypothesis, that the substituent at C-3 prefers the pseudoaxial over the pseudoequatorial position in the equilibrium. Next, the size of the groups at C-3 determines the diastereomeric ratio of the products, as shown in Table 3. When C-3 is replaced with a larger group, **TS-B** will be most favored conformation and it provides an excellent diastereomeric ratio. In contrast, the small

Table 3. Rationalism for selectivity.



Entry	C-3 (R^1 group) Substituent	*dr* ratios
1	isobutyl (**9c**)	19:1
2	isopropyl (**9o**)	9:1
3	benzyl (**9s**)	4:1
4	methyl (**9q**)	1.6:1

group at C-3 will be in equilibrium with **TS-A** and **TS-B**; this leads to a low diastereomeric ratio.

The relative stereochemistry of the major diastereomer of compound **9b** was assigned unambiguously with the help of NOESY experiments and X-ray crystallography.[19] All other 2,3,6-trisubstituted morpholine (major) products were assigned by analogy. The hydrogen interaction of compound **9b** was confirmed by 2D NMR, as shown in Figure 4.

From the literature, we were aware that hypervalent iodine reagents can decompose into other iodo species such as AcOI[20a] and $TBAI(OAc)_2$.[20b] Therefore, some control experiments were conducted to understand the stability of reagent **B** under the optimized conditions, as shown in Scheme 1. Thus, reagent **B** was reacted with NaOAc, KBr, or KI in CH_2Cl_2 at room temperature for 24 h (Scheme 1a), and the reaction without KBr or KI was also performed (Scheme 1b). In both the reactions, reagent B was not decomposed and its structure was confirmed by NMR.

A plausible mechanism was proposed to synthesize compound **9** from an alkenol in Scheme 2, based on the results obtained from previous reports.[21] The electrophilicity of the alkene was enhanced by coordination with chiral reagent **B** to give intermediate **10**. Then, intermediate **10** underwent an intramolecular 6-*exo-trig* cyclization to afford intermediate **11**. Finally, intermediate **11** reacted with a halide source, yielding the desired compound **9** with the expulsion of iodobenzene and *N*-benzoylphenylalanine *via* an intermolecular substitution reaction.

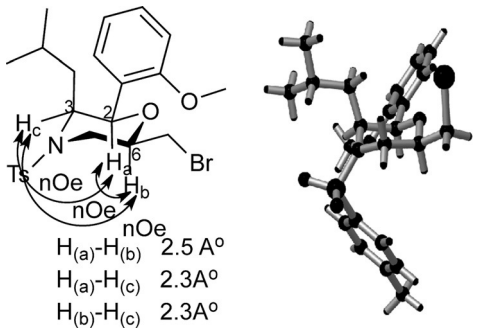
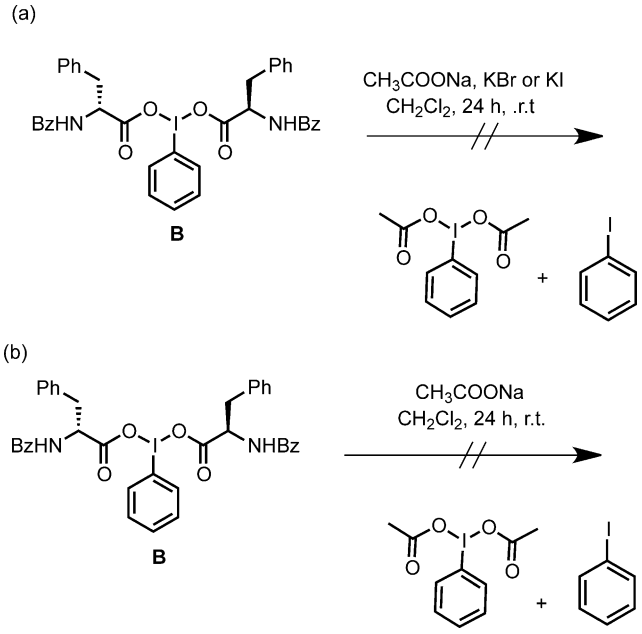


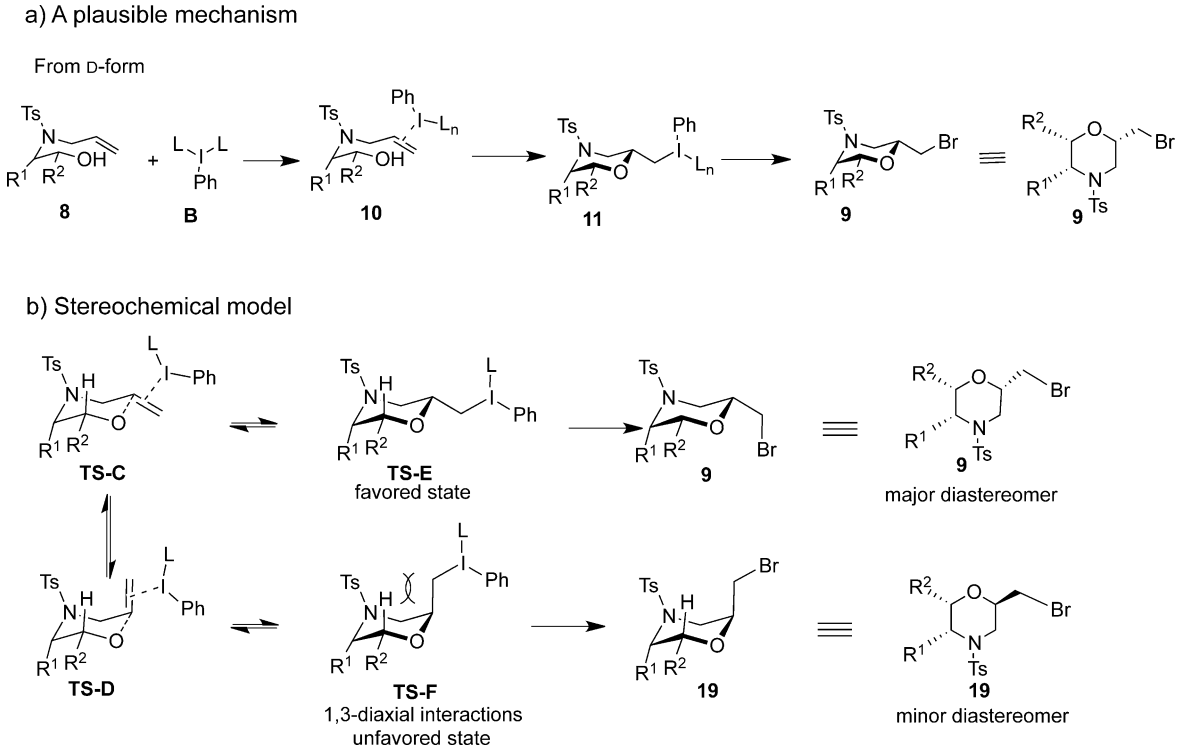
Figure 4. NOESY for determining the H-bond interactions of **9b**.



Scheme 1. Control experiments.

The probable interpretation of the observed stereoselectivity is thermodynamic control, and this arises because of the difference in the stability of chair-like transition states **TS-C** and **TS-D**, and/or **TS-E** and **TS-F** (Scheme 2).[22] The olefin or iodo species in **TS-D** and **TS-F** occupies a pseudoaxial position, which will enforce unfavorable 1,3-diaxial interactions. These diaxial interactions favor equilibria towards **TS-C** and **TS-E**. However, the degree of the interactions for aryl ligands is high and prefers **TS-C** or **TS-E**, which leads to a high diastereomeric ratio. The observed results were consistent with our speculations, and the stereochemical outcome from **TS-C** and **TS-E** both led to a major diastereomer (compound **9**), whereas **TS-D** and **TS-F** generated a minor diastereomer (compound **19**).

In conclusion, a transition metal-free, simple, and efficient method for synthesizing biologically important 2,3,6-trisubstituted morpholines *via* a 6-*exo-trig* cyclization has been explored with an amino acid-derived iodine(III) reagent. The relative configuration of compound **9** was confirmed *via* X-ray and 2D NMR studies. The key advantages of the proposed approach are broad functional group compatibility, steric-based diastereoselectivity, and atom/time economy.



Scheme 2. A plausible mechanism and model for the stereoselective morpholine synthesis.

Experimental Section

Typical Experimental Procedure for the Synthesis of Compound 9

A mixture of compound **8** (0.1 g, 1 mmol), amino acid-derived iodobenzene dicarboxylate (**B**) (1 mmol), KBr/KI (1 mmol), and sodium acetate (1 mmol) in CH_2Cl_2 (10.0 mL) was stirred at room temperature under open atmosphere conditions in a round-bottom flask for 30 min. The reaction was monitored by TLC, and then, water was added. Next, the mixture was extracted with dichloromethane; the combined organic phases were dried over Na_2SO_4 (anhydrous) and concentrated under vacuum, and the resulting residue was purified by column chromatography on silica gel with EtOAc/hexane (1/10) to afford the desired product **9**.

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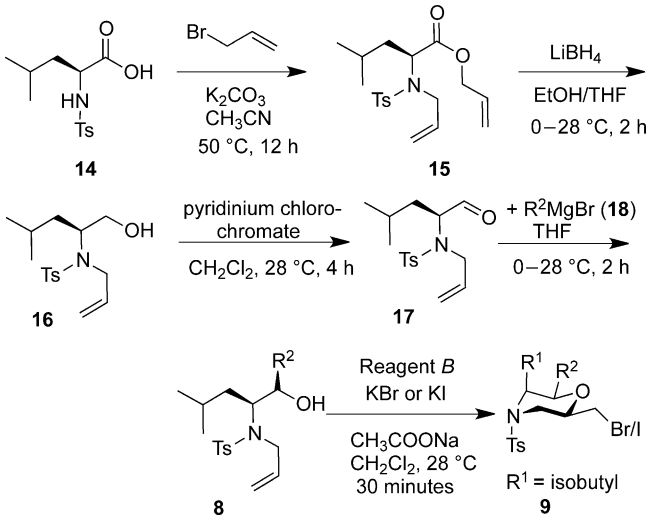
[15] General scheme for the synthesis of compound **9**:



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