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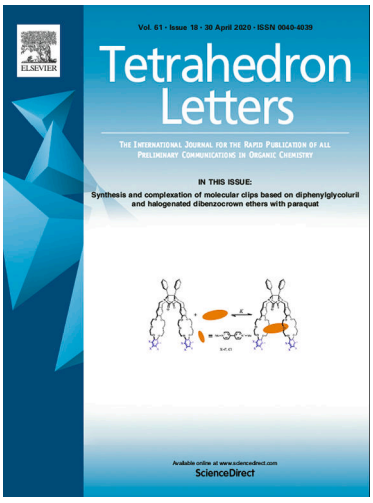

Stereoselective Approach to Access 3-*tert*-Butyl-Dimethylsiloxy-2,6-Substituted Piperidines Through Nucleophilic Addition of *N,O*-acetals with Organozinc Reagents

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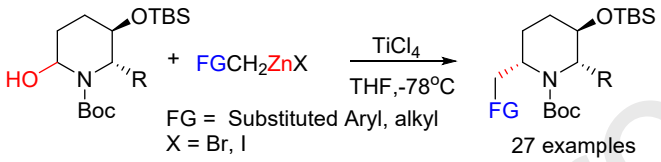

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Stereoselective Approach to Access 3-*tert*-Butyl-Dimethylsiloxy-2,6-Substituted Piperidines Through Nucleophilic Addition of *N,O*-acetals with Organozinc Reagents

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ABSTRACT

An efficient approach to access chiral 3-*tert*-butyl-dimethylsiloxy 2,6-disubstituted 6-benzyl piperidines was developed through nucleophilic addition of *N,O*-acetals with organozinc reagents. A number of substituted benzyl zinc reagents could react with *N,O*-acetals **6a-6e**, affording the desired products **7a-7j** and **9a-9q** in good to excellent yields and with high diastereoselectivities.

The development of efficient methods to access privileged structural motifs is one of the most important tasks in contemporary organic chemistry.[1-2] As a prime instance, 3-hydroxy 2,6-disubstituted piperidines/3-hydroxy 2,5-disubstituted pyrrole exist as subunits for many natural products[3] and biologically active molecules in life-science industry.[4] Some representative pyrrolidine and piperidine alkaloids are shown in **Figure 1**, which include hyacinthacine B_5 (**1**),[5] (-)-morusimic acid D (**2**),[6] (-)-sedacryptine (**3**),[7] (-)-azimine (**4**)[8] and (-)-carpaine (**5**).[9] Due to the divergent activities and attractive

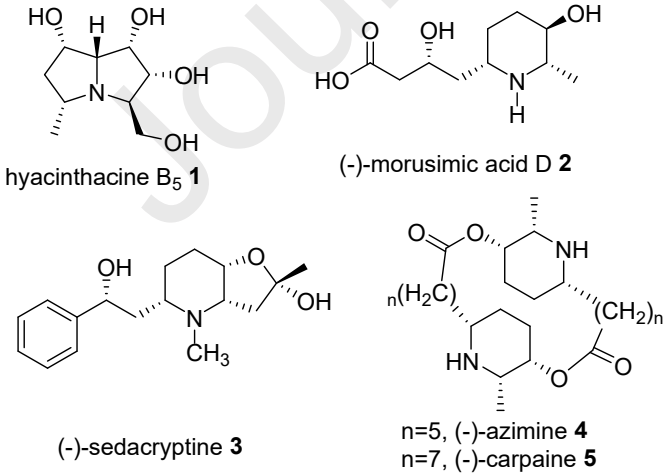


Figure 1. Representative 2,6-disubstituted piperidine/2,5-disubstituted pyrrole alkaloids.

structures, asymmetrically synthetic approaches to these natural products and their analogies have attracted wide attention and a number of powerful approaches have been reported.[5-9,13] Particularly, it is very difficult to selectively introduce the substituents to C-6/C-5 position for piperidine or pyrrole skeleton.[3,6c,10-13] Although a number of powerful approaches including one-pot successive addition- reduction process of imide (Figure 2, eq.1)[11], or nucleophilic substitution of silyl enol ether[12a] or organoboron reagent[12b] with *N,O*-acetal (Figure 2, eq.2) have been achieved in past decade, the direct method to introduce the substituents at C-6/C-5 position of piperidine or pyrrole skeleton is still a challenging work. For examples, the former needs a harsh reaction condition, the latter has limited substrate scope. Recently, our group have established approach to 3-hydroxy-2,6-disubstituted piperidine scaffold through one–pot Mannich process of *N,O*-acetal with ketone (Figure 2, eq.3)[13]. To our best knowledge, there is no direct way to introduce benzyl substituents in C-6/C-5 position for piperidine or pyrrole. In the past decade, functionalized organozinc reagents, which are generally prepared through insertion reaction of zinc metal into various substituted organic halides, have demonstrated advantages for many transformations in modern organic synthesis.[14] For example, functionalized organozinc reagents were successfully applied in single-step reactions with *N,O*-acetals by Konakahara and our group,[15] carbonyl,[16] nitrones,[17] as well as in cascade process like addition-elimination[18] or addition-migration.[19] Encouraged by our previous work on *N,O*-acetals (Fig. 2, eq. 1-2),[12,13,15b] we envisioned that the chiral 3-*tert*-butyl-dimethylsiloxy-2-substituted 6-benzyl piperidine scaffold **7** could be prepared through the nucleophilic substitution process of *N,O*-acetal **6** with functionalized organozinc reagents (Fig.2, eq. 4).

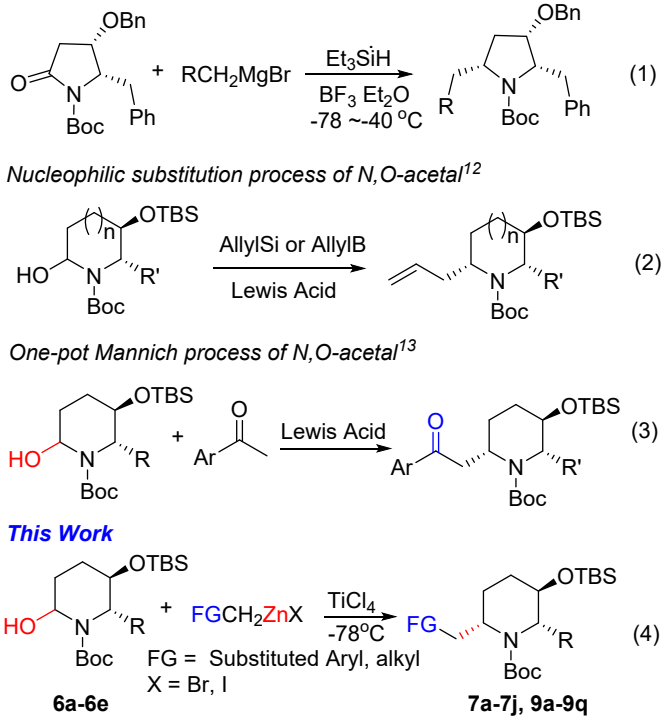
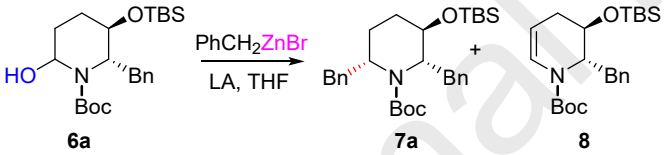


Figure 2. Our strategy to access chiral 3-*tert*-butyl-dimethylsiloxy-2-substituted 6-benzyl piperidine scaffold.

The substrate, chiral *N,O*-acetal (*5R,6S*)-**6a**, was readily prepared according to our previous intramolecular tandem sequence of the *α*-chiral aldimine with Grignard reagents[20] and the known reduction procedure.[21] When **6a** was treated with benzylzinc bromide in the presence of $BF_3{\cdot}OEt_2$ at -78 °C for 12 h, the desired product **7a** was obtained in 44% yield, albeit with low diastereoselectivity (Table 1, entry 1). To improve the reaction yield and diastereoselectivity, various Lewis acids were

Table 1. Optimization of reaction conditions.



Entries[a]	LA (equiv.)	Y% (**7a**)[b]	Y% (**8**)[b]	*dr* (**7a**)[c]
1	$BF_3{\cdot}Et_2O$ (2.0)	44	-	64:36
2	$SnCl_4$ (2.0)	-	-	-
3	$AlCl_3$ (2.0)	34	-	94:6
4	TMSOTf (2.0)	84	-	>99:1
5	TMSCl (2.0)	96	-	>99:1
6	$TiCl_4$ (2.0)	99	-	>99:1
7	$TiCl_4$ (1.0)	76	-	>99:1
8	$Tm(OTf)_3$ (0.2)	-	75%	-
9	$Pr(OTf)_3$ (0.2)	-	70%	-
10	$Nd(OTf)_3$ (0.2)	-	60%	-
11	$Ce(OTf)_3$ (0.2)	-	78%	-

[a] The reactions were performed with **6a** (100 mg), $PhCH_2ZnBr$ (4 eq.) and LA in THF (1 mL) at -78 °C for 12 h. The reaction was quenched with saturated $NaHCO_3$ solution and diluted with EtOAc.

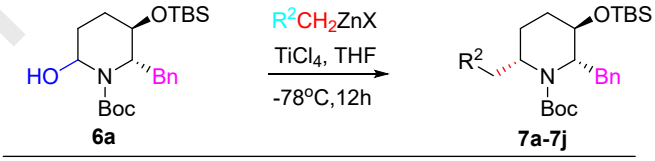
[b] Isolated yield.

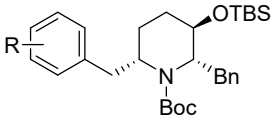
[c] *dr* was determined by ^1H NMR.

eral Lewis acids except $SnCl_4$ could afford the desired product (Table 1, entries 2-6), and $TiCl_4$ turned out to be the best one, producing **7a** not only in extremely high yield (up to 99%), but also with excellent diastereoselectivity (Table 1, entry 6). Decreasing the use of $TiCl_4$ to 1 eq. resulted in significant drop for the reaction yield although high diastereoselectivity of **7a** was maintained (Table 1, entry 7). Lanthanide salts like $Tm(OTf)_3$, $Pr(OTf)_3$, $Nd(OTf)_3$ and $Ce(OTf)_3$ proved to be ineffective for this transformation, instead an olefin by-product **8** was generated (Table 1, entries 8-11).

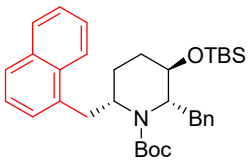
Next, we turned to investigate the scope and limitation of the nucleophilic addition of *N,O*-acetal **6a** by organozinc reagents (**Table 2**). Different substituted (methyl, fluoro, trifluoromethyl and chloro) benzylzinc bromides were surveyed under the optimal conditions, as summarized in Scheme 1. In general, the reactions of *N,O*-acetal **6a** with *ortho*-, *meta*- and *para*-substituted benzylzinc reagents underwent smoothly, affording the desired 3-*tert*-butyl-dimethylsiloxy-2,6-disubstituted piperidines **7b-7j** in moderate to excellent yields and with high diastereoselectivities. It is worth mentioning that cyano substitution was tolerated and the corresponding product **7h** was obtained in 72% yield (*dr* > 99:1). When chloro substituted zinc reagent was used, the desired product **7g** was also produced in excellent yield and with high diastereoselectivity. Notably, allyl zinc bromide and α-naphthalene methyl zinc bromide also showed good reactivities in this transformation, though affording the desired products **7i** and **7j** with slightly lower diastereoselectivities.

Table 2. The scope of this method to 3-*tert*-butyl-dimethylsiloxy-2,6-disubstituted piperidines **7a-7j**[a-c].

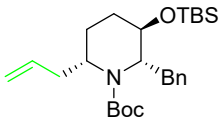




7a, R = H, 99%, *dr* > 99:1
7b, R = 2-CF_3, 96%, *dr* > 99:1
7c, R = 3-CF_3, 87%, *dr* > 99:1
7d, R = 4-Me, 97%, *dr* > 99:1
7e, R = 4-CF_3, 80%, *dr* > 99:1
7f, R = 3-Me, 69%, *dr* > 99:1
7g, R = 3-Cl, 90%, *dr* > 99:1
7h, R = 4-CN, 72%, *dr* > 99:1



7i, 71%, *dr* = 90:10



7j, 70%, *dr* = 85:15

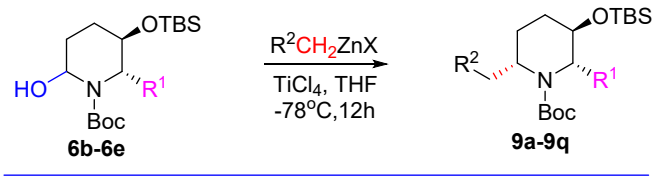
[a]The reactions were performed with **6a** (100 mg), $FGCH_2ZnX$ (4 eq.) and $TiCl_4$ (2 eq.) in THF (1 mL) at -78 °C for 12 h. The reaction was quenched with saturated $NaHCO_3$ solution and diluted with EtOAc.

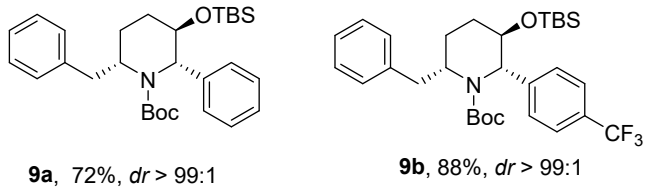
[b] Isolated yield.

[c] *dr* was determined by ^1H NMR.

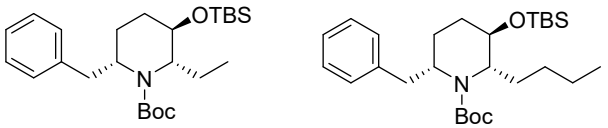
Then, the scope and limitation of different *N,O*-acetals **6b-6e** were explored and the results are summarized in **Table 3**. Different *N,O*-acetals **6b-6e** were surveyed under the optimal conditions, all of them reacted smoothly with various benzyl zinc reagents, affording the desired 3-*tert*-butyl-dimethylsiloxy-2,6-disubstituted piperidines **9a-9p** in moderate to excellent yields and with high diastereoselectivities. Consistent with previous research, when allyl zinc reagent was used, the desired product **9q** was also produced with lower diastereoselectivities (*dr* = 65:35).

Tab
2,6-disubstituted piperidines **9a-9q**[a].

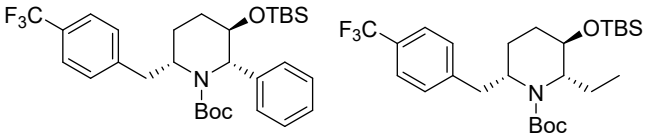




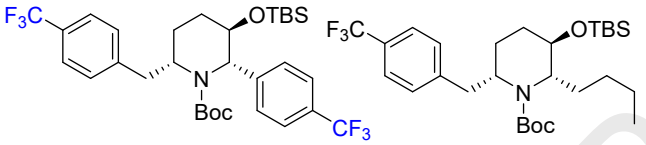
9a, 72%, *dr* > 99:1 **9b**, 88%, *dr* > 99:1



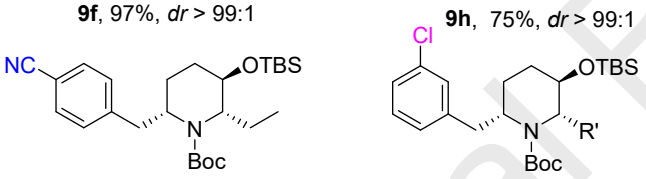
9c, 92%, *dr* > 99:1 **9d**, 73%, *dr* > 99:1



9e, 75%, *dr* > 99:1 **9g**, 77%, dr > 99:1

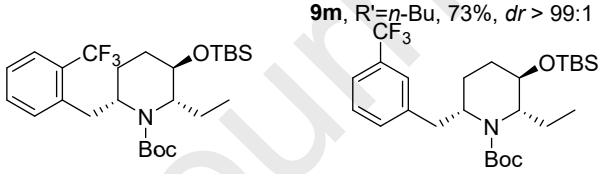


9f, 97%, *dr* > 99:1 **9h**, 75%, *dr* > 99:1

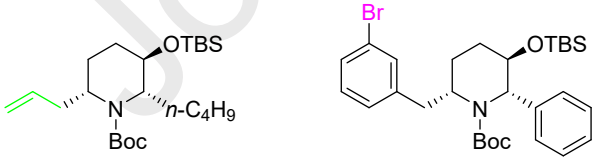


9i, 99%, *dr* > 99:1

9j, R'=Ph, 73%, *dr* > 99:1
9k, R'=4-CF_3Ph, 98%, *dr* > 99:1
9l, R'=C_2H_5, 74%, *dr* = 85:15
9m, R'=*n*-Bu, 73%, *dr* > 99:1



9n, 90%, *dr* > 99:1 **9o**, 80%, *dr* > 99:1



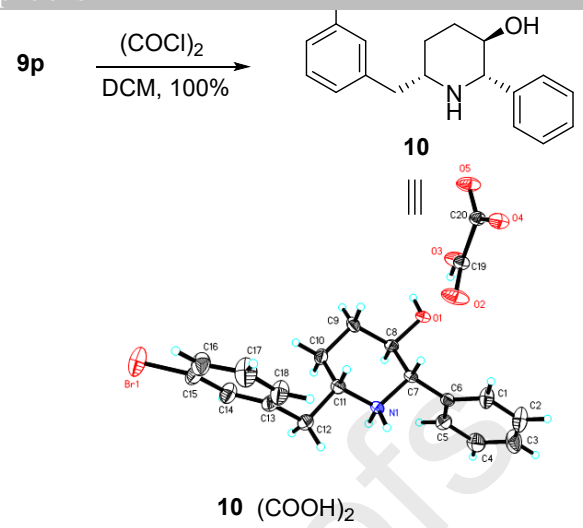
9q, 50%, *dr* = 65:35 **9p**, 98%, *dr* > 99:1

[a]The reactions were performed with **6b-6e** (100 mg), $FGCH_2ZnX$ (4 eq.) and $TiCl_4$ (2 eq.) in THF (1 mL) at -78 °C for 12 h. The reaction was quenched with saturated $NaHCO_3$ solution and diluted with EtOAc.

[b] Isolated yield.

[c] *dr* was determined by ^1H NMR.

The attempts to obtain single crystal for **9p** were unsuccessful, fortunately the oxalic acid salt of deprotected compound **10** could afford good co-crystal (Scheme 1), from which the stereochemistry of **9p** was unambiguously assigned as 2,6-*cis*-form based on its X-ray crystallography[22] (see Supporting Information).



Scheme 1. Synthesis of **10**.

A possible mechanism for this nucleophilic addition was illustrated in **Figure 3**. When *N,O*-acetal **6a** reacted with organic zinc, imide onium was first generated under Lewis acid conditions. Conformation **a** is more stable than **b** due to the smaller steric hindrance between OTBS and Bn. Then, the organic zinc would take place from the less steric side of form **c** to generate *cis*-product **7a**.

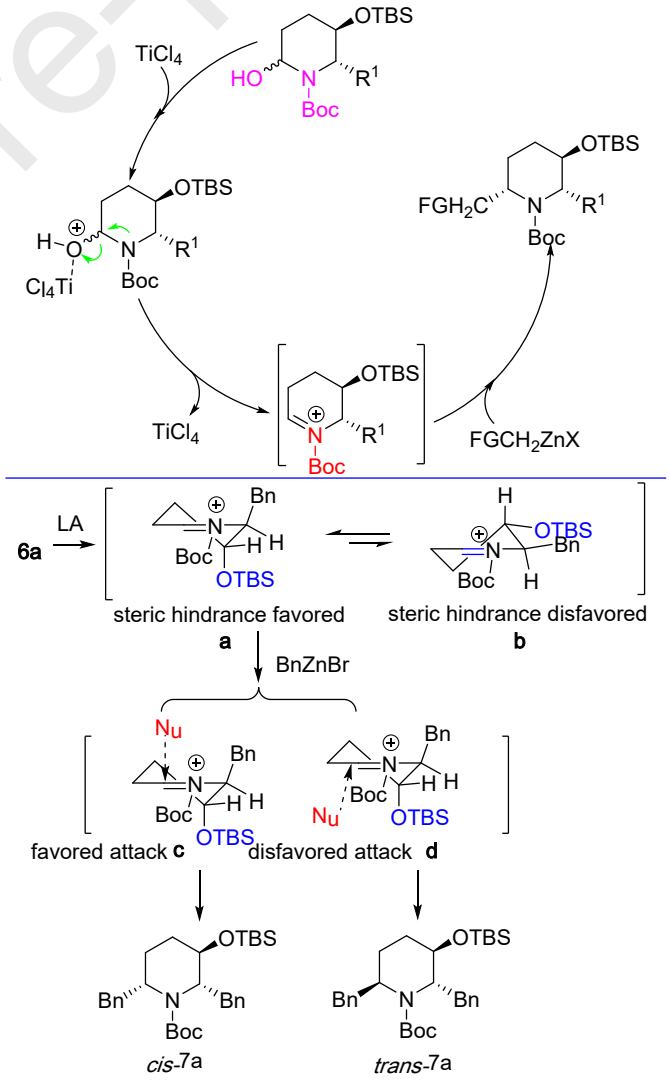


Figure 3. Proposed mechanism of the nucleophilic addition.

In summary, we have established a novel and practical approach for the synthesis of chiral 3-*tert*-butyl-dimethylsiloxy-

nucleophilic addition of *N*,O-acetals **6a-6e** with organozinc reagents. $TiCl_4$ was found to be the most effective lewis acid for this transformation, and a variety of chiral 3-*tert*-butyl-dimethylsiloxy-2-substituted 6-benzyl piperidines were successfully synthesized in moderate to excellent yields and with high diastereoselectivities. To the best of our knowledge, the present process is the first direct method for the preparation of chiral 3-*tert*-butyl-dimethylsiloxy-2-substituted 6-benzyl piperidines.

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22. CCDC 1990470 contains the supplementary crystallographic data for this paper.

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronicfile. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal

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the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

3-*tert*-butyl-dimethylsiloxy 2,6-disubstituted 6-benzyl piperidines

- Nucleophilic addition of *N,O*-acetals with organozinc reagents
- $TiCl_4$ was found to be the most effective

lewis acid for this transformation

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Stereoselective Approach to Access 3-*tert*-Butyl-Dimethylsiloxy-2,6-Substituted Piperidines Through Nucleophilic Addition of *N,O*-acetals with Organozinc Reagents

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