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# Diastereoselective formation of aziridines from diazocarbonyl compounds and *N*-(*O*-pivaloylated D-galactosyl)benzylideneamines and ring-opening reactions with *p*-toluenethiol†

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***N*-Galactosyl aziridines were synthesized *via* $BF_3{\cdot}OEt_2$ promoted addition of carbenes generated from diazocarbonyl compounds with *O*-pivaloylated β-D-galactosylimines in good yields and high diastereoselectivity. The ring-opening reactions with *p*-toluenethiol of the aziridines provided enantiometrically pure β-S-substituted phenylalanine derivatives in a highly regioselective manner.**

Aziridines are among the most versatile intermediates in organic synthesis as precursors to many biologically active molecules, because of their high reactivity due to the strain energy of the three-membered ring.[1] As a consequence, much effort has been devoted to the synthesis and ring-opening reactions of aziridines.[2] The addition of carbenes formed from diazo compounds with imines, which has many advantages such as good yields, operational simplicity and high stereoselectivity, is a highly attractive method for the synthesis of aziridines.[3] In recent years, chiral aziridines have been obtained by either asymmetric catalysis or chiral auxiliary-assisted reactions.[4] In particular, chiral auxiliaries have been successfully used to prepare chiral aziridines with moderate to high diastereoselectivity.[5]

Sugars have been considered as a useful tool for asymmetric synthesis because of the chiral environment constituted by the sugar scaffold,[6] and they play an important role in synthetic organic chemistry as chiral building blocks, especially in natural product synthesis.[7] One successful example of this type of chiral agent is the per-*O*-pivaloylated galactosyl amine first introduced by Kunz's group. It generated excellent results in the asymmetric Strecker reaction,[8] Ugi reaction,[9] Mannich reaction,[10] Michael addition reaction,[11] aza-Friedel–Crafts reaction,[12] and Povarov-like reaction.[13] Furthermore, per-*O*-pivaloylated galactosyl amine has also been successfully employed in a number of reactions, giving rise to homoallyl amines, β-amino acids, aminophosphonic acids, and natural products such as nupharamine,[14] in moderate to excellent diastereomeric excess.

The advantage of preparing aziridines with the assistance of per-*O*-pivaloylated galactosyl amine is that a series of non-natural amino acid derivatives can be obtained by ring-opening reactions. Such derivatives with novel side chains would be useful for the investigation of the stereochemical requirements of side chain groups in peptide ligand–receptor/acceptor interactions.[15] Especially, β-S-substituted phenylalanine derivatives have been shown to be potent DPP-IV inhibitors for the treatment of type 2 diabetes mellitus.[16] Furthermore, some tripeptides containing β-substituted phenylalanine derivatives act as structural analogues of HIV protease inhibitors.[17] The ring-opening conditions for aziridines carrying an *N*-electron-withdrawing protecting group, such as Cbz, Ts, Boc, Piv, or Ac, are well established.[18] However, to the best of our knowledge, it remains difficult to open the *N*-alkyl (in particular, galactosyl) substituted aziridines.[2f,19]

Herein, we report a $BF_3{\cdot}OEt_2$ catalyzed reaction of diazocarbonyl compounds with *O*-pivaloylated β-D-galactosylimines, through which aziridines can be obtained with high diastereoselectivity. The subsequent ring-opening reaction of the ensuing aziridines with *p*-toluenethiol provided enantiometrically pure β-S-substituted phenylalanine derivatives in excellent regioselectivity.

We initially investigated the most suitable Lewis acid catalyst and solvent for the reaction of *O*-pivaloylated *N*-galactosylimine **1a** and ethyl diazoacetate **2a** (1.5 equiv.). The results showed that zinc triflate, tin tetrachloride, titanium tetrachloride, copper triflate, aluminium trichloride and indium trichloride gave lower yields of the product **3a** than $BF_3{\cdot}OEt_2$ (Table 1, entries 3 and 7–12). Therefore, $BF_3{\cdot}OEt_2$ was selected as the most suitable Lewis acid to catalyze this reaction. When the catalyst loading was decreased to 0.1 or 0.2 equiv., the yields

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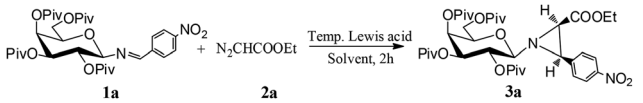
**Table 1** Optimization of the conditions for the reaction of *O*-pivaloylated *N*-galactosylimines and ethyl diazoacetate[a]



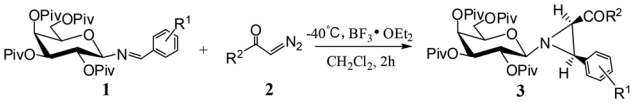

| Entry | Lewis acid | Lewis acid (equiv.) | Temp. (°C) | Solvent | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $BF_3{\cdot}OEt_2$ | 0.5 | 0 | $CH_2Cl_2$ | 69 |
| 2 | $BF_3{\cdot}OEt_2$ | 0.5 | −20 | $CH_2Cl_2$ | 67 |
| 3 | $BF_3{\cdot}OEt_2$ | 0.5 | −40 | $CH_2Cl_2$ | 80 |
| 4 | $BF_3{\cdot}OEt_2$ | 0.5 | −60 | $CH_2Cl_2$ | 78 |
| 5 | $BF_3{\cdot}OEt_2$ | 0.1 | −40 | $CH_2Cl_2$ | 59 |
| 6 | $BF_3{\cdot}OEt_2$ | 0.2 | −40 | $CH_2Cl_2$ | 71 |
| 7 | $Zn(OTf)_2$ | 0.5 | −40 | $CH_2Cl_2$ | 5 |
| 8 | $SnCl_4$ | 0.5 | −40 | $CH_2Cl_2$ | 56 |
| 9 | $TiCl_4$ | 0.5 | −40 | $CH_2Cl_2$ | 52 |
| 10 | $Cu(OTf)_2$ | 0.5 | −40 | $CH_2Cl_2$ | 57 |
| 11 | $AlCl_3$ | 0.5 | −40 | $CH_2Cl_2$ | 47 |
| 12 | $InCl_3$ | 0.5 | −40 | $CH_2Cl_2$ | 46 |
| 13 | $BF_3{\cdot}OEt_2$ | 0.5 | −40 | Toluene | 70 |
| 14 | $BF_3{\cdot}OEt_2$ | 0.5 | −40 | THF | 57 |
| 15 | $BF_3{\cdot}OEt_2$ | 0.5 | −35[c] | $Cl(CH_2)_2Cl$ | 44 |
| 16 | $BF_3{\cdot}OEt_2$ | 0.5 | −40 | $CHCl_3$ | 67 |
| 17 | $BF_3{\cdot}OEt_2$ | 0.5 | −40 | $CH_3CN$ | 40 |
| 18 | $BF_3{\cdot}OEt_2$ | 0.5 | −20[d] | $PhCF_3$ | 53 |

[a] Reactions were carried out with 0.15 mmol of **1a**. [b] Isolated yield after column chromatography. [c] The melting point of $Cl(CH_2)_2Cl$ is −40 °C. [d] The melting point of $PhCF_3$ is −29 °C.

decreased obviously (Table 1, entries 5 and 6). The optimal reaction temperature was −40 °C, and we found that either increasing or decreasing the temperature resulted in lower yields (Table 1, entries 1–4). We next identified the most suitable solvent for the reaction of **1a** and **2a**. The reaction in toluene, tetrahydrofuran, 1,2-dichloroethane, chloroform, acetonitrile and toluenetrifluoride produced **3a** in lower yields than in dichloromethane (Table 1, entries 13–18). We also found that the diastereoselectivity of the reaction was excellent (Table 2, entry 1). Therefore, the optimal conditions were identified to be 0.5 equiv. $BF_3{\cdot}OEt_2$ and 1.5 equiv. **2** in dry dichloromethane at −40 °C for 2 h.

Under these optimal conditions, the reaction of diazo acetate **2a** with other aryl-substituted *N*-(galactosyl) benzylideneamines **1** was examined. The results are summarized in Table 2. We found that *O*-pivaloylated β-D-galactosyl imines **1**, bearing electron-withdrawing groups such as nitro-, cyano- and halogen element groups, produced the corresponding asymmetric aziridines in moderate to good yields and good to excellent diastereoselectivities. With imines **1** bearing *o*-chloro substituent the usual aziridines **3** still occurred in good yield but with a relatively low diastereoselectivity (Table 2, entries 8 and 9). However, no aziridine product was obtained in the presence of a *p*-methoxyl group (Table 2, entry 7), which was also reported in previous work.[20] Additionally, when the imine **1a** was reacted with diazo acetophenone, the desired galactosylaziridine was similarly formed with excellent diastereoselectivity, though to a significantly lower extent (Table 2, entries 1 and 11).

**Table 2** The reaction of *O*-pivaloylated *N*-galactosylimines with diazo compounds[a]




| Entry | $R^1$ | $R^2$ | Yield[b] (%) | dr[c] | ee[d] (%) |
|---|---|---|---|---|---|
| 1 | *p*-$NO_2$ | OEt | 80 | >99 : 1 | >99 |
| 2 | *p*-F | OEt | 88 | 57 : 1 | 97 |
| 3 | *p*-Cl | OEt | 76 | 42 : 1 | 95 |
| 4 | *p*-Br | OEt | 75 | 70 : 1 | 91 |
| 5 | *p*-CN | OEt | 70 | >99 : 1 | >99 |
| 6 | *p*-$CF_3$ | OEt | 72 | 30 : 1 | 83 |
| 7 | *p*-$OCH_3$ | OEt | 0 | — | — |
| 8 | *o*-Cl | OEt | 77 | Low | — |
| 9 | 2,4-Di-Cl | OEt | 80 | Low | — |
| 10 | 3,4-Di-Cl | OEt | 71 | 76 : 1 | >99 |
| 11 | *p*-$NO_2$ | $C_6H_5$ | 50 | >99 : 1 | >99 |

[a] Reactions were carried out with 0.15 mmol of **1**. [b] Isolated yield after column chromatography. [c] *cis* : *trans*, determined by a $^1$H NMR spectrum of the product by integration of aziridine methine protons. [d] Determined by chiral HPLC.

The ratio of *cis*/*trans* isomers of the product **3** was determined using a $^1$H NMR spectrum. The results showed that only the *cis* product was obtained in most cases. The HPLC analysis indicated that a diastereomerically pure product **3** was obtained without further purification.

To further characterize the absolute configuration of the *cis* products, X-ray diffraction analysis of a single crystal of **3a** was performed. The crystal structure of **3a** (Fig. 1) shows that the absolute configuration of the main isomer is (2*R*,3*S*), in agreement with the $^1$H NMR spectrum.

In order to explain the *cis* stereoselectivity of this process, we propose the mechanism depicted in Scheme 1. The attack of $BF_3$ on the diazoacetate produces a zwitterion which reacts with the imine to give an iminium ion. The consequent intramolecular ring-closing step occurs *via* path a to provide the *cis* stereoselectivity. On the other hand, path b is not favoured because of the large steric interactions between the ester group and the *N*-chiral auxiliary of the imine.[22]

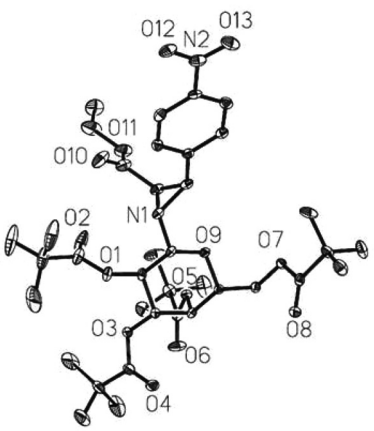
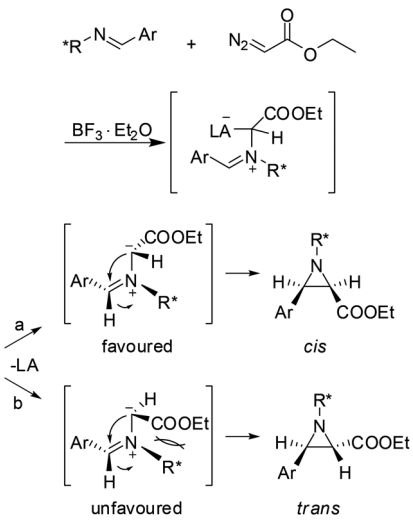
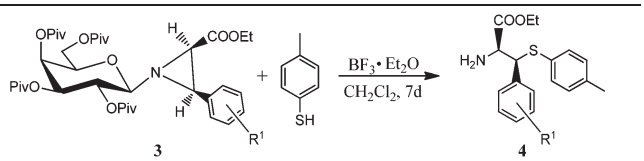



**Fig. 1** X-ray structure of the product **3a**.[21]




**Scheme 1** Proposed mechanism for $BF_3{\cdot}OEt_2$-catalysed addition of diazoacetoacetates to imines.

**Table 3** The ring-opening reaction accompanied with the release of the chiral auxiliary[a]



| Entry | $R^1$ | Yield[b] (%) |
|---|---|---|
| 1 | *p*-$NO_2$ | 62 |
| 2 | *p*-F | 63 |
| 3 | *p*-Cl | 64 |

[a] Reactions were carried out with 2.0 equiv. of 4-methylbenzenethiol and 1.3 equiv. of $BF_3{\cdot}OEt_2$. [b] Isolated yield after column chromatography.

To our surprise, the glycosidic C–N bond was much more stable than anticipated, which was demonstrated by the unfruitful cleavage of the chiral auxiliary using established methods.[8–14,23] Therefore, we started to test different reagents to remove the sugar moiety, which included hydrogen fluoride-pyridine, hydrobromic acid in acetic acid, or indole, methylmagnesium bromide, diethyl malonate, cyclohexane-1,3-dione, TMSCN, and $TMSN_3$ in the presence of a Lewis acid. Unfortunately, all of the above reagents failed to remove the sugar moiety. Finally, the sugar was cleaved using *p*-toluenethiol in the presence of $BF_3{\cdot}OEt_2$, and we obtained β-S-substituted phenylalanine derivatives in acceptable yields without racemates (Table 3).

## Conclusions

We have optimized the reaction conditions of diazo-compounds and *O*-pivaloylated β-D-galactosylimines to form aziridines in high diastereoselectivity and moderate to high yields. A novel method, using *p*-toluenethiol as the nucleophilic reagent, was developed to open the aziridine ring and release the chiral auxiliary to yield the enantiometrically pure β-S-substituted phenylalanine derivatives.

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