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Expedient catalytic construction of azabicyclo[4.1.0]/[5.1.0] carbaldehydes via intramolecular cyclopropanation

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ABSTRACT

Three types of aza-bicycles, 3-azabicylo[4.1.0]heptane-6-carbaldehyde, 3-azabicylo[4.1.0]heptane-1-carbaldehyde, and 3-azabicyclo[5.1.0]octane-7-carbaldehyde, are constructed conveniently from corresponding carbene progenitors of *N*-allyl or *N*-homoallyl triazoles. Yields are modest to high. These transformations feature a key rhodium catalyzed intramolecular cyclopropanation of the pendent C–C double bond and show complete stereo specificity.

1. Introduction

Cyclopropyl group is a class of important motif in organic and medicinal chemistry. It was not only found in numerous natural products and pharmaceutical agents,[1] it also served as unique synthons and building blocks in organic synthesis.[2] Specially, cyclopropanes fused with N-heterocycle have obtained much interest[3] as many biologically active compounds contain azabicyclo [*n*.1.0] system (several examples are shown in Fig. 1).[4]

The majority body of literature that described the construction of N-bicycles of these types adopted two-phase strategies, namely, building the two rings via two isolated steps. On the other hand, methods that enable formation of the two-ring framework in a single reaction are more efficient and highly desirable. In this respect, several elegant methods have been developed including intramolecular cyclopropanation of ester/amide/nitrile with pendent titanacyclopropane,[3r,t] metal-catalyzed enynec cycloisomerization reactions,[3b,h,o] ruthenium-catalyzed transformations of enynes with aiazoalkanes,[3n] rhodium-catalyzed cycloisomerizations of bicyclobutanes,[5] palladium-catalyzed cyclopropanation of allenenes,[3q] oxidative intramolecular cyclopropanation of *N*-allyl enamine carboxylates.[3a] These methods all suffer from narrow substrate scope or/and poor functional group toleration and the products are almost all limited to azabicyclo[3.1.0] system. In this context, intramolecular cyclopropanation of alkene with a tethered metal carbene has stand out for its efficiency, excellent practicability.[6] Conventionally, diazoamide compound has been used as metal carbene precusors and the possibility that the use of the emerging 1-sulfonyl 1,2,3-triazoles as carbene progenitor[7] in related system to access azabicyclo[4.1.0]/[5.1.0] framework is an undressed question and, if viable, would provide a complementary alternative.

We have previously developed an efficient and convenient entry to 3-azabicyclo[3.1.0]-1-carbaldehyde **3**, which bears a sophisticated reaction handle of aldehyde group.[8] This highly valued

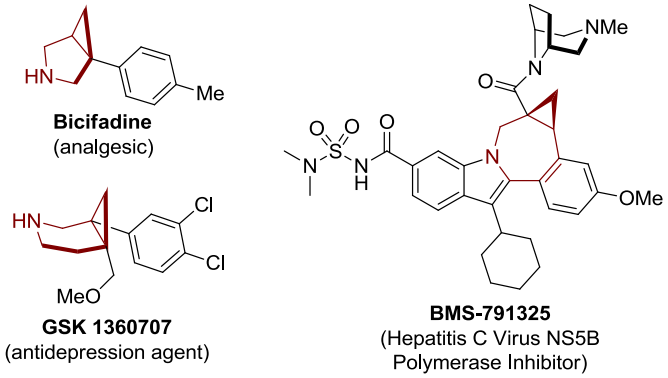

Fig. 1. Preventative azabicyclo[*n*.1.0] systems in bioactive molecules.

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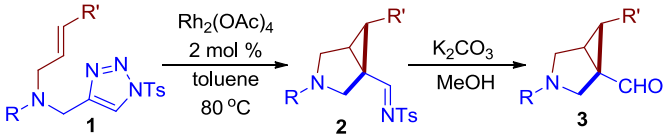
N-heterocycle could be obtained easily via a two-step-one-pot protocol, i.e., the convenient carbene precursor sulfonyl triazoles **1** was firstly decomposed to a rhodium carbene and converted to sulfonimine **2** in the action of $Rh_2(OAc)_4$ and subsequent hydrolysis delivered aldehyde **3** (Scheme 1). Now we wish to extend this practical method to the synthesis of other important azabycyclic systems: azabicyclo[4.1.0]heptane and azabicyclo[5.1.0]octane.

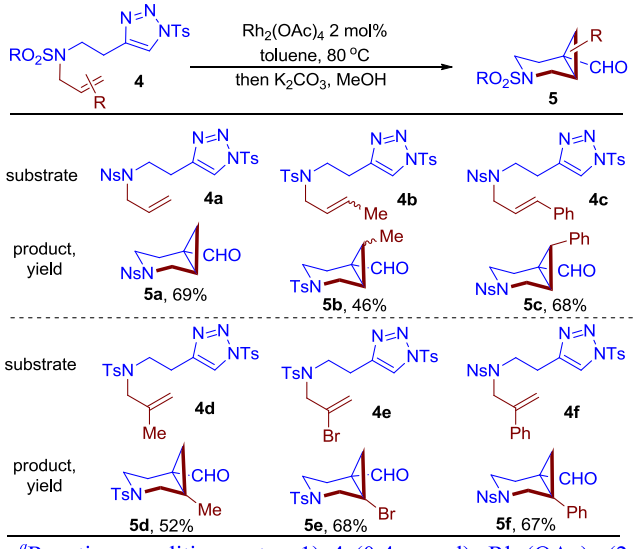


Scheme 1. Catalytic synthesis of 3-azabicylo[3.1.0]hexane-1-carbaldehyde.

2. Results and discussion

4-(*N*-allyl-*N*-sulfonyl-2-aminoethyl)-*N*-sulfonyl-1,2,3-triazoles **4** were made from corresponding amino enynes with sulfonyl azide conveniently and conditions developed in our previous work were applied to these triazoles. Thus, a toluene solution of **4** was stirred at 80 °C in the presence of 2 mol % $Rh_2(OAc)_4$ for 2 h, the volatiles were removed under vacuum and the residue was treated with K_2CO_3 in methanol. The desired 3-azabicylo[4.1.0]heptane-6-carbaldehydes **5** were obtained in medium to high yields. Substitution with alkyl, phenyl, and halogen groups at either site of the alkene all give viable yields. The exclusively observed cis-isomer of **5c** was inherited from the *trans*-alkenyl group in **4c**. The inseparable cis/trans isomeric mixture **5b** was derived from the cis/trans mixture of **4b** (Table 1).

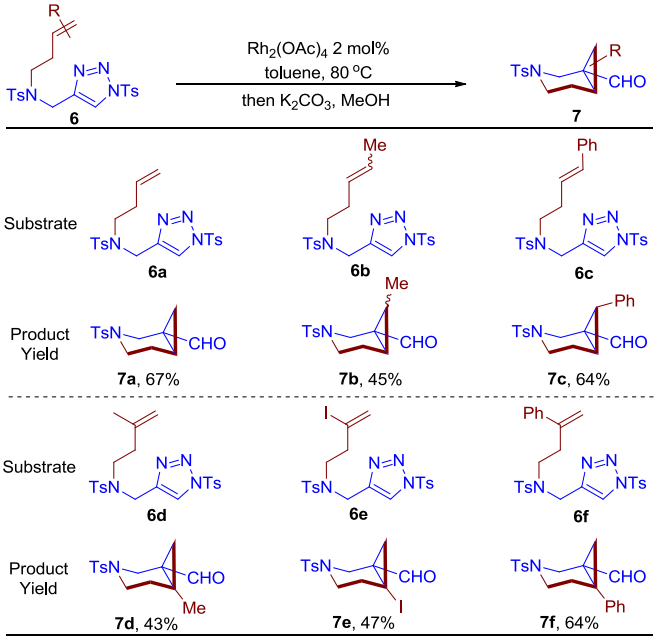
Table 1
Catalytic synthesis of 3-azabicyclo[4.1.0]heptane-6-carbaldehyde[a,b]



[a]Reaction conditions: step 1) **4** (0.4 mmol), $Rh_2(OAc)_4$ (2.0 mol %), toluene (4 mL), under N_2 for 2 h, then volatiles removed under vacuum; step 2) K_2CO_3 (1.6 mmol), MeOH (4 mL), rt, in air overnight. [b]Isolated yield.

The close regioisomers 3-azabicylo[4.1.0]heptane-1-carbaldehydes **7a**–**f** could be also accessed effectively from homoallyl triazide **6**. Again the yields spanned from 43% to 67% for the two-step-one-pot transformations, and the reaction was highly stereospecific with respect to the double bond. Phenyl substitution on both sites of the alkene group gave higher yields than their methyl congeners (**6c**, **6f** vs **6b**, **6d**). It is worth to note that the iodine group normally vulnerable to transition metal catalyst survived this reaction successfully to give a comparable yield (Table 2).

Table 2
Catalytic synthesis of 3-azabicyclo[4.1.0]heptane-1-carbaldehyde[a,b]



[a]Reaction conditions: step 1) **6** (0.4 mmol), $Rh_2(OAc)_4$ (2.0 mol %), toluene (4 mL), under N_2 for 2 h, then volatiles removed under vacuum; step 2) K_2CO_3 (1.6 mmol), MeOH (4 mL), rt, in air overnight. [b]Isolated yield.

Next extension of this protocol to *N*-allyl aminoproyltriazole system has met much difficulty. In most cases, the reactions just gave complex reaction mixtures from which collecting substantial quantities of major compound was not possible. This phenomenon is in line with the fact that there is rare practical examples of constructing bicylo[5.1.0]heptane framework via intramolecular cyclopropanation of carbenoid with alkene[6a] due to side reactions of carbenoid.[9] However, we could render the cyclopropanation to take place by using substrates with substitution at the 2-position of the alkene group. As shown in Table 3, phenyl, methyl, and halides all give 3-azabicyclo [5.1.0] in similar yields. The reason for this intriguing phenomenon is unclear and the nucleophilicity of the C–C double bond may play a critical role in the cyclopropanation step.[10]

To demonstrate its advantage in synthesis, we have applied this methodology to the synthesis of anti-depression agent GSK1360707.[3h,11] As shown in Scheme 2, commercially available boronic acid **10** was coupled with vinyl iodine **11** followed by tosylation providing allyl tosylate **12** quickly. N-Allylation of nosyl amide **13** with **12** and subsequent cycloaddition with TsN_3 afford substrate **4g** ready for the key intramolecular cyclopropanation in high yield. The desired aldehyde **5g** was obtained smoothly from **4g** in 65% yield following the standard conditions. Routine reduction and methylation finished **15** in high yield. Protecting group removal has been accomplished to give (+/−) GSK1360707 by Elitzin and co-workers using modified Fukuyama conditions.[12]

3. Conclusion

In summary, we have applied our previously developed method for synthesis of azabicyclo[3.1.0]-1-carbaldehyde to the synthesis of