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Lewis Acid Catalyzed Formal [3+2] Cycloaddition of Donor-Acceptor Cyclopropanes and 1-Azadienes: Synthesis of Imine Functionalized Cyclopentanes and Pyrrolidine Derivatives

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Abstract: Lewis acid catalyzed formal [3+2] cycloadditions of 1-azadienes with donor acceptor cyclopropanes to synthesize varieties of imine functionalized cyclopentanes and pyrrolidine derivatives in moderate to high yield have been developed. Moreover, pharmaceutically relevant azabicyclo[3.2.1]octane, bearing two all-carbon quaternary stereogenic centers at the bridgehead positions, has been synthesized by nosyl group deprotection and intramolecular amidation of imine functionalized cyclopentane derivative.

Keywords: Donor-Acceptor Cyclopropane; 1-Azadienes; Imine Functionalized Cyclopentanes; Pyrrolidine; azabicyclo[3.2.1]octane

Nitrogen-containing carbocycles and heterocycles are ubiquitous in many biologically active natural products and pharmaceutically relevant molecules.[1] In this regard, imine functionalized cyclopentanes and pyrrolidine derivatives are of particular interest. Gababutin analogues, constituting amine functionalized cyclopentanes, are having anti-inflammatory activity.[2] In addition, 1-sulfonyl pyrrolidine derivatives play a potential role for the treatment of neurological disorder.[3] Azabicyclic amino acid shows inhibitory activity against tumor cell[4] (Figure 1). Owing to the tremendous pharmaceutical applications, developments of efficient and credible methodologies for the synthesis of these structural motifs are of greater interest.

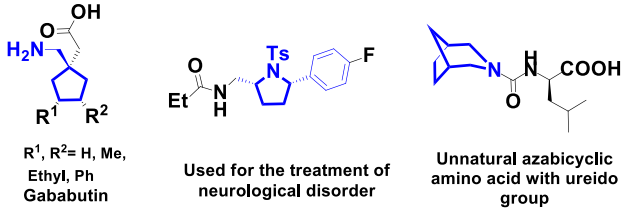
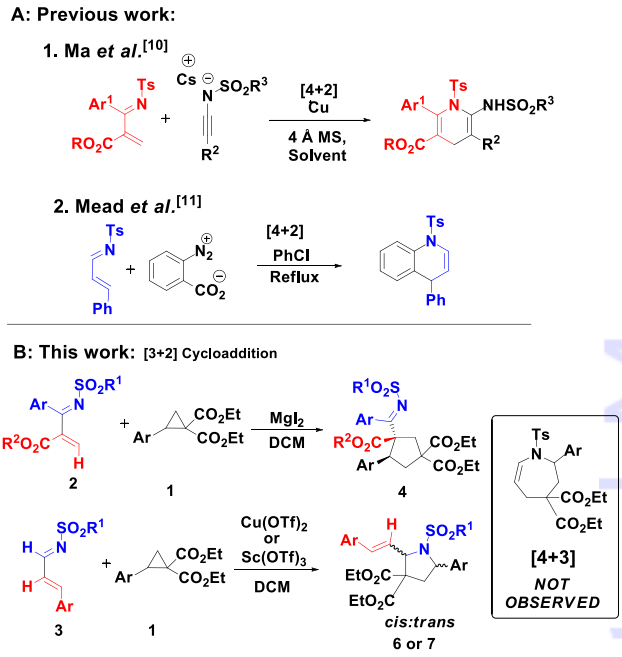


Figure 1. Example of drugs and amino acid.



Scheme 1. Cycloaddition reactions.

In general, donor-acceptor cyclopropanes (DACs) consisting a versatile three-carbon synthon, offer synthetic flexibility and atom economy in organic synthesis.[5] In the last few decades, it is being used as 1,3-dipoles, which undergoes formal [3+n] annulation reactions with numerous reactive partners to form carbo- and heterocycles.[5,6] In a series of reports, the competition between [3+2] and [4+3] annulations of cyclopropanes and 1,3-conjugated dienes, was recently explored by Budynina group. In addition, they discussed Lewis acid-catalyzed formal [3+2] cycloadditions of DACs with acyclic and cyclic butadienes.[7] To the best of our knowledge, [4+3] cycloaddition of DACs[8] and 1-azadienes are not reported yet, even though Diels-Alder reactions of 1-azadienes through [4+2] are common in literature. In this regards, Ma *et al.* described a versatile path to 2-amino-1,4-dihydropyridines through an inverse

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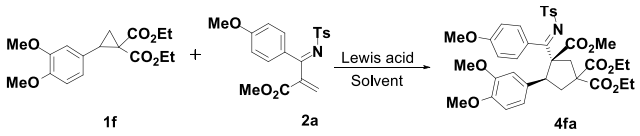
electron-demand Diels-Alder reaction of electron-deficient azadienes[9] and ynamides.[10] Mead *et al*. reported [4+2] cycloadditions between conjugated aldimine and benzyne at elevated temperature (Scheme 1).[11] Encouraged by these results, we subjected the cycloaddition reaction between DACs and 1-azadiene, divergent products were obtained, depending upon substituent present in 1-azadiene, *C*-attack of DACs to 1-azadienes furnished imine functionalized cyclopentane derivatives, whereas *N*-attack of 1-azadienes to DACs furnished pyrrolidine derivatives through [3+2] annulations. Herein, we wish to report an efficient method for the synthesis of *N*-tosyl or nosyl imine functionalized cyclopentanes and pyrrolidine derivatives *via* formal [3+2]-cycloaddition of DACs and 1-azadiene. Further utilization of imine functionalized cyclopentane towards the synthesis of valuable pharmaceutical important analog of azabicyclo[3.2.1]octane with the generation of two quaternary carbon stereogenic centers at the bridgehead positions also being presented in this article.

Table 1. Optimization of reaction condition.[a]

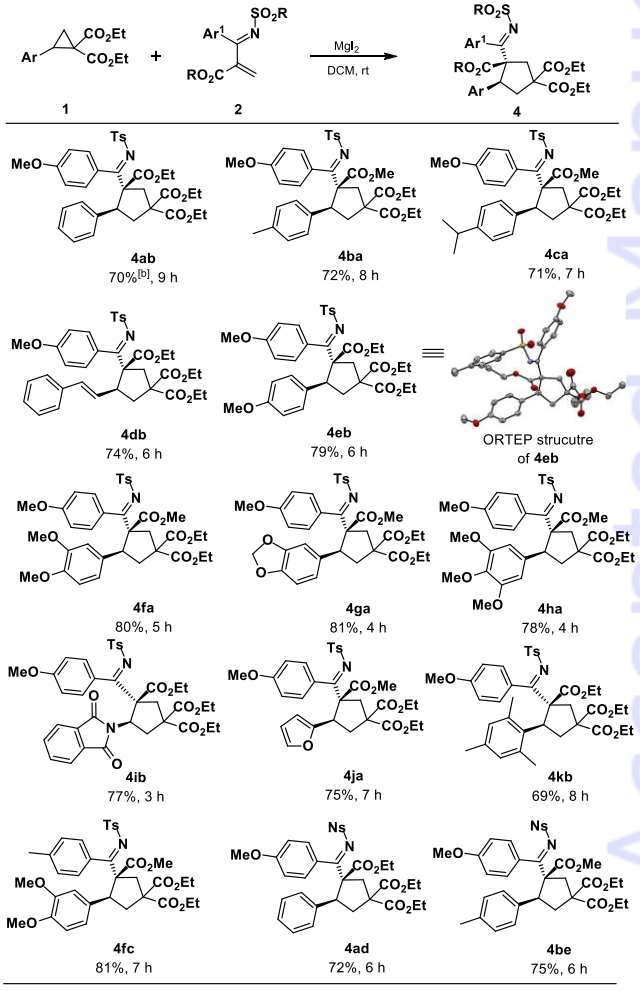


Entry	LA	LA (mol %)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	None	0	CH_2Cl_2	25	24	n.r[c]
2	MgI_2	5	CH_2Cl_2	25	8	45
3	MgI_2	10	CH_2Cl_2	25	8	61
4	**MgI_2**	**20**	**CH_2Cl_2**	**25**	**5**	**80**
5	MgI_2	50	CH_2Cl_2	25	4	77
6	MgI_2	100	CH_2Cl_2	25	2	60
7	$MgBr_2$	20	CH_2Cl_2	25	12	5
8	**$MgBr_2$**	**20**	**DCE[d]**	**80**	**10**	**81**
9	$MgBr_2$	20	Toluene	110	12	75
10	MgI_2	20	$CHCl_3$	25	5	77
11	MgI_2	20	CH_3CN	25	9	69
12	MgI_2	20	THF[e]	25	4	75

[a] All reactions were carried out under inert atmosphere: **1f** (0.10 mmol, 1 equiv.), **2a** (0.10 mmol, 1 equiv.), Lewis acid, solvent (1 mL).
[b] Isolated yield after flash column chromatography. No minor isomer could be isolated or detected.
[c] n.r = no reaction.
[d] DCE = 1,2-dichloroethane.
[e] THF = Tetrahydrofuran.

The present studies began with the optimization of the reaction conditions for the formal [3+2] cycloaddition reaction of DAC **1f** and 1-azadiene **2a** (Table 1). Our group previously displayed the utility of MgI_2 as an effective catalyst for the ring opening of strained rings such as epoxides, aziridines and cyclopropanes.[12] In the beginning, 5 mol% of MgI_2 was used as catalyst for this transformation and 45% of **4fa** was obtained (Table 1, entry 2). This motivated us to increase the loading of MgI_2 upto 20 mol%, which provided us the best yield (Table 1, entry 4). Further increment of MgI_2, gradually decreased the yield of the reaction (Table 1, entry 5, 6). $MgBr_2$ acted as a best catalyst on heating (Table 1, entry 9), while others, like $MgCl_2$ and $Mg(OTf)_2$ produced inferior results (see supporting information (SI)). Lewis acids, eg. $Cu(OTf)_2$, $Sc(OTf)_3$, $Ni(ClO_4)_2.6H_2O$, $InCl_3$, $Zn(OTf)_2$, $FeCl_2$ failed to produce the desired product (see SI). Solvents were also screened to check feasibility of the reaction, chlorinated solvent such as chloroform gave almost similar efficiency like dichloromethane (Table 1, entry 10). Coordinating solvent, like tetrahydrofuran produced 75% of **4fa** (Table1, entry 12) while in acetonitrile, poor yield was noticed (Table 1, entry 11).

Table 2. Scope of cycloadditions between **1** and **2**.[a]



[a] All reactions were carried out under inert atmosphere: **1** (0.10 mmol, 1 equiv.), **2** (0.10 mmol, 1 equiv.), MgI_2 (0.02 mmol, 0.2 equiv.), solvent (1 mL).
[b] Isolated yield after flash column chromatography.

With the optimized reaction conditions in hand, we focused our attention to evaluate the scope of [3+2]

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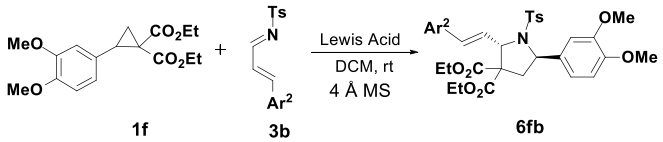
cycloaddition reaction between **1** and **2** to produce cyclopentane derivatives **4** (Table 2). A series of DACs bearing electron-donating or electron withdrawing groups present in variable position of phenyl ring were examined. DACs **1e**, **1f**, **1g**, **1h** containing electron donating methoxy substituent in *para* and *meta* position afforded **4eb**, **4fa**, **4ga**, **4ha**, respectively with greater yield. 2-Furan substituted DAC **1j** provided **4ja** with 75% yield in 7h. Nitrogen functionalized DAC **1i** furnished the desired cycloadduct **4ib** in 3h with 77% yield. DACs containing less electronically enriched alkyl group, methyl **1b** and isopropyl group **1c** substituted at *para* position in the vicinal phenyl ring gave 72% and 71% yield of the product, respectively. 2-Styryl DAC **1d** gave good yield of **4db** in 6h. Phenyl substituted DAC gave 70% yield of **4ab** at room temperature. 2,4,6-Trimethyl substituted DAC **1k** was able to produce the desired product **4kb** with 69% yield. Methyl incorporation at *para* position in phenyl ring of 1-azadiene **2b,** gave **4fc** in good yield. As nosyl group can be removed easily under mild condition, we conducted the cycloaddition reactions of *N*-nosyl azadienes **2d** and **2e** with DACs, which gave **4ad** and **4be**, respectively. The stereochemistry of **4eb** was determined by single crystal X-ray analysis (Table 2).[13]

Table 3. Optimization of reaction condition.[a]



1f 3b 6fb

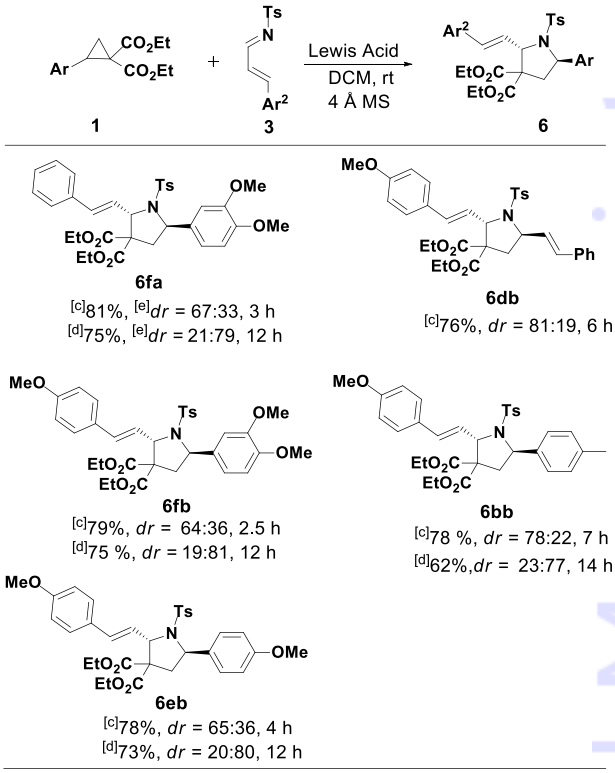
Ar^2 = 4-$OMeC_6H_4$

Entry	LA	LA (mol %)	Temp (°C)	Time (h)	Dr[c]	Yield (%)[b]
1	$Sc(OTf)_3$	5	25	5	15:85	75
2	$Sc(OTf)_3$	10	25	3	50:50	80
3	$Sc(OTf)_3$	20	25	2.5	64:36	79
4	$Sc(OTf)_3$	50	25	2	98:2	75
5	$Cu(OTf)_2$	5	25	14	1:99	10
6	$Cu(OTf)_2$	10	25	12	19:81	75
7	$Cu(OTf)_2$	20	25	12	20:80	72
8	$Cu(OTf)_2$	50	25	8	23:77	50
9	MgI_2	20	25	6	-	-

[a] All reactions were carried out under inert atmosphere: **1** (0.10 mmol, 1 equiv.), **2** (0.10 mmol, 1 equiv.), Lewis acid, solvent (1 mL).
[b] Isolated yield after flash column chromatography.
[c] Determined by ^{1}H NMR.

Initially, we tried the cycloaddition of **1f** and **3a** in the presence of MgI_2 (Table 3, entry 9) , but only dimerized product of cyclopropane was obtained, whereas other Lewis acids like $Cu(OTf)_2$ and $Sc(OTf)_3$ in dichloromethane furnished the desired products **6fb** and **7fb**, respectively (Table 3). As the loading of $Sc(OTf)_3$ was increased from 5 to 50 mol%, the diastereomeric ratios (*dr*) gradually gets converted from *cis*-**7fb** to *trans*-**6fb** isomer (Table 3, entry 1, 2, 3, 4). While, 10 or 20 mol% loading of $Cu(OTf)_2$ gave good yield of *cis*-**7fb** as a major isomer at room temperature (Table 3, entry 6, 7). However, lower (5 mol%) and higher (50 mol%) loading delivered inferior results (Table 3, entry 5, 8).

Table 4. Scope of cycloadditions between **1** and **3**.[a]



1 3 6

6fa
[c]81%, [e]*dr* = 67:33, 3 h
[d]75%, [e]*dr* = 21:79, 12 h

6db
[c]76%, *dr* = 81:19, 6 h

6fb
[c]79%, *dr* = 64:36, 2.5 h
[d]75 %, *dr* = 19:81, 12 h

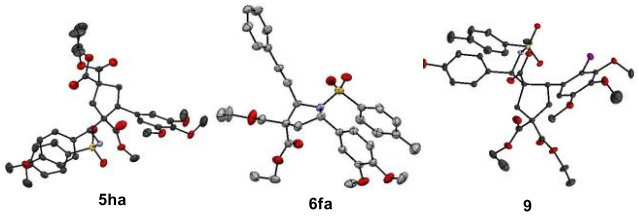
6bb
[c]78 %, *dr* = 78:22, 7 h
[d]62%,*dr* = 23:77, 14 h

6eb
[c]78%, *dr* = 65:36, 4 h
[d]73%, *dr* = 20:80, 12 h

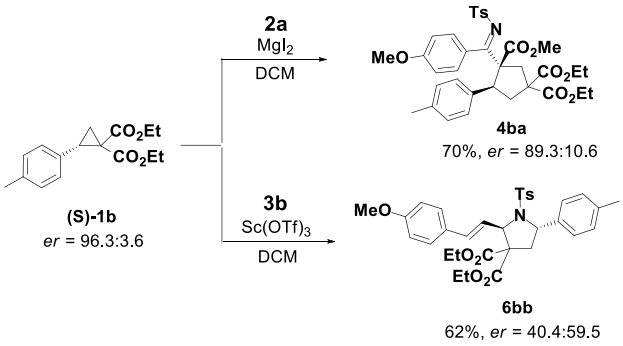
[a] All reactions were carried out under inert atmosphere: **1** (0.15 mmol, 1 equiv.), **3** (0.15 mmol, 1 equiv.), Lewis Acid, solvent (1 mL).
[b] Isolated yield after flash column chromatography.
[c] $Sc(OTf)_3$ (20 mol%).
[d] $Cu(OTf)_2$ (10 mol%).
[e] Determined by ^{1}H NMR.

Scope of [3+2] cycloadditions between **1** and **3** is presented in Table 4. The annulation of *N*-benzyl aldimine with DACs to form five-membered *N*-benzyl pyrrolidines derivatives has been previously reported in the literature, [14] while, to the best of our knowledge, no reports are available with *N*-tosyl substituted aldimine. After standardizing the reaction condition, we performed the cycloaddition of 1-azadienes **3a** with DAC **1f**, which gave two isomers of pyrrolidine derivatives **6fa** and **7fa** with combined 81% yield. Next, we examined this reaction with methoxy substituted at *para*-position of the phenyl ring of aldimine **3b** with more activated DACs containing an electron-donating group, such as methoxy (**1e** and **1f**) which yielded the products **6eb** & **7eb** and **6fc** & **7fc**. Less electronically enriched, *p*-tolyl-(**1b)** or 2-styryl-substituted **1d** cyclopropanes gave the diastereomeric mixtures of the corresponding products with good yield. Phenyl-

substituted DAC **1a** was unable to provide desired products.



Scheme 2. ORTEP structures of **5ha**, **6fa** and **9**.

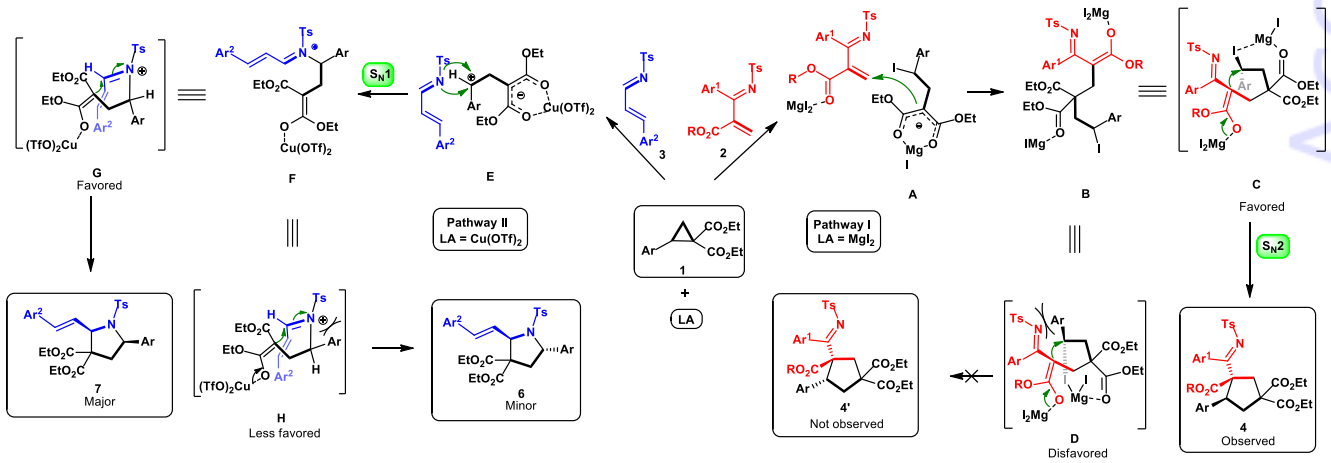


Scheme 3. [3+2] Cycloaddition of enantioenrich DAC **(s)-1b** and 1-azadienes (**2a** or **3b**).

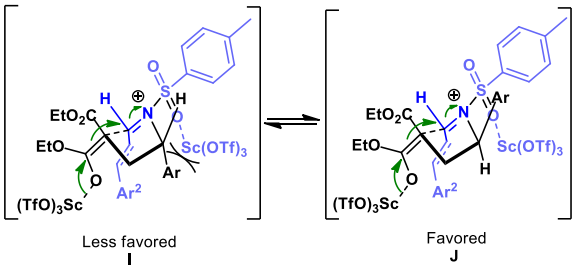
To gain some mechanistic insights, experiments were carried out and the results are shown in Scheme 3. The cycloaddition reaction of enantiopure DAC **(*S*)-1b** and both azadienes (**2a** and **3b**) were carried out seperately, **2a** leads to optically enriched cycloadduct **4ba**, whereas, **3b** gave almost racemic adduct **6bb**. This observation concluded that in 1st case the key substitution reaction (Scheme 4) proceeds *via* almost S_N2 fashion and for 2nd case it follows almost S_N1 way.

Based on the above experimental evidence and literature reports, plausible mechanism for the formal cycloaddition reactions between **1** and **2** or **3** is illustrated in Scheme 4. 1-Azadienes **2** or **3** follow two different pathways I and II, respectively. In the pathway I, DAC **1** undergoes iodide promoted nucleophilic ring opening to convert into the open-chain intermediate **A**. The highly unstable intermediate **A** attacks the 1-azadiene **2** and then gets converted into key intermediate **B**, which can adopt two possible conformations **C** and **D**. In this case, conformer **C** produced more preferably due to less steric hindrance of two bulky groups. Further cyclizes *via* S_N2 fashion to give cyclopentane **4** as a major product. In the catalytic pathway II, $Cu(OTf)_2$ generates zwitterionic intermediate **E**. Lone pair of electrons on nitrogen of 1-azadienes **3** attacks the cationic carbon of intermediate **E** *via* S_N1 fashion and generates intermediate **F**. This intermediate can adopt two possible conformational structures **G** and **H**. Conformer **G** is more relevant than **H** because of less steric hindrance between tosyl and aryl group. This may be the reason for the *cis*-isomer **6** to be major than the *trans*-**7**. Stereochemistry of **6fa** was confirmed by single crystal X-ray structure analysis (scheme 2 and see SI).[13] Previous reports have explained that phenyl-substituted *N*-sulfonyl imine was inactive in a reaction due to steric crowding[14a], [12e] but 2-styryl-substituted *N*-sulfonyl imine could reduce the steric effect. For this reason, *N*-sulfonyl imine of 1-azadienes **3** and activated alkene ester of 1-azadienes **2** participate individually in the formal cycloaddition process.

Stereochemical model of *trans*-favored isomers has proposed in scheme 5. Higher loading of $Sc(OTf)_3$, increases the coordination with tosyl group, which reflects in the ratios of the diastereomeric mixture. In this case, Conformer **I** found to be less favourable due to the repulsion between coordinated-scandium triflate and aryl group. On the other hand, the conformer **J** featuring less steric hindrance leads to the *trans*-**6** as a major product.

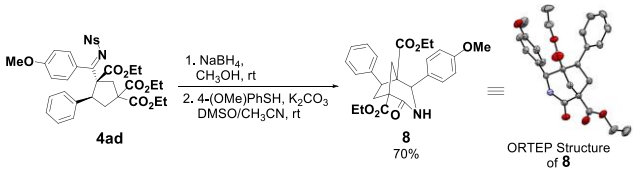


Scheme 4. Plausible Mechanism.



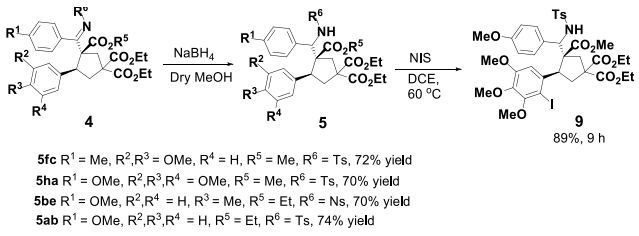
Scheme 5. Stereochemical model.

Utilizing the advantage of reactive nature of *N*-nosyl amine and carbonyl ester at position 1 and 3 in cyclopenatne **5ad**, azabicyclo[3.2.1]octane **8** was synthesized in good yield. In presence of 4-methoxythiophenol and potassium carbonate, nosyl deprotection followed by intermolecular amidation took place to afford **8** with 70% yield (Scheme 6).[13]



Scheme 6. Imine reduction followed by nosyl deprotection steps.

Furthermore, to demonstrate the potential of the developed methodology, selective reduction of imine functionalized cycloadduct **4** was performed, using $NaBH_4$ to synthesize product **5** which is the structural scaffold of gababutin (Scheme 7). Cycloadduct **5** was subjected to a regioselective iodination of arenes[15] to obtain iodinated product **9**. ORTEP structure of **5ha** & **9** is presented in Scheme 2.[13]



Scheme 7. Imine reduction and Iodination of arenes.

Conclusion

In conclusion, we have demonstrated Lewis acid catalyzed [3+2] cycloadditions reaction of DACs with 1-azadienesto synthesize a variety of imine functionalized cyclopentane and pyrrolidine derivatives *via* S_N2 and S_N1 fashion, respectively. Furthermore, two-step synthesis of valuable pharmaceutically relevant azabicyclo[3.2.1]octane, including two quaternary carbon stereogeniccenters has been achieved. In addition, we also report regioselective iodination of arenes of imine functionalized cyclopentane derivatives. Further application of this protocol towards natural product synthesis and development of catalytic enantioselective version of the present transformation are in progress in our lab.

Experimental Section

General procedure cycloadditions reaction between 1 and 2

A two-necked round bottom flask was charged with Donor-Acceptor Cyclopropane **1** (1.0 equiv.), 1-Azadiene **2** (1.0 equiv.), MgI_2 (0.2 equiv.) and DCM (1 mL) under nitrogen atmosphere. The reaction mixture was stirred it at room temperature until the consumption of cyclopropane (as monitored by TLC). Solution of reaction was filtered through thin pad of celite and solvent was concentrated in rotary evaporator. The residue was purified by silica gel flash column chromatography using diethyl ether/hexane as eluent.

General procedure cycloadditions reaction between 1 and 3

A two-necked round bottom flask was charged with Donor-Acceptor Cyclopropane **1** (1.0 equiv.), *N*-tosyl imine **3** (1.0 equiv.), 4 Å MS and Lewis acid (0.2 equiv.) under nitrogen atmosphere. DCM was added to the reaction mixture and solution was stirred it at room temperature until the consumption of cyclopropane (as monitored by TLC). Reaction mixture was filtered through thin pad of celite and solvent was concentrated in rotary evaporator. The residue was purified by flash column chromatography on silica gel using ethyl acetate/hexane as eluent.

Acknowledgements

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UPDATE

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