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<td>Kaga, Atsushi; Gandamana, Dhika Aditya; Tamura, Sayako; Demirelli, Mesut; Chiba, Shunsuke</td>
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[3+2]-Annulation of Donor-Acceptor Cyclopropanes with Vinyl Azides

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Abstract A Sc(OTf)₃-catalyzed reaction of vinyl azides with donor-acceptor cyclopropanes affords highly-functionalized azidocyclopentanes in a diastereoselective fashion. The resulting azidocyclopentanes could be transformed into various cyclic scaffolds.

Key words vinyl azides, donor-acceptor cyclopropanes, cyclopentanes, [3+2]-annulation, Lewis acids

Vinyl azides have exhibited unique chemical reactivity in their molecular transformations. Our group recently disclosed that vinyl azides perform as an enamine-type nucleophile to various carbon or halogen electrophiles [E⁺] to construct a new C-C or C-X bond. While the Stork enamine reaction forms an iminium ion, the reactions of vinyl azides with [E⁺] result in generation of an iminodiazonium ion, that undergoes further transformations such as Schmidt type rearrangement to form amides and regeneration of an azide through trap of the electrophilic C=N bond with nucleophiles in both intramolecular and intermolecular manners (Scheme 1-a). As for synthesis of nitrogen-heterocycles, synthesis of 1-pyrrolines was enabled by TiCl₄-catalyzed reactions of vinyl azides with 2-alkylidenemalonates (Scheme 1-b). The process is initiated by conjugate addition of vinyl azides onto 2-alkylidenemalonates to form the iminodiazonium ions I bearing a γ-carbanion. Subsequent cyclization generates azidocyclobutanes II, that undergoes strain-release denitrogenative ring-expansion to afford 1-pyrroline products.

In seeking to develop a new type of molecular transformation by taking advantage of the nucleophilic reactivity of vinyl azides, we became interested in use of donor-acceptor cyclopropanes as a potential 3-atom unit electrophile (Scheme 1-c). Herein, we report Sc(OTf)₃-catalyzed [3+2]-annulation of donor-acceptor cyclopropanes with vinyl azides for construction of highly functionalized azidocyclopentanes in a diastereoselective fashion. Electrophilically activated donor-acceptor cyclopropanes III were attacked by vinyl azides in an Sₘ₂ type fashion as a predominant pathway, forming iminodiazonium ions IV bearing a δ-carbanion. Further cyclization delivered azidocyclopentanes. Several conversions of azidocyclopentanes into useful carbo- and heterocyclic scaffolds were also demonstrated.

Scheme 1 Nucleophilic reactivity of vinyl azides

We commenced our study to optimize the reaction settings using vinyl azide 1a and cyclopropanes 2a-5a (Table 1). Extensive screening of acid activators revealed that use of...
Sc(OTf)$_3$ in MeNO$_2$ is optimal to realize desired [3+2]-annulation of cyclopropane 2a for construction of cyclopentane 6aa in good yield albeit in poor diastereoselectivity (run 1). We assumed that the steric effect of the ester moiety should affect the diastereoselectivity. Indeed, bulkier esters 3a-5a resulted in better diastereoselectivity (runs 2-4) and 2,6-dimethylbenzyl ester 5a provided the best result (d.r. = 82:18) (run 4). Screening of the solvent systems (runs 5-7) revealed that use of CH$_2$Cl$_2$-MeNO$_2$ co-solvent (4:1) system at 0 °C improved the yield of 9aa with further improvement of the diastereoselectivity (runs 6 and 7).

### Table 1: Optimization of the reaction conditions

<table>
<thead>
<tr>
<th>run</th>
<th>Cyclopropanes</th>
<th>solvent</th>
<th>Temp. [°C]</th>
<th>Time [h]</th>
<th>Yields (%)</th>
<th>d.r.</th>
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<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>MeNO$_2$</td>
<td>23</td>
<td>5</td>
<td>6aa 94</td>
<td>53:47</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>MeNO$_2$</td>
<td>23</td>
<td>10</td>
<td>7aa 81</td>
<td>77:23</td>
</tr>
<tr>
<td>3</td>
<td>4a</td>
<td>MeNO$_2$</td>
<td>23</td>
<td>10</td>
<td>8aa 77</td>
<td>71:29</td>
</tr>
<tr>
<td>4</td>
<td>5a</td>
<td>MeNO$_2$</td>
<td>23</td>
<td>24</td>
<td>9aa 55</td>
<td>82:18</td>
</tr>
<tr>
<td>5</td>
<td>5a</td>
<td>CH$_2$Cl$_2$-MeNO$_2$ (4:1)</td>
<td>23</td>
<td>24</td>
<td>9aa 72</td>
<td>84:16</td>
</tr>
<tr>
<td>6$^d$</td>
<td>5a</td>
<td>CH$_2$Cl$_2$-MeNO$_2$ (4:1)</td>
<td>0</td>
<td>24</td>
<td>9aa 80</td>
<td>89:11</td>
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<tr>
<td>7$^d$</td>
<td>5a</td>
<td>CH$_2$Cl$_2$-MeNO$_2$ (4:1)</td>
<td>0</td>
<td>24</td>
<td>9aa 95</td>
<td>88:12</td>
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$^a$ Unless otherwise stated, the reactions were carried out using 0.3-0.5 mmol of cyclopropanes with vinyl azide 1a (2 equiv) in the presence of 10 m mol% of Sc(OTf)$_3$ in the solvent (0.3 M). $^b$ Isolated yields based on cyclopropanes. $^c$ Diastereoselectivities (major:minor) were determined by $^1$H NMR analysis of isolated mixture of cyclopentanes. $^d$ Reaction was conducted in 0.50 M. $^e$ 15 mol% of Sc(OTf)$_3$ was used.

Using the optimized reaction conditions (Table 1, run 7), we investigated the substrate scope for the diastereoselective [3+2]-annulation of cyclopropanes 5 with vinyl azides 1 (Scheme 3). As for substituent $R^1$ on vinyl azides 1, several aryl groups such as 4-tolyl (for 1b), 2-naphthyl (for 1c), and 4-bromophenyl (for 1d) groups could be used for the reaction with the cyclopropanes 5a to afford the corresponding cyclopentanes 9ba-9da with good diastereoselectivity, whereas installation of an alkyl group as $R^1$ on vinyl azide 1e resulted in the moderate diastereoselectivity in cyclopentane 9ea. Next, the effect of substituent $R^2$ on cyclopropanes 5 was examined using vinyl azide 1d. The process allowed for the use of cyclopropanes having electron-rich 4-methoxyphenyl (for 5b), sterically bulky aryl (for 5c and 5d), and thienyl (for 5e) moieties, forming the corresponding cyclopentanes 9db-9de in good yields and diastereoselectivity. Moreover, cinnamyl (for 5f) and phthalimido (for 5g)$^{14a,b}$ groups were also well tolerated in the present annulation process, forming the corresponding cyclopentanes 9df and 9dg, respectively.

Finally, we demonstrated versatility of the azidocyclopentane products by transforming 6aa and 9aa into a variety of synthetically useful derivatives (Schemes 3 and 4). The reaction of 6aa with LiCl in the presence of HzO in DMSO promoted decarboxylation$^{14}$ and subsequent elimination of the azido ion to afford cyclopentene 10, whereas treatment of 6aa with TIOH gave another regioisomeric cyclopentene 11 (Scheme 3-a,$^b$). Furthermore, denitrogenative ring-expansion of 6aa was enabled by the reaction with SnCl$_4$, forming tetrahydropyridines 12 and 13 (that is formed through subsequent decarboxylation) in 39% and 34% yields, respectively (Scheme 3-c). Similarly with our previous 1-pyrroline formation (Scheme 1-b), migration of the secondary carbon occurred dominantly over that of the quaternary carbon, which is deactivated by the two methoxy carbonyl groups.
Use of diastereomerically enriched 9aa for azide-allyne cycloaddition reaction delivered the corresponding triazole 14 in 98% yield (Scheme 4-a). Reduction of the azido moiety by PMe3 gave primary amine,14 that was isolated as acetamide 15 by subsequent treatment with acetic anhydride in pyridine (Scheme 4-b).

This work demonstrated that nucleophilic attack of vinyl azides onto donor-acceptor cyclopropanes in the presence of Sc(OTf)3 as a Lewis acid activator enables an efficient construction of azidocyclopentanes.15 Further study in exploration of other types of bond-forming processes using vinyl azides is in progress.

Acknowledgment
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Supporting Information
YES

Primary Data
No

References and Notes


(10) During the revision of this manuscript, conceptually the same work on Lewis-acid catalyzed [3+2] annulation of donor-acceptor cyclopropanes and vinyl azides was reported by Banerjee, see: Roy, R.; Banerjee, P. Org. Lett. in press [DOI 10.1021/acs.orglett.6b03276].

(11) The reactions of vinyl azide 1a with optically active cyclopropene (S)-2a (99% ee) gave [3+2] annulation products in up to 93% ee, suggesting that the 1° C-C bond forming process between 1a and 2a takes place predominantly in an S2-type manner (See the Supporting Information for the details). For relevant reports, see: (a) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. J. Am. Chem. Soc. 2008, 130, 8642. (b) Pohlhaus, P. D.; Johnson, J. S. J. Am. Chem. Soc. 2005, 127, 16014.

(12) See the Supporting Information.

(13) The stereochemistry of the major isomer of 6aa (CCDC 1519381), 7aa (CCDC 1519383), 9aa (CCDC 1519478), and 9ca (CCDC 1519384) were secured by X-ray crystallographic analysis.


(17) Procedure for the synthesis of cyclopentane 9aa:

To a stirred solution of cyclopropene 5a (218 mg, 0.493 mmol) and vinyl azide 1a (144 mg, 0.993 mmol) in CH2Cl2 (0.8 mL) and MeNO2 (0.2 mL) was added Sc(OTf)3 (37.6 mg, 0.0764 mmol) at 0 °C under an Ar atmosphere. The solution was stirred at 0 °C for 24 h and then quenched with saturated aqueous NaHCO3. The mixture was extracted with CH2Cl2 and the combined extracts were washed with brine, dried over MgSO4 and concentrated in vacuo. The resulting crude material was purified by flash column chromatography (hexane : EtOAc = 100:1 to 90:1) to yield cyclopentane 9aa (275 mg, 0.468 mmol) in 95% yield as a mixture of diastereomers (major:minor = 88:12, which was determined by 1H NMR analysis). The major isomer could be recrystallized from CH3Cl/Hexane as a colorless crystal.

bis(2,6-dimethylbenzyl) [(25,4R*)-2-azido-2,4-diphenylcyclopentane-1,1-di carbonate (9aa major):

mp: 100-101 °C; 1H NMR (400 MHz, CDCl3) δ 2.04 (6H, s), 2.16 (6H, s), 2.52 (1H, dd, J = 6.8, 14.4 Hz), 2.79-2.91 (2H, m), 3.03 (1H, dd, J = 10.4, 14.4 Hz), 3.57-3.66 (1H, m), 4.94 (1H, d, J = 12.0 Hz), 5.08-5.14 (2H, m), 5.29 (1H, d, J = 12.0 Hz), 6.93 (2H, d, J = 7.6 Hz), 6.99 (2H, d, J = 7.6 Hz), 7.07-7.22 (6H, m), 7.27-7.31 (4H, m), 7.37 (2H, d, J = 7.2 Hz); 13C NMR (100 MHz, CDCl3) δ 19.2, 19.3, 39.9, 43.2, 47.3, 62.2, 62.4, 69.8, 78.3, 126.4, 127.3, 127.4, 127.9, 128.09, 128.12 (overlapped), 128.8, 128.7, 128.8, 130.7, 131.1, 138.2, 138.4, 138.5, 144.4, 169.4, 170.1; ESIMS: Found: m/z 560.2806. Calcd for C31H29NO2C (M+N+H)+: 560.2801