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[3+2]-Annulation of Donor-Acceptor Cyclopropanes with Vinyl Azides

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Abstract A $\text{Sc}(\text{OTf})_3$ -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.¹ Our group recently disclosed that vinyl azides perform as an enamine-type nucleophile to various carbon or halogen electrophiles $[\text{E}^+]$ to construct a new C-C or C-X bond.^{2,3} While the Stork enamine reaction forms an iminium ion,⁴ the reactions of vinyl azides with $[\text{E}^+]$ results in generation of an iminodiazonium ion, that undergoes further transformations such as Schmidt type rearrangement⁵ to form amides and regeneration of an azide through trap of the electrophilic C=N bond with nucleophiles in both intra- and intermolecular manners (Scheme 1-a). As for synthesis of nitrogen-heterocycles, synthesis of 1-pyrrolines was enabled by TiCl_4 -catalyzed reactions of vinyl azides with 2-alkyldienemalonates (Scheme 1-b).^{2b} The process is initiated by conjugate addition of vinyl azides onto 2-alkyldienemalonates to form the iminodiazonium ions **I** bearing a γ -carbanion. Subsequent cyclization generates azidocyclobutanes **II**, that undergoes strain-release denitrogenative ring-expansion to afford the 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).^{6,7} Herein, we report $\text{Sc}(\text{OTf})_3$ -catalyzed [3+2]-annulation of donor-acceptor cyclopropanes^{8,9} with vinyl azides for construction of highly functionalized azidocyclopentanes in a diastereoselective fashion.¹⁰ Electrophilically activated donor-acceptor

cyclopropanes **III** were attacked by vinyl azides in an $\text{S}_{\text{N}}2$ type fashion as a predominant pathway,¹¹ 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.

We commenced our study to optimize the reaction settings using vinyl azide **1a** and cyclopropanes **2a-5a** (Table 1). Extensive screening of acid activators¹² revealed that use of

Sc(OTf)₃ in MeNO₂ 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).¹³ 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 CH₂Cl₂-MeNO₂ 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

run	Cyclopropanes	solvent	Temp [°C]	Time [h]	Yields [%] ^b	d.r. ^c
1	2a	MeNO ₂	23	5	6aa 94	53:47
2	3a	MeNO ₂	23	10	7aa 81	77:23
3	4a	MeNO ₂	23	10	8aa 77	71:29
4	5a	MeNO ₂	23	24	9aa 55	82:18
5	5a	CH ₂ Cl ₂ -MeNO ₂ (4:1)	23	24	9aa 72	84:16
6 ^d	5a	CH ₂ Cl ₂ -MeNO ₂ (4:1)	0	24	9aa 80	89:11
7 ^{d,e}	5a	CH ₂ Cl ₂ -MeNO ₂ (4:1)	0	24	9aa 95	88:12

^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 mol% of Sc(OTf)₃ in the solvent (0.3 M). ^b Isolated yields based on cyclopropanes. ^c Diastereoselectivities (major:minor) were determined by ¹H 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 R¹ 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 cyclopropane **5a** to afford the corresponding cyclopentanes **9ba–9da** with good diastereoselectivity, whereas installation of an alkyl group as R¹ on vinyl azide **1e** resulted in the moderate diastereoselectivity in cyclopentane **9ea**. Next, the effect of substituent R² 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**)^{6e,8o} groups were also well tolerated in the present annulation process, forming the corresponding cyclopentanes **9df** and **9dg**, respectively.

Scheme 2 Substrate scope:^{a,b} ^a Unless otherwise noted, the reactions were conducted using 0.5 mmol of cyclopropanes **5** and 1 mmol vinyl azides **1** in the presence of Sc(OTf)₃ (15 mol%) in CH₂Cl₂-MeNO₂ (4:1) (1 mL) under an Ar atmosphere. ^b Isolated yields based on cyclopropanes **5** and diastereoselectivities were recorded above. ^c 20 mol% of Sc(OTf)₃ was used. ^d 30 mol% of Sc(OTf)₃ was used.

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 H₂O in DMSO promoted decarboxylation¹⁴ and subsequent elimination of the azido ion to afford cyclopentene **10**, whereas treatment of **6aa** with TfOH gave another regioisomeric cyclopentene **11** (Scheme 3-a,b).¹⁵ Furthermore, denitrogenative ring-expansion of **6aa** was enabled by the reaction with SnCl₄, 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 methoxycarbonyl groups.

Scheme 3 Derivatization of azidocyclopentane **6aa**. a) LiCl (3.6 equiv), H₂O (14 equiv), DMSO, 130 °C, 29 h. d) TfOH (1 equiv), DCE, 0 °C, 1 h. e) SnCl₄ (1.2 equiv), DCE, 23 to 60 °C, 16 h.

Use of diastereomerically enriched **9aa** for azide-alkyne cycloaddition reaction delivered the corresponding triazole **14** in 98% yield (Scheme 4-a). Reduction of the azido moiety by PMe₃ gave primary amine,¹⁶ that was isolated as acetamide **15** by subsequent treatment with acetic anhydride in pyridine (Scheme 4-b).

Scheme 4 Derivatization of azidocyclopentane **9aa**. a) phenyl acetylene (6 equiv), CuTC (0.5 equiv), *i*-Pr₂NEt (4 equiv), DMF, 80 °C, 50 h; b) PMe₃ (2 equiv), THF-H₂O (20:1), 0 °C, then Ac₂O (2 equiv), pyridine, 0 to 23 °C.

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.¹⁷ Further study in exploration of other types of bond-forming processes using vinyl azides is in progress.

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Supporting Information

YES

Primary Data

No

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- (17) **Procedure for the synthesis of cyclopentane 9aa:**
To a stirred solution of cyclopropane **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 : Et₂O = 100:1 to 90:1) to yield cyclopentane **9aa** (275 mg, 0.468 mmol) in 95% yield as a mixture of diastereomer (major:minor = 88:12, which was determined by ¹H NMR analysis). The major isomer could be recrystallized from CH₂Cl₂/hexane as a colorless crystal.
- bis(2,6-dimethylbenzyl) (2S*,4R*)-2-azido-2,4-diphenylcyclopentane-1,1-dicarboxylate (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), 128.2, 128.7, 128.8, 130.7, 131.1, 138.2, 138.4, 138.5, 144.4, 169.4, 170.1; ESIHRMS: Found: m/z 560.2806. Calcd for C₃₇H₃₈NO₄: (M-N₂+H)⁺ 560.2801