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

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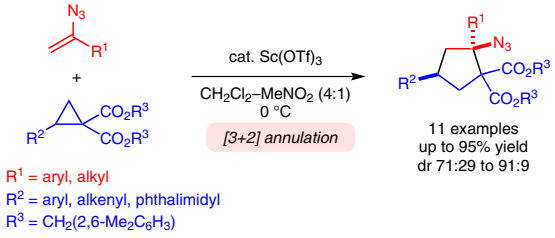

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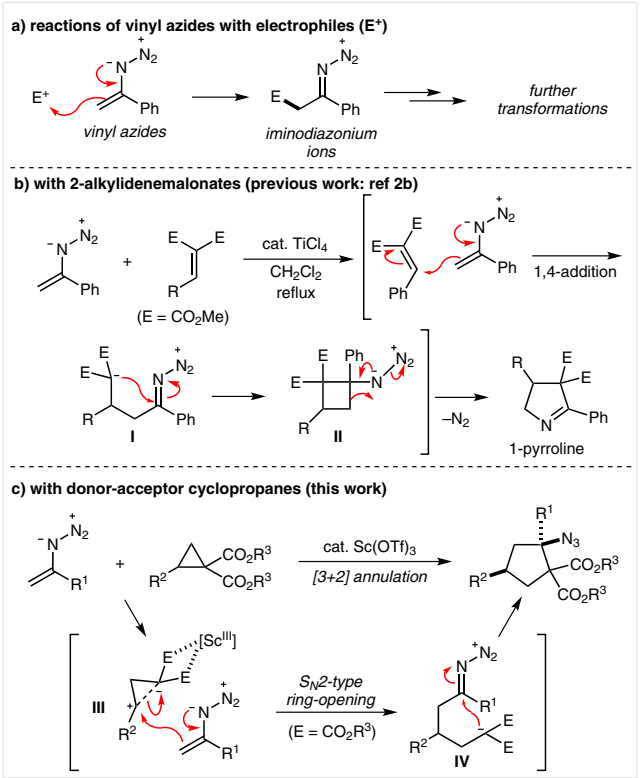
Abstract A $Sc(OTf)_3$-catalyzed reaction of vinyl azides with donor–acceptor cyclopropanes affords highly functionalized azidocyclopentanes in a diastereoselective fashion. The resulting azidocyclopentanes could be transformed into various cyclic scaffolds.

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

Vinyl azides have exhibited unique chemical reactivity in their molecular transformations.[1] 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.[2,3] While the Stork enamine reaction forms an iminium ion,[4] the reactions of vinyl azides with [E^+] result in generation of an iminodiazonium ion that undergoes further transformations such as Schmidt-type rearrangement[5] 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-alkylidenemalonates (Scheme 1, b).[2b] 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 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



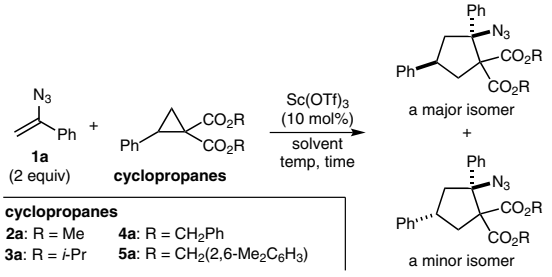
Scheme 1 Nucleophilic reactivity of vinyl azides

(Scheme 1, c).[6,7] Herein, we report $Sc(OTf)_3$-catalyzed [3+2] annulation of donor–acceptor cyclopropanes[8,9] with vinyl azides for the construction of highly functionalized azidocyclopentanes in a diastereoselective fashion.[10] Electrophilically activated donor–acceptor cyclopropanes **III** were attacked by vinyl azides in an S_N2-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 cyclopropropanes **2a**–**5a** (Table 1). Extensive screening of acid activators[12] revealed that use of $Sc(OTf)_3$ in $MeNO_2$ is optimal to realize the desired [3+2] annulation of cyclopropane **2a** for the construction of cyclopentane **6aa** in good yield albeit in poor diastereoselectivity (Table 1, entry 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 (Table 1, entries 2–4) and 2,6-dimethylbenzyl ester **5a** provided the best result (dr = 82:18, Table 1, entry 4). Screening of the solvent systems (Table 1, entries 5–7) revealed that use of CH_2Cl_2–$MeNO_2$ co-solvent (4:1) system at 0 °C improved the yield of **9aa** with further improvement of the diastereoselectivity (Table 1, entries 6 and 7).

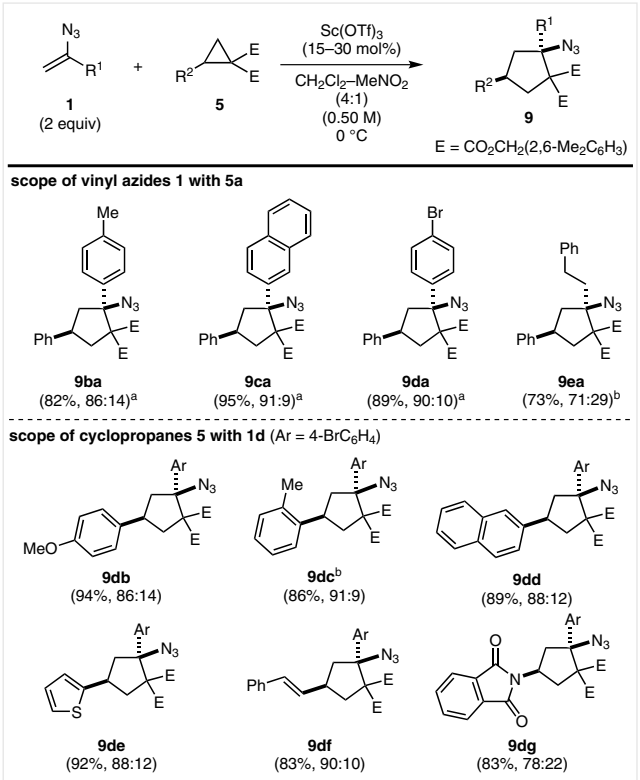
Table 1 Optimization of the Reaction Conditions[a]



Entry	Cyclopropane	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	dr[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_2Cl_2–$MeNO_2$ (4:1)	23	24	**9aa** 72	84:16
6[d]	**5a**	CH_2Cl_2–$MeNO_2$ (4:1)	0	24	**9aa** 80	89:11
7[d,e]	**5a**	CH_2Cl_2–$MeNO_2$ (4:1)	0	24	**9aa** 95	88:12

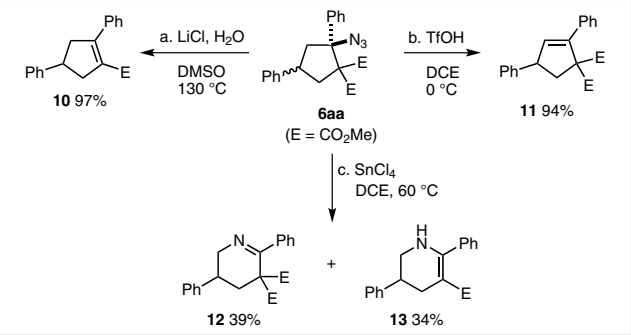
[a] Unless otherwise stated, the reactions were carried out using 0.3–0.5 mmol of cyclopropanes with vinyl azide **1a** (2 equiv) in the presence of 10 mol% of $Sc(OTf)_3$ in the solvent (0.3 M).
[b] Isolated yields based on cyclopropanes.
[c] Diastereoselectivities (major/minor) were determined by ^1H 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, entry 7), we investigated the substrate scope for the diastereoselective [3+2] annulation of cyclopropanes **5** with vinyl azides **1** (Scheme 2). 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 cyclopropane **5a** to afford the corresponding cyclopentanes **9ba–da** 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–de** 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.



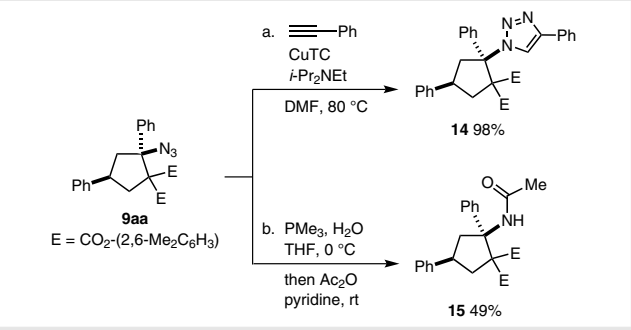
Scheme 2 Substrate scope. Unless otherwise noted, the reactions were conducted using 0.5 mmol of cyclopropanes **5** and 1 mmol vinyl azides **1** in the presence of $Sc(OTf)_3$ (15 mol%) in CH_2Cl_2–$MeNO_2$ (4:1, 1 mL) under an Ar atmosphere. Isolated yields based on cyclopropanes **5** and diastereoselectivities were recorded above. [a] 20 mol% of $Sc(OTf)_3$ used. [b] 30 mol% of $Sc(OTf)_3$ 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 H_2O in DMSO promoted decarboxylation[14] 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 and b).[15] 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 methoxycarbonyl groups.



Scheme 3 Derivatization of azidocyclopentane **6aa**. *Reagents and conditions*: a) LiCl (3.6 equiv), H_2O (14 equiv), DMSO, 130 °C, 29 h; b) TfOH (1 equiv), DCE, 0 °C, 1 h; c) $SnCl_4$ (1.2 equiv), DCE, 23 °C 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 PMe_3 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**. *Reagents and conditions*: a) phenyl acetylene (6 equiv), CuTC (0.5 equiv), *i*-Pr_2NEt (4 equiv), DMF, 80 °C, 50 h; b) PMe_3 (2 equiv), THF–H_2O (20:1), 0 °C, then Ac_2O (2 equiv), pyridine, 0 °C 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

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588703.

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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 CH_2Cl_2 (0.8 mL) and $MeNO_2$ (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 sat. aq $NaHCO_3$. The mixture was extracted with CH_2Cl_2, and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting crude material was purified by flash column chromatography (hexane–Et_2O, 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 CH_2Cl_2–hexane as a colorless crystal.

Bis(2,6-dimethylbenzyl) (2*S,4*R**)-2-azido-2,4-diphenylcyclopentane-1,1-dicarboxylate (9aa major)**

Mp 100–101 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.04 (6 H, s), 2.16 (6 H, s), 2.52 (1 H, dd, *J* = 6.8, 14.4 Hz), 2.79–2.91 (2 H, m),

3.03 (1 H, dd, *J* = 10.4, 14.4 Hz), 3.57–3.66 (1 H, m), 4.94 (1 H, d, *J* = 12.0 Hz), 5.08–5.14 (2 H, m), 5.29 (1 H, d, *J* = 12.0 Hz), 6.93 (2 H, d, *J* = 7.6 Hz), 6.99 (2 H, d, *J* = 7.6 Hz), 7.07–7.22 (6 H, m), 7.27–7.31 (4 H, m), 7.37 (2 H, d, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 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. ESI-HRMS: *m/z* calcd for $C_{37}H_{38}NO_4$ [M – N_2 + H]$^+$: 560.2801; found: 560.2806.