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Nickel-catalyzed [3 + 2] cycloaddition of diynes with methyleneaziridines *via* C–C bond cleavage†

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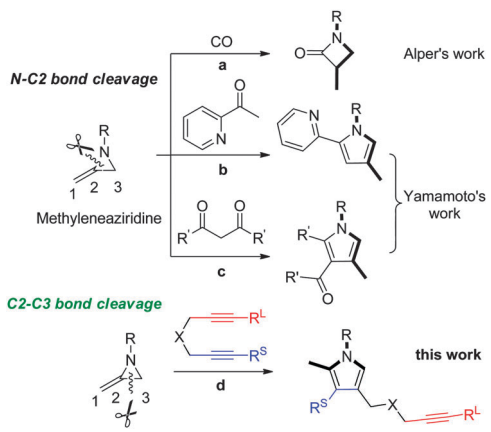
A Ni-catalyzed [3 + 2] cycloaddition *via* C–C bond cleavage of methyleneaziridines under mild conditions was developed. This reaction gave substituted pyrroles with excellent regioselectivity and a pendant alkyne unit, which is advantageous for further derivatization.

Cleavage of C–C σ bonds by transition metals presents a fundamental challenge[1] attributed to the inertness of the C–C σ bond and the poor interaction of the orbitals of the C–C σ bond with transition metals. Strained rings as substrates offer a feasible approach for C–C σ bond activation.

Methyleneaziridines (MAs), a class of highly strained heterocycle derived aziridines bearing an exocyclic alkene group (Scheme 1),[2] have drawn less attention in organic synthesis than other three-membered rings.[3] Although the ring-opening couplings of MAs with strong electrophiles and organometallics have been studied,[4] the metal-catalyzed ring expansion reactions of MAs have been less investigated. Alper and co-workers reported a palladium-catalyzed carbonylation reaction[5] of MAs which proceeded *via* N–C2 bond cleavage (Scheme 1, a). Later, Yamamoto and co-workers reported the palladium-catalyzed reactions of MAs with 2-acetylpyridines[6a] or 1,3-diketones,[6b] giving pyrrole derivatives in good yields (Scheme 1, b and c), which also involved N–C2 bond cleavage steps. Despite these achievements, metal-catalyzed ring expansion reactions *via* C2–C3 bond cleavage of MAs have not been reported.



Scheme 1 Metal-catalyzed ring expansion reactions of methyleneaziridines.

We have recently reported the [2 + 2 + 2] cycloaddition reactions of diynes with nitriles or oximes to give pyridine derivatives.[7] As a continuation of our interest in the metal-catalyzed cycloaddtion reactions of diynes, we turned our attention to the reaction of diynes and MAs. It is well-known that Ni(0) can catalyze the carbon–carbon bond cleavage of methylenecyclopropanes in coupling reactions,[3d-f] including [3 + 2 + 2] cycloaddition reactions.[8] Given the structural similarity between methylenecyclopropanes and MAs, we surmised that Ni(0) might also activate the C2–C3 bond of MAs to undergo coupling with diynes to give [3 + 2 + 2] cycloaddition products. Surprisingly, such a [3 + 2 + 2] cycloaddition product was not obtained after extensive screening. In contrast, only [3 + 2] selectivity occurred and a series of substituted pyrroles were obtained (Scheme 1, d).[9] To the best of our knowledge, this is the first example of metal-catalyzed cycloaddition of MAs *via* the C2–C3 bond cleavage.

Our initial attempts to explore the viability of the cycloaddition reaction using 1-benzyl-2-methyleneaziridine (**1a**) and diyne (**2a**) as model compounds were conducted in the presence of several Ni(0) catalysts (Table 1). When $Ni(cod)_2$ (10 mol%) and *N*-heterocyclic carbene (NHC) SIPr (10 mol%) were used as catalysts,[10] a formal [3 + 2] cycloaddition reaction took place at room temperature to afford pyrrole **3aa** in 27% yield (entry 1). Further attempts using IPr, SIMes or PPh_3 as a ligand, which has been successfully applied in other cycloadditions,[11] were completely futile (entries 2–4). Given that Ni(0) species is significantly important in this reaction, we then examined different nickel(0) sources. Unfortunately, *in situ* generated Ni(0) by the reduction of Ni(II) salts failed (entries 5–7). Interestingly, the optimal conditions were eventually obtained using $Ni(cod)_2$ as a catalyst without other ligands. Screening of the solvent showed that the reaction proceeded well in 1,4-dioxane giving the desired products **3aa** in 60% yield.[12] The identity of **3** was unambiguously secured

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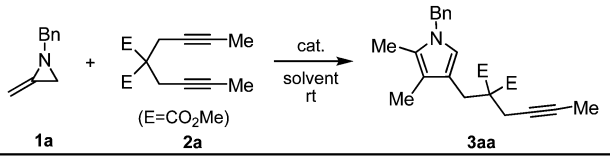
† Electronic supplementary information (ESI) available: General experimental procedures, characterization data, ^1H and ^{13}C NMR spectra and X-ray crystallographic analysis of compound **3da**. CCDC 923335. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc41061g

Table 1 Optimization of reaction conditions[a]



1a 2a 3aa

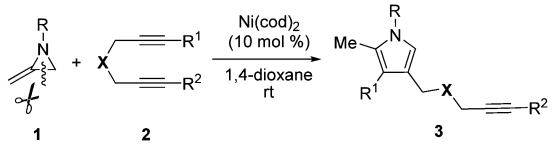
Entry	Catalyst	Solvent	Yield[b] (%)
1	$Ni(cod)_2$/SIPr[c]	Toluene	27
2	$Ni(cod)_2$/IPr[d]	Toluene	0
3	$Ni(cod)_2$/SIMes[e]	Toluene	0
4	$Ni(cod)_2/PPh_3$	Toluene	0
5	$NiCl_2$/Zn/SIPr	Toluene	0
6	$Ni(acac)_2$/Zn/SIPr	Toluene	0
7	(DME)$NiBr_2$/Zn	Toluene	0
8[f]	(DME)$NiBr_2$/Zn	Toluene	21
9	$Ni(cod)_2$	Toluene	49
10	$Ni(cod)_2$	1,4-Dioxane	60

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.2 mmol), 10 mol% catalyst and 10 mol% ligand in 1 mL solvent. [b] Isolated yield. [c] SIPr = 1,3-bis-(2,6-diisopropylphenyl)imidazolidin-2-ylidene. [d] IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. [e] SIMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene. [f] At 60 °C.

by X-ray crystallographic analysis of **3da**[13] which confirmed the connectivity and the cleavage of the C2–C3 bond in MAs.

The scope of substrates was explored under the optimal conditions, and the results are summarized in Table 2. Electron-donating and electron-withdrawing groups on the benzyl moiety of **1** are compatible, providing the desired products in moderate yields (entries 2–6). Methyleneaziridines with an electron-donating –OMe group (**1d–1f**, entries 4–6) afforded the corresponding products in better yields compared to those with an electron-withdrawing –Cl group (**1c**, entry 3). And, the steric effect may be the primary reason leading to the different yields of **3da–3fa** (**3da** < **3ea** < **3fa**).

Table 2 [3 + 2] cycloaddition of MAs **1** with diynes **2**[a]



1 2 3

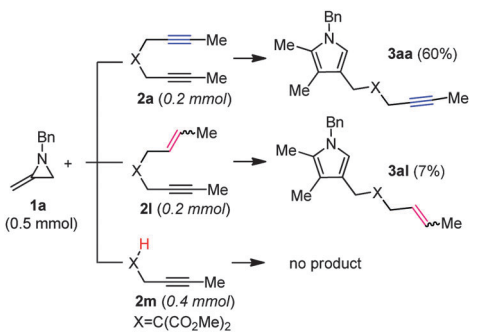
Entry	1 (R)	X	R^1	R^2	3 yield (%)
1	**1a** (Bn)	**2a** [$C(CO_2Me)_2$]	Me	Me	**3aa** (60)
2	**1b** (4-$MeC_6H_4CH_2$)	**2a**	Me	Me	**3ba** (64)
3	**1c** (4-$ClC_6H_4CH_2$)	**2a**	Me	Me	**3ca** (45)
4	**1d** (2-$OMeC_6H_4CH_2$)	**2a**	Me	Me	**3da** (51)
5	**1e** (3-$OMeC_6H_4CH_2$)	**2a**	Me	Me	**3ea** (58)
6	**1f** (4-$OMeC_6H_4CH_2$)	**2a**	Me	Me	**3fa** (62)
7	**1g** (Cy)	**2a**	Me	Me	**3ga** (40)
8	**1f**	**2b** (CH_2)	Me	Me	**3fb** (81)
9	**1a**	**2b**	Me	Me	**3ab** (75)
10	**1a**	**2c** [$C(CO_2Et)_2$]	Me	Me	**3ac** (72)
11	**1a**	**2d** [$C(CO_2Bn)_2$]	Me	Me	**3ad** (65)[b]
12	**1a**	**2e** (O)	Me	Me	**3ae** (33)
13	**1a**	**2f** (NTs)	Me	Me	**3af** (5)
14	**1a**	**2g** [$C(CO_2Me)_2$]	H	H	**3ag** (0)[c]
15	**1a**	**2h** [$C(CO_2Me)_2$]	H	Me	**3ah** (0)[c]
16	**1a**	**2i** [$C(CO_2Me)_2$]	Me	TMS	**3ai** (57)
17	**1a**	**2j** (O)	Me	TMS	**3aj** (50)
18	**1a**	**2k** (CH_2CH_2)	Me	Me	**3ak** (0)[c]

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.2 mmol), 10 mol% $Ni(cod)_2$ in 1 mL 1,4-dioxane. [b] At 60 °C. [c] Product could not be detected by GC-MS of the crude mixture.

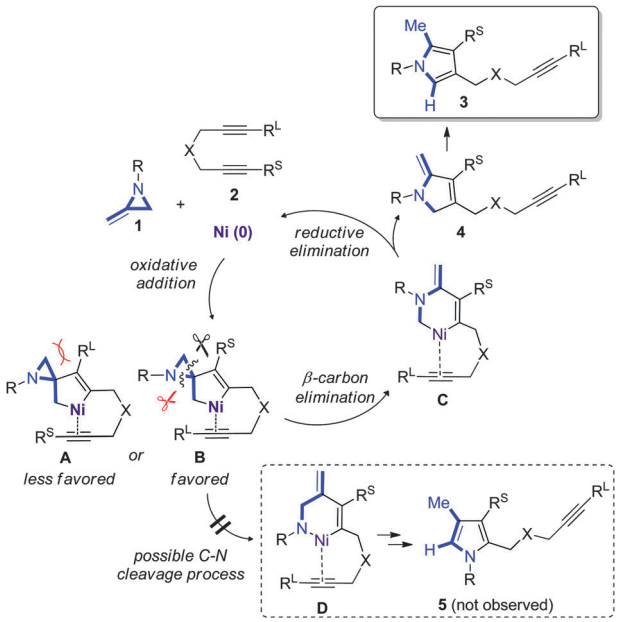
The aliphatic Cy-substituted methyleneaziridine gave a lower yield (**3ga**) than benzyl-substituted methyleneaziridines (**3aa–3fa**, entries 1–6). The dimerization of diyne more likely happened under these conditions than in other cases. Subsequently, the scope of diynes was investigated. Not only malonate-(**2a**, **2c**, **2d**, **2i**), but also oxygen-(**2e**, **2j**), tosylamide- (**2f**) and CH_2-linked (**2b**) 1,6-diynes could undergo this coupling. The different ester moieties of the malonate-diynes (**2a**, **2c**, **2d**) significantly influenced the yields and the diethyl malonate-diyne **2c** gave better yield. It is noteworthy that unlike CH_2-linked 1,6-diyne **2b** gave the product in best yield; the reaction turned out to be messy when a tosylamide linker (**2f**, entry 13) was employed, only giving a trace amount of the corresponding pyrrole (**3af**). Unfortunately, terminal 1,6-diynes (**2g**, **2h**) were also not suitable partners for **1a**, and no desired products were generated due to the rapid diyne dimerization. It seems that the length of the linker plays a significant role, as no desired product was detected in the reaction of 1,7-diyne **2k** under the standard conditions (entry 18, *versus* entry 8). Importantly, when TMS-protected unsymmetrical 1,6-diynes (**2i**, **2j**) were applied in the reaction, the corresponding cycloadducts were obtained in moderate yield with excellent regioselectivity, where a less hindered alkyne unit participated in the reaction. The steric hindrance of the trimethylsilyl moiety somewhat inhibited the dimerization of **2j** (entry 17), thus giving better yield than its methyl-substituted analogue **2e** (entry 12).

To clarify the effects of the two alkynyl moieties and to understand the mechanism of this process, the reactions of diyne (**2a**), eneyne (**2l**) and monalkyne (**2m**) with **1a** were examined under optimized conditions (Scheme 2). The reaction of 1,6-eneyne (**2l**) only gave a trace amount of the desired product **3ak**. In contrast, no desired product was detected when monalkyne **2m** was employed in the reaction with **1a**. These results suggested that (1) the free alkyne unit on the diyne was crucial to the reactivity, which may play an intramolecular stabilizing role. (2) The contribution of alkenyl for similar stabilization was smaller than that of alkynyl.

Based on the above results, a plausible mechanism is depicted in Scheme 3. Typically, such a cyclization begins with oxidative coupling between Ni(0) and π-electron donors.[14] In this case, oxidative addition would first afford a spirocyclic Ni(II) intermediate **A** or **B**, which is stabilized by a proximal alkyne unit. Intermediate **B** is more favored than **A** as a result of the relatively minor interaction between the alkyne substituent and the aziridine moiety. Metalacycle **B** then undergoes β-carbon elimination to give a six-membered nicklacycle **C**. Eventually, reductive elimination occurs to give 2-methylene-2,5-dihydro-1*H*-pyrrole **4** and regenerates the catalyst. Product **4** should



Scheme 2 Control experiments.



Scheme 3 Proposed reaction mechanism.

readily isomerize to product **3**. It is noteworthy that although the possible C–N cleavage of intermediate **B** to **D** also existed in this reaction, it would be difficult to explain that product **5** was not observed.

In summary, we have developed a Ni-catalyzed [3 + 2] cycloaddition of methyleneaziridines with diynes to give pyrroles with a free alkyne unit under mild conditions. This investigation includes a significant indirect C–C bond activation of three-member azacycles and represents an alternative strategy for the ring-enlargement of methyleneaziridines compared with previous C–N bond cleavage.[5,6] The excellent regioselectivity and the free alkyne unit of products are advantageous for further derivatization. The success of C−C bond cleavage of the methyleneaziridines makes it possible to promote metal-catalyzed cycloaddition of this three-membered azacycle with other substrates to give a structure various heterocycles. Further studies on the mechanism and expanding this strategy to other reactions are underway.

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