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Communication

One-Step Synthesis of Diazaspiro[4.5]decane Scaffolds with Exocyclic Double Bonds

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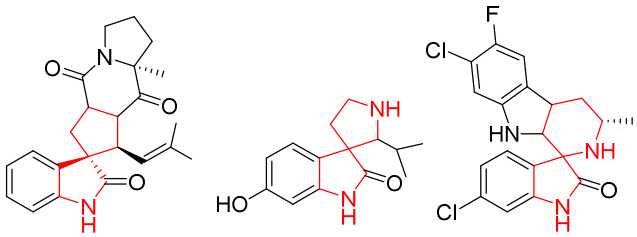
Unactivated yne-en-ynes reacted with a range of substituted aryl halides in the presence of $Pd(OAc)_2/PPh_3$ to afford diazaspiro[4.5]decane with exocyclic double bonds. Three carbon–carbon bonds are formed in this domino reaction, which involves highly regioselective C–C coupling and spiro scaffolds steps.

Natural-product-inspired scaffolds are a rich source of compounds with diverse bioactivities.[1] The challenging molecular architecture and potential biological activities are developed by a synthesis based on rational synthetic design both efficiently and economically.[2] Ding and co-workers developed the efficient synthesis of chiral aromatic spiroketals and the relevant diphosphine ligands.[3] Methods for the synthesis of four spiro [4.5], [5.5], and [5.6] system scaffolds were reported for drug discovery (Scheme 1).[4] Barbas reported on a highly efficient organocatalytic domino Michael–aldol approach for the direct construction of quaternary bispirocyclic oxindole derivatives.[5]



Scheme 1. Representative examples of diazaspiro ring scaffolds.

Waldmann reported a highly enantioselective Lewis acid-catalyzed 1,3-dipolar cycloaddition for the synthesis of biological 3,3′-pyrrolidinyl-spirooxindoles.[6]

Domino reaction strategies for the preparation of spiro scaffolds have produced significant applications in synthetic design.[7,8] In the current study, novel domino methods[9] have been developed to synthesize 4,9-dimethylene-2,7-diazaspiro[4.5]decane compounds through intermolecular and subsequent coupling reduction that lead directly to spiro ring scaffolds through the treatment of the linear yne-en-yne. This study focuses on the development of palladium-catalyzed strategy[10] for the design of spiro scaffolds. Thus, we used the palladium-catalyzed reactions of **a** to **g** (Table 2) with aryl halides, providing a direct, efficient, and economical methodology for the construction of naturally occurring and biologically active azaspirodecane core.[11]

A survey of the reaction conditions using yne-en-yne (**a**) and 4-bromobezonitrile as a test experiment was performed (Table 1). The efficiency of the domino reaction can be considerably enhanced by increasing the reaction temperature to 130 °C. By contrast, higher reaction temperature (>145 °C) lead to the decomposition of **aa**, as indicated by TLC. The additive bases played an important role in the efficiency of this domino reaction by simply varying the bases from caesium carbonate to tributylamine under other identical conditions, as well as furnishing the unexpected 4,9-dimethylene-2,7-diazaspiro[4.5]decane **aa** in 86 % yield. Among the catalysts {$Pd(PPh_3)_4$, $Pd(dba)_2/PPh_3$, $PdCl_2/PPh_3$, $Pd(OAc)_2/PPh_3$, and $[AuCl(PPh_3)/AgSbF_6]$, $[Rh(COD)_2]^+SbF_6^-$}, $Pd(OAc)_2/PPh_3$ had been found to be the most effective. DMF had been proven to be a better solvent than toluene. Thus, the following standard reaction condition have been selected to conduct substrate investigations: yne-en-yne (1 equiv) reacted with different aryl halides (1.1 equiv) in the presence of 2 mol% of $Pd(OAc)_2$ and 4 mol% of Ph_3P with $n$$Bu_3N$ (2 equiv) as an additive in DMF at 130°C.

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization of all new compounds. CCDC965252, 965254, 965256. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

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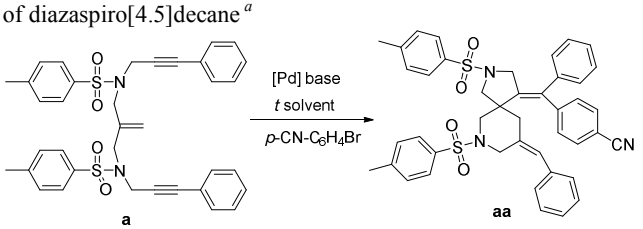
Table 1 Palladium-catalyzed domino reaction for the formation of diazaspiro[4.5]decane [a]



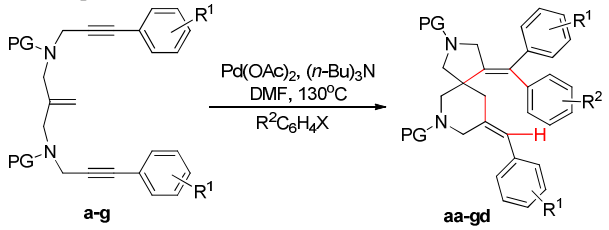
a aa

Entry	[Pd] [mol %]	Base [equiv]	Solvent	t [h]	T [°C]	Yield[b] (%)
1	$Pd(OAc)_2$/PPh_3 (1:2)	nBu_3N (2)	DMF	20	130	22
2	$Pd(OAc)_2$/PPh_3 (2:4)	nBu_3N (2)	DMF	16	130	79
3	$Pd(OAc)_2$/PPh_3 (2:4)	nBu_3N (2)	DMF	20	130	86
4	$Pd(OAc)_2$/PPh_3 (2:4)	nBu_3N (2)	DMF	24	130	86
5	$Pd(OAc)_2$/PPh_3 (2:4)	nBu_3N (2)	DMF	20	145	53
6	$Pd(OAc)_2$/PPh_3 (2:4)	nBu_3N (2)	DMF	20	120	73
7	$Pd(OAc)_2$/PPh_3 (2:4)	nBu_3N (2)	DMF	20	110	19
8	$Pd(OAc)_2$/PPh_3 (2:4)	Cs_2CO_3 (2)	DMF	20	130	13
9	$Pd(OAc)_2$/PPh_3 (2:4)	nBu_3N (2)	DMSO	20	130	30
10	$Pd(OAc)_2$/PPh_3 (2:4)	nBu_3N (2)	Toluene	20	130	41
11	$Pd(PPh_3)_4$ (2)	nBu_3N (2)	DMF	20	130	11
12	$Pd(dba)_2$/PPh_3(2:4)[d]	nBu_3N (2)	DMF	20	130	50
13	$PdCl_2$/PPh_3(2:4)	nBu_3N (2)	DMF	20	130	14
14	$AuCl(PPh_3)$ /$AgSbF_6$(2)	nBu_3N (2)	DMF	20	130	38
15	$[Rh(COD)_2]^+SbF_6^-$ (2)	nBu_3N (2)	DMF	20	130	59

[a] *General conditions:* All reaction were carried out under argon. [b] Isolated yield after flash column chromatography. dba = dibenzylidene acetone.

Illustrative examples of the novel spiro scaffolds scope are shown in Table 2. Interestingly, various yne-en-ynes and substituted aryl halides are compatible with this palladium-catalyzed one-pot domino reaction. Diazaspiro[4.5]decane compounds with exocyclic double bond were readily isolated in good to excellent yields when the aryl halides with electron-withdrawing groups, including ketyl or cyano, were employed. Additionally, 2-methylene-N^1,N^3-bis(3-phenylprop-2-yn-1-yl)propane-1,3-diamine was employed with various substituted groups including *para*- or *ortho*-substituted groups on the benzene ring (i.e., methyl and fluoro). Using aryl halides with yn-en-ynes substrates, the reaction yielded 9-benzylidene-4-(diphenylmethylene)-2,7-diazaspiro[4.5]decanes **aa**, **ca**, **cb**, **da**, and **db**, with yields above 80%. The yield of compound **aa** was the highest at 86%. Simultaneously, the desired 4,9-dimethylene-2,7-diazaspiro[4.5]decanes were obtained in good yields ranging from 66% to 78% when a number of yn-en-ynes was used in the reaction with aryl bromides (**ab**–**ae**, **ba**–**bc**, **cc**, **cd**, **dc**, **dd**, **fa**–**fc**, **ga**–**gd**). The comparison of the substrate **f** and **g** indicated that the electronic properties of the substrates also influenced the regioselectivity of both yne-en-ynes and aryl bromides. The results indicated that **fc** and **gc** exhibited good yields at 69% and 75%, respectively. However, the yield of the desired product was slightly reduced when iodobenzene was employed.

Table 2 Palladium-catalyzed domino reaction for the formation of fused spiro scaffolds [a]



a-g aa-gd

PG = Ts, Benzenesulfonyl; X = Br, I

Entry	S	Y/R^1	$R^2C_6H_4X$	Product	Yield[b] (%)
1	**a**	PG = Ts; R^1 = H	*p*-NCC_6H_4Br	**aa**	86
2	**a**	PG = Ts; R^1 = H	*p*-$CH_3OCC_6H_4Br$	**ab**	76
3	**a**	PG = Ts; R^1 = H	*p*-$OHCC_6H_4Br$	**ac**	78
4	**a**	PG = Ts; R^1 = H	*m*-NCC_6H_4Br	**ad**	77
5	**a**	PG = Ts; R^1 = H	*m*-$CH_3OCC_6H_4Br$	**ae**	71
6	**b**	PG = Ts; R^1 = *p*-CH_3	*p*-NCC_6H_4Br	**ba**	76
7	**b**	PG = Ts; R^1 = *p*-CH_3	*p*-$CH_3OCC_6H_4Br$	**bb**	74
8	**b**	PG = Ts; R^1 = *p*-CH_3	*m*-NCC_6H_4Br	**bc**	78
9	**c**	PG = Ts; R^1 = *p*-F	*p*-NCC_6H_4Br	**ca**	85
10	**c**	PG = Ts; R^1 = *p*-F	*p*-$CH_3OCC_6H_4Br$	**cb**	83
11	**c**	PG = Ts; R^1 = *p*-F	*p*-CHO	**cc**	76
12	**c**	PG = Ts; R^1 = *p*-F	*m*-NCC_6H_4Br	**cd**	78
13	**d**	PG = Ts; R^1 = *o*-F	*p*-NCC_6H_4Br	**da**	83
14	**d**	PG = Ts; R^1 = *o*-F	*p*-$CH_3OCC_6H_4Br$	**db**	84
15	**d**	PG = Ts; R^1 = *o*-F	*m*-NCC_6H_4Br	**dc**	68
16	**d**	PG = Ts; R^1 = *o*-F	*m*-$CH_3OCC_6H_4Br$	**dd**	66
17	**e**	PG = Benzenesulfonyl; R^1 = H	*p*-NCC_6H_4Br	**ea**	61
18	**e**	PG = Benzenesulfonyl; R^1 = H	*p*-$CH_3OCC_6H_4Br$	**eb**	62
19	**e**	PG = Benzenesulfonyl; R^1 = H	*m*-$CH_3OCC_6H_4Br$	**ec**	51
20	**f**	PG = Benzenesulfonyl; R^1 = *p*-CH_3	*p*-NCC_6H_4Br	**fa**	74
21	**f**	PG = Benzenesulfonyl;	*p*-$CH_3OCC_6H_4Br$	**fb**	67

		R^1 = *p*-CH_3			
22	**f**	PG = Benzenesulfonyl; R^1 = *p*-CH_3	*m*-NCC_6H_4Br	**fc**	69
23	**g**	PG = Benzenesulfonyl; R^1 = *p*-F	*p*-NCC_6H_4Br	**ga**	77
24	**g**	PG = Benzenesulfonyl; R^1 = *p*-F	*p*-$CH_3OCC_6H_4Br$	**gb**	72
25	**g**	PG = Benzenesulfonyl; R^1 = *p*-F	*m*-NCC_6H_4Br	**gc**	75
26	**g**	PG = Benzenesulfonyl; R^1 = *p*-F	*m*-$CH_3OCC_6H_4Br$	**gd**	67
27	**a**	PG = Ts; R^1 = H	*p*-NCC_6H_4I	**aa**	76

[a] *General conditions:* **a–g**(1.0 equiv), $R^2C_6H_4X$ (X = Br; I) (1.1 equiv), $Pd(OAc)_2$ (2 mol %), PPh_3 (4 mol%), nBu_3N (2 equiv), DMF 10 mL, 130°C, 20 h. [b] Isolated yield after flash column chromatography.

All the resulting spiro scaffolds were confirmed by one- (^1H, ^{13}C) and two-dimensional (COSY) NMR spectral analyses, and elemental or HR-MS analyses, respectively. The molecular structures of **fa**, **ga** (Figure 1), and **gb**, were confirmed using single-crystal X-ray analyses (see the supplementary materials for details).[12]

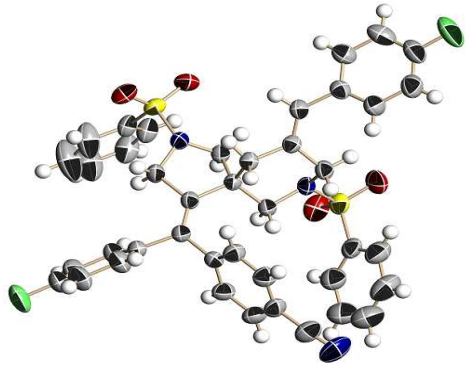


Fig. 1 The molecular structure of compound **ga**. Thermal ellipsoids are drawn at the 30% probability level.

In summary, we have developed a palladium-catalyzed domino reaction for the synthesis of spiro scaffold dicycles through multistep C–C bond formation by treatment of the yne-en-ynes with a range of substituted aryl halides that afford diazaspiro[4.5]decane with exocyclic double bonds derivatives in moderate to very good yields and excellent regioselectivity. This process provides a new methodology for the synthesis of spiro heterocyclic ring system. The ready accessibility of the starting materials, a wide range of compatible of substrates including both yne-en-ynes and aryl halides, and the generality of this process, make the reaction highly valuable because of the synthetic and medicinal importance for these spiro heterocycles. The mechanism is not clear so far. Further investigations to better understand this catalytic transformation, evaluate the process with a broader scope of substrates, synthesize more complex products, and explore their biological activity tests are in progress in our laboratory.

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12 CCDC 965252 (**fa**), 965254 (**ga**), and 965256 (**gb**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, U.K.; Fax: (+44)-1223-336-033; or deposit@ccdc.cam.ac.uk.