Synthetic Methods

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Diverse Reactivity of Zirconacyclocumulenes Derived from Coupling of Benzynezirconocenes with 1,3-Butadiynes towards Acyl Cyanides: Synthesis of Indeno[2,1-*b*]pyrroles or [3]Cumulenones**

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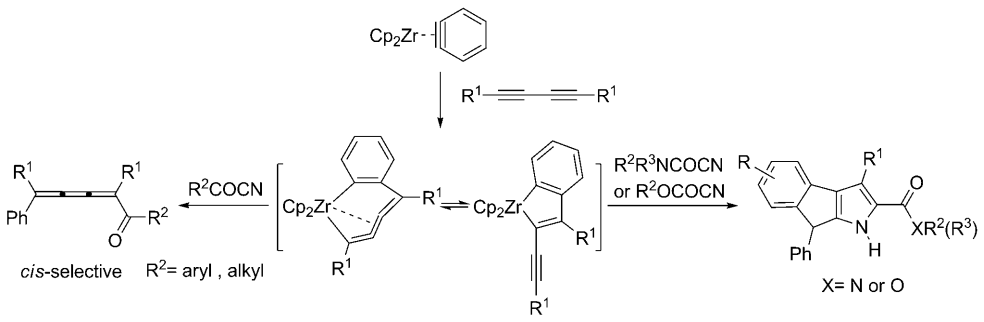
The Group 4 metal complexes have attracted considerable attention owing to their fascinating structural features, their unique M–C bonding, and their unusual capacity to induce highly selective transformation reactions.[1] One of the most extensively studied areas is the chemistry of diynes $R(C{\equiv}C)_2R$ and polyynes $R(C{\equiv}C)_nR$ with metallocenes.[2–4] An extensive investigation by Rosenthal and co-workers[2] was performed using the metallocene source $[Cp_2M(L)(\eta^2\text{-}Me_3SiC{\equiv}CSiMe_3)]$ (M = Ti, L = –; M = Zr, L = THF; Cp = C_5H_5) as a low-valent metal equivalent. These studies revealed a variety of interesting reaction modes, such as complexation, C–C single-bond cleavage, and coupling reactions. The most notable work was the discovery of the five-membered metallacyclocumulenes $[Cp_2M(\eta^4\text{-}1,2,3,4\text{-}RC_4R)]$ (R = *t*Bu, M = Zr, Ti; η^4-complexes), which formed an equilibrium with a metallacyclopropene (η^2-complex) in some reactions. Seven-membered zirconacyclocumulenes have also been accessed through homocoupling of butadiynes[4c] or cross-coupling of benzynezirconocenes with butadiynes.[4a] However, the utilization of these complexes in organic synthesis has rarely been reported. Recently, we showed that zirconium-mediated coupling of 1,3-butadiynes with aldehydes or ketones provides an efficient, general, one-pot method for *cis*-[3]cumulenol formation.[5a] We also investigated the C–C bond formation reactions of α-alkynylzirconacyclopentenes by cyclization or by a copper- and palladium-mediated sequence of cyclization and cross-coupling with aryl iodides. We suggested that zirconacyclocumulenic intermediates were involved in our reactions.[5b] These original results prompted us to study the chemistry of zirconacycles with a cumulenic structure. We report herein an unprecedented cycloaddition of carbamoyl cyanides to 1,3-butadiynes via seven-membered zirconacyclocumulenes to form dihydroindeno[2,1-*b*]pyrroles. It turns out that an sp^2 C–H bond activation on the aromatic substituent of 1,3-butadiynes takes place during the process. We also report the diverse reactivity of the same zirconacycles towards aryl or alkyl acyl cyanides, which provides a stereoselective route to *cis*-[3]cumulenones (Scheme 1).



Scheme 1. Diverse reactivity of zirconacyclocumulenes.

Meunier et al. reported that the coupling reaction of 1,4-diphenyl-1,3-butadiyne **1a** with benzynezirconocene $[Cp_2Zr(\eta^2\text{-}C_6H_4)]$ occurs by heating **1a** with diphenylzirconocene at 80 °C for several hours, furnishing a seven-membered zirconacyclocumulene **2a** (Table 1, Ar = Ph). Theoretical calculations revealed that an interaction between the d_{xy} metal atomic orbital with one terminal σ orbital and with the in-plane π orbital of the cumulene contribute to the remarkable stability of **2a**.[4a] In our continuing effort to explore the new synthetic potential of functionalized zirconacycles towards carbon electrophiles,[6] we found that treatment of zirconacycle **2a** formed in situ with *N*,*N*-dimethylcarbamoyl cyanide at 80 °C overnight afforded 1,8-dihydroindeno[2,1-*b*]pyrrole **3a** in 74% yield after hydrolysis (Table 1, entry 1). The structures of **3a** and **3h** were unambiguously confirmed by X-ray crystallographic analysis,[7] which clearly showed the pyrrole ring. The structure of **3h** also indicated that the phenyl group on the indenyl sp^3 carbon atom is derived from benzynezirconocene.

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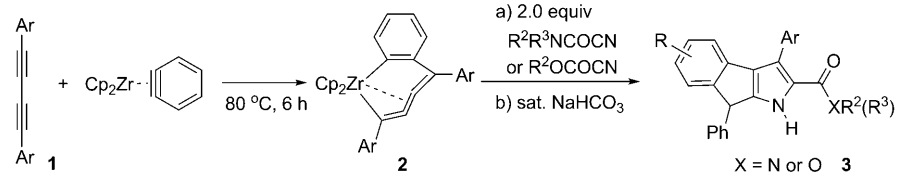
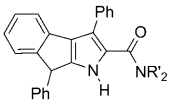
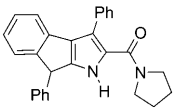
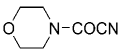
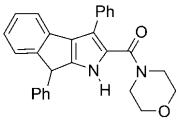
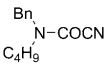
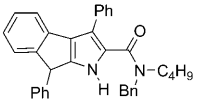
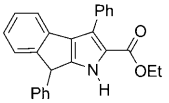
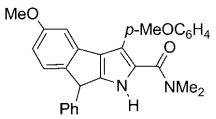
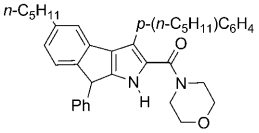
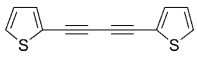
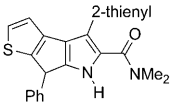
Table 1: Preparation of 1,8-dihydroindeno[2,1-*b*]pyrrole-2-carboxamide or -carboxylate.



1 **2** **3**

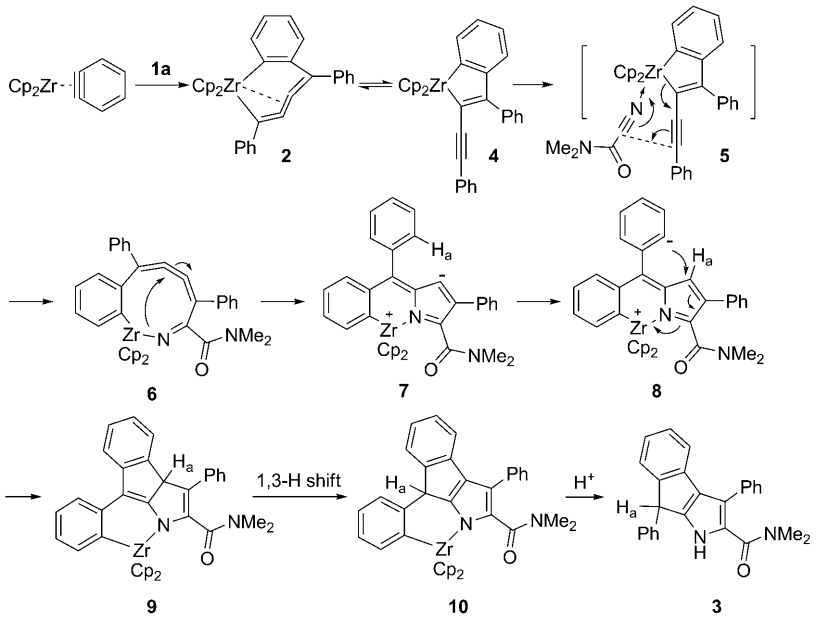
Entry	Butadiyne	Cyanide compound	Product		Yield [%][a]
1	Ph—≡—≡—Ph	Me_2NCOCN		**3a**	74
	1a		$R' = Me$		
2	**1a**	Ph_2NCOCN	$R' = Ph$	**3b**	74
3	**1a**	iPr_2NCOCN	$R' = iPr$	**3c**	74
4	**1a**			**3d**	67
5	**1a**			**3e**	76
6	**1a**			**3f**	40
7	**1a**	EtOCOCN		**3g**	53
8	Ar—≡—≡—Ar **1b**, Ar = *p*-$MeOC_6H_4$	Me_2NCOCN		**3h**	51
9	Ar—≡—≡—Ar **1c**, Ar = *p*-(*n*-C_5H_{11})C_6H_4			**3i**	70
10	 **1d**	Me_2NCOCN		**3j**	33

[a] Yield of isolated product. All reactions were carried out overnight at 80 °C.

It is interesting to note that in this novel transformation, the reactions of benzene-fused zirconacyclocumulene **2** proceeded selectively at the cumulenic zirconium moiety, while the Zr–C(sp^2) bond at the side of benzene ring remained intact. Most striking is the conversion of one of the free phenyl groups on the butadiyne moiety into the fused indene ring, which can be explained by the activation of the C–H bond at the *ortho* position of the phenyl ring.

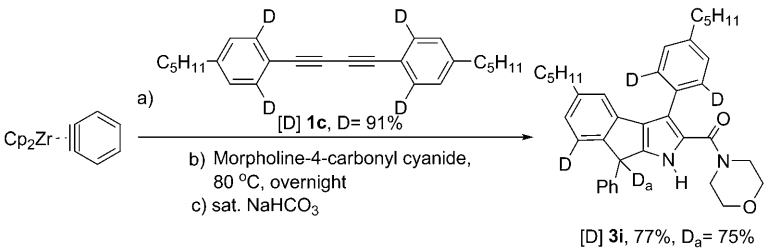
Pyrroles are important heterocycles that widely occur as key structural subunits in numerous natural products,[8] which can find various applications in pharmaceuticals[9] and materials science.[10] The tandem sequence described herein allows the efficient synthesis of complex pyrrole derivatives. As shown in Table 1, a variety of carbamoyl cyanides smoothly underwent cycloaddition reactions to yield pyrrole derivatives with the formamide functionality $CONR^1R^2$ in 33–76% yields. *N*,*N*-Diphenyl-substituted carbamoyl cyanide afforded the corresponding pyrrole **3b** in 74% yield, indicating that the aryl substituents on carbamoyl cyanides have little influence on the cycloaddition reaction (Table 1, entry 2). The addition of cyclic carbamoyl cyanides similarly gave **3d** and **3e** in 67 and 76% yields, respectively (Table 1, entries 4 and 5). The *N*-benzyl-*N*-alkyl carbamoyl cyanide afforded the corresponding product **3f** in 40% yield (Table 1, entry 6). Interestingly, ethyl cyanoformate could also be used for this reaction, and the pyrrole **3g** bearing an ester functionality was obtained in 53% yield (Table 1, entry 7). When bis(thienyl)butadiyne **1d** was employed, the corresponding product **3j** was formed in 33% yield (Table 1, entry 10).

We tentatively propose the following plausible mechanism for this cascade reaction (Scheme 2): first, a seven-membered zirconacyclocumulene **2** is produced in the reaction mixture, which is assumed to be in equilibrium with the five-membered α-alkynylzirconacyclopentadiene **4**. An S_E2'-type addition[11] of carbamoyl cyanide to the zirconacycle intermediate **4**, presumably via a cyclic transition state by coordination of cyano group to zirconium, gives a nine-membered azazirconacycle **6** with a cumulenic moiety. In this case, the cyanide group is much more reactive than the carbonyl group, as the electronic delocalization over the O-C-N unit caused by resonance of the nitrogen lone pair with the carbonyl π system would decrease the reactivity of the carbonyl group. However, direct insertion of the cyano group into the cumulenic Zr–C(sp^2) bond of **2** cannot be excluded. Intramolecular attack of the nitrogen atom at the cumulenic double bond results in the formation of a zwitterionic intermediate **7**, which immediately abstracts a hydrogen from the adjacent phenyl ring to afford **8**. Metal-assisted attack of the triene double bond by oxygen or carbon nucleophiles has precedent in the literature.[5b,12] Compound **8** undergoes ring closure and subsequent 1,3-H shift to give intermediate **10**. Hydrolysis of **10** affords the desired product **3**.



Scheme 2. Proposed mechanism for the formation of indeno[2,1-*b*]pyrroles.

To support the proposed reaction mechanism, a deuterated butadiyne 1,4-di(*para*-(*n*-pentyl)phenyl)buta-1,3-diyne [D]**1c** was prepared (deuterium incorporation is 91%). The coupling reaction with morpholine-4-carbonyl cyanide successfully afforded the pyrrole [D]**3i** with 75% incorporation of D_a (Scheme 3). The result clearly indicates that one of the *ortho* C–H bonds of the aromatic ring on the butadiyne terminus was activated during the reaction.



Scheme 3. The reaction with a deuterated butadiyne.

In light of the unusual reactivity of zirconacycle **2**, we proceeded to investigate the reactions of **2** with aryl acyl cyanides. Interestingly, it was found that [3]cumulenone **11** was formed in good to high yields after hydrolysis. Representative results are shown in Table 2. Functionalized aryl acyl cyanides bearing a chlorine (88%), NO_2 (91%), methyl (85%), or heterocyclic group (83%) reacted very well with zirconacycle **2a**, leading to the corresponding products in high yields (Table 2, entries 2–4, 6). An alkyl acyl cyanide such as *t*BuCOCN could also be used; product **11g** was formed in 66% yield, although a higher reaction temperature of 80°C was required (Table 2, entry 7). When alkyl-substituted butadiynes **1e** and **1f** were used, the reaction selectively afforded *cis*-[3]cumulenones **11i** and **11j** in 69 and 74% yields, respectively, with high stereoselectivity, as confirmed by X-ray crystallographic analysis of **11i**[7] (Table 2, entries 9 and 10). Butadiyne **1g** with an OPh group was also compatible with this reaction, furnishing **11k** in 72% yield (Table 2, entry 11). It should be noted that *cis–trans* isomerization[13] easily occurred during the workup of **11h** and **11k**. It turned out that if all of the operations were carried out at room temperature, isomerization could be minimized, and *cis*/*trans* ratios of 91:9 (**11h**) and 90:10 (**11k**) were obtained.

These results indicated that aryl acyl cyanides behaved differently than carbamoyl cyanides. A plausible reaction mechanism is shown in Scheme 4. In this scenario, a carbonyl group instead of a CN group reacts with the Zr–C bond to form nine-membered zirconacycle **12**. Hydrolysis of **12** may afford cyanohydrin **13**, which was unstable and easily converted into the cumulenone **11** upon direct isolation by column chromatography or treatment with Et_3N prior to column separation. An attractive advantage of this strategy is the stereoselective construction of cumulenic compounds that are not easily available by other methods.

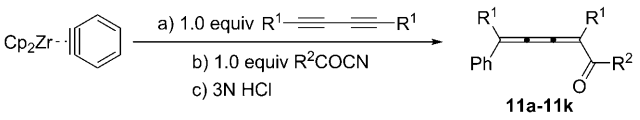
In summary, we have shown that cycloaddition of carbamoyl cyanide compounds to zirconacyclocumulenes derived from zirconium-mediated benzyne–1,3-butadiyne coupling reactions afforded 1,8-dihydroindeno[2,1-*b*]pyrroles, while the reactions of aryl or alkyl acyl cyanides provided access to an efficient one-pot procedure for the *cis*-selective synthesis of tetrasubstituted [3]cumulenones. Clarification of the reaction mechanism and further application of this chemistry are in progress.

Experimental Section

General procedure for the preparation of 1,8-dihydroindeno[2,1-*b*]pyrrole-2-carboxamides or -carboxylate **3**: PhLi (1.4 mmol, 2.0 M in dibutyl ether, 0.7 mL) was added dropwise to a solution of $[Cp_2ZrCl_2]$ (0.19 g, 0.65 mmol) in toluene (5 mL) at 0°C. After stirring for 1 h at that temperature, 1,3-butadiyne **1** (0.5 mmol) was added, and the reaction mixture was warmed up to 80°C and stirred for 6 h. The resulting orange-yellow solution was allowed to return to room temperature, and carbamoyl cyanide or ethyl cyanoformate (1.0 mmol) was added. Then the reaction mixture was warmed up to 80°C and stirred overnight. The reaction mixture was allowed to return to room temperature, was quenched with saturated aqueous $NaHCO_3$ and extracted with diethyl ether. The extract was washed with water and brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo, and the residue was purified by column chromatography on silica gel to afford the desired pyrrole products **3**.

General procedure for the preparation of [3]cumulenones **11**: PhLi (1.4 mmol, 2.0 M in dibutyl ether, 0.7 mL) was added dropwise to a solution of $[Cp_2ZrCl_2]$ (0.19 g, 0.65 mmol) in toluene (5 mL) at 0°C. After stirring for 1 h at that temperature, 1,3-butadiyne **1** (0.5 mmol)

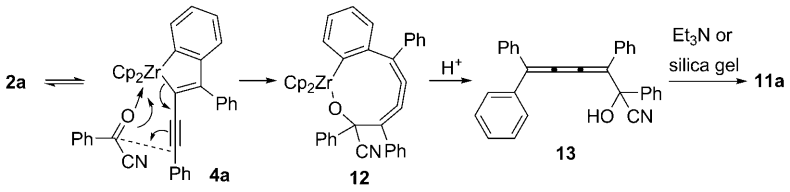
Table 2: One-pot synthesis of penta-2,3,4-trien-1-one.



11a-11k

Entry	Butadiyne	R^2COCN	Product	Yield [%][a]	*cis/trans*
1	Ph—≡—≡—Ph **1a**	PhCOCN	**11a**	84	
2	**1a**	*p*-ClC_6H_4COCN	**11b**	88	
3	**1a**	*p*-$NO_2C_6H_4COCN$	**11c**	91	
4	**1a**	*p*-MeC_6H_4COCN	**11d**	85	
5	**1a**	1-naphthyl-COCN	**11e**	90	
6	**1a**	2-furanyl-COCN	**11f**	83	
7	**1a**	*t*BuCOCN	**11g**	66[b]	
8	Ar—≡—≡—Ar **1b** (Ar = *p*-$MeOC_6H_4$)	*p*-$NO_2C_6H_4COCN$	**11h**	67	91:9
9	C_5H_{11}—≡—≡—C_5H_{11} **1e**	*p*-$NO_2C_6H_4COCN$	**11i**	69	95:5
10	C_6H_{13}—≡—≡—C_6H_{13} **1f**	*p*-$NO_2C_6H_4COCN$	**11j**	74	97:3
11	$PhOCH_2$—≡—≡—CH_2OPh **1g**	PhCOCN	**11k**	72	90:10

[a] Yield of isolated product. [b] The reaction was carried out overnight at 80 °C. The product was formed together with a small amount of by-product.



Scheme 4. Proposed mechanism for the formation of cumulenones.

was added, and the reaction mixture was warmed up to 80 °C and stirred for 6 h. The resulting orange-yellow solution was allowed to return to room temperature, and acyl cyanide (0.5 mmol) was added. After stirring for 1 h, the reaction mixture was quenched with 3 N HCl and then extracted with diethyl ether three times. The extract was washed with saturated aqueous $NaHCO_3$, water, and brine and dried over anhydrous $MgSO_4$. The solvent was removed by rotary evaporation and oil pump successively at room temperature to minimize *cis-trans* isomerization, and the residue was purified by chromatography on silica gel to afford the [3]cumulenone derivatives **11**. When pivaloyl cyanide was used, the reaction was carried out overnight at 80 °C and quenched with saturated $NaHCO_3$ solution. In some cases, several drops of Et_3N were added to the extract of the reaction mixture after workup and then the solution was stirred for ca. 1 h to promote the elimination of HCN. This step should be carefully handled in the ventilating hood.

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