Phosphine-Catalyzed [3+2] Annulation of Cyanoallenes

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Abstract: Cyanoallenes were successfully used in organophosphine-catalyzed [3+2]-type annulation to give cyano-substituted dihydropyrroles in good yield. Chiral phosphines were also screened, leading to some initial results in the asymmetric version of cyanoallene-based annulations.

Key words: cyanoallene, [3+2] annulation, phosphine, organocatalysis, dihydropyrrole

Cyanoallene [2,3-butadienenitrile, (1)] is the smallest cyano-containing 2,3-diene. Its presence in interstellar gas clouds was recently discovered using far infrared spectroscopy.¹ Closer to home, the compound is easily synthesized from propargyl bromide and potassium cyanide (Scheme 1).² Cyanoallene and its derivatives (CAUTION strong lachrymators) have not found widespread use in synthesis,³ probably because the related allenoates (e.g. methyl-2,3-butadienoate) do not require cyanides for their synthesis. The rare use of cyanoallenes in synthesis so far and the expected increased reactivity compared to allenoates prompted us to revisit cyanoallenes as useful starting materials for synthesis in general and cycloadditions in particular.



Scheme 1

With allenoates many reactions have been developed,⁴ but the recently disclosed [3+2]- and [4+2]-type annulations, catalyzed by alkyl- or arylphosphines as nucleophilic trigger, caught our attention.⁵ In this communication we present a short survey on the reactivity of cyanoallenes in the [3+2]-type of annulations. The research started by reacting cyanoallene with methyl vinyl ketone (**2**) as well as with *N*-methyl maleimide (**4**) in the presence of a catalytic amount of triphenylphosphine (10–20 mol%, Scheme 2).



Scheme 2

SYNLETT 2011, No. 12, pp 1693–1696 Advanced online publication: 21.06.2011 DOI: 10.1055/s-0030-1260804; Art ID: B07111ST © Georg Thieme Verlag Stuttgart · New York As expected, both compounds **3a** and **3b** were formed, albeit in low yield. The outcome of an equimolar product ratio came as a surprise to us, since a strong bias towards formation of the α -addition product ($\alpha/\gamma > 75:25$) with methyl 2,3-butadienoate was known.^{5a} Together with the products, oligomerization of **1** was observed. Reacting **1** with maleimide **4** gave a similar yield at elevated temperature using 20 mol% of catalyst (Scheme 3).





Although these reactions were not fully optimized, we already noticed the trend that cyanoallenes were more reactive and prone to oligomerization than the corresponding allenoates. Probably, since a more electron-withdrawing ester functionality to form the more stable zwitterion is lacking, the lesser stabilizing cyano functionality causes an increased overall reactivity together with lower selectivity for reaction at the α -position (Scheme 4).





The facile formation of oligomers using cyanoallene does not come as a surprise, since Horner already in 1955 reported the triphenylphosphine-catalyzed oligomerization of acrylonitrile.⁶ To see its reactive behavior towards more electrophilic double bonds and to suppress oligomerization, we investigated Lu's [3+2] cycloaddition using electron-poor imines (Table 1).^{5c} Yields for this annulation reaction were much better, giving **7a** and **7b** in 91% and 80% yield, respectively, using 20 mol% PPh₃ in benzene at room temperature overnight (entries 1 and 2).⁷

Relative electron-poor substrates gave good results as well, with 63% yield for **7c** and 95% yield for **7d** (entries 3 and 4). These cyano-containing heterocycles are less known in literature than the related esters.⁸ Next, the same reaction was tested using 3-methyl cyanoallene [2,3-pen-

 Table 1
 Lu's [3+2] Annulation with Cyanoallene (1)



^a Isolated yield after column chromatography.

tadienenitrile (8)], easily prepared using the literature procedures.^{2a,b} For this sterically more demanding annulation, the conditions developed by the group of Kwon for γ -substituted allenoates were used.^{5d} Following this protocol, cyanoallene 8 was reacted with different *N*-sulfonyl imines 6 in the presence of 20 mol% PBu₃ as catalyst in benzene at room temperature (Table 2).

 Table 2
 [3+2] Annulation with 3-Methyl Cyanoallene (8)

Me	8 CN + Ar	PG (20 mol ^c H benzene, 6 h	%) r.t. Ar	Me PG 9
Entry	Ar	PG	Product	Yield (%) ^a
1	Ph	SO_2Ph	9a	72
2	$4-MeC_6H_4$	Ts	9b	54
3	$4-CF_3C_6H_4$	Ts	9c	73
4	3-furanyl	Ts	9d	51
5	cinnamyl	Ts	9e	72
6	4-tolyl	SES	9f	81

^a Isolated yield after column chromatography.

In most cases, almost full conversion was observed in less than six hours. Longer reaction times mostly led to more polymerization of **8** and degradation of imine leading to side products. In all cases the reaction provided high diastereoselectivities (dr > 90:10). In all instances only the major *cis*-diastereoisomer was isolated after column chromatography.⁹ The (substituted) benzaldimines gave the annulation products **9a–c** in good yields ranging from 54– 73% (entries 1–3). The sensitive 3-furanyl sulfonylimine gave product **9d** in 51% yield (entry 4) and the cinnamyl sulfonylimine provided the desired product in good yield (entry 5). Use of the b-trimethylsilylethanesulfonyl (SES) protecting group actually gave the best yield (81%) in this series (entry 6).

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Sterically even more demanding annulations were tested with 3,3-disubstituted cyanoallenes **10** and **12** (Schemes 5 and 6).¹⁰ Since such [3+2] annulations with the corresponding 3,3-disubstituted allenoates have not been reported in literature, we were very pleased to see the formation of **11** in moderate isolated yield using 20 mol% PBu₃ in benzene at 50 °C (Scheme 5).



The limit for this reaction was set by using 3-cyclohexylideneacrylonitrile (12), which did not give the desired product (Scheme 6). The only isolated product from this reaction arose from imine hydrolysis and subsequent 1,4addition of tosylamide to cyanoallene 12.





Figure 1 Chiral phosphines tested

Finally, a number of (commercially) available enantiopure phosphines were screened in the [3+2] cyanoallene annulation (Figure 1).¹¹ For unsubstituted allenoates several literature reports on successful enantioselective [3+2] annulations have been reported.¹² Especially asymmetric annulations using 3-methyl cyanoallene were of interest to us, since virtually no literature reports on asymmetric [3+2] annulations with the corresponding 3substituted allenoates have been reported so far.^{12f} Of the array of catalysts screened (Figure 1), phosphine catalysts like (*R*)-MeO-Biphep, (*R*,*R*)-Me-Duphos, (*R*)-Synphos and Miller's amino acid derived phosphine^{12f} provided very low yields and ee values. Other catalysts that provided significant ee values and reasonable to good yields are listed in Table 3.





Entry	Cyanoallene Catalyst		Time (h)	Product ee (%) ^a		Yield $(\%)^{b}$
1	1	(S)-NMDPP	96	7a	+5	99
2	1	(S),(S)-Chiraphos	16	7a	-10	77
3	1	(-)-DIOP	72	7a	+10	81
4	1	DUANPhos	168	7a	-10	54
5	8	(S)-NMDPP	24	9a	+28	50
6	8	(S),(S)-Chiraphos	16	9a	0	78
7	8	(-)-DIOP	16	9a	+12	85
8	8	DUANPhos	168	9a	-60	18
9	8	catASium®D(<i>R</i>)	16	9a	+13	79

^a Determined by chiral HPLC, OD column, *n*-heptane–*i*-PrOH (90:10), the sign is given relative to each other.

^b Isolated yield after column chromatography.

Interestingly, we found no account on the use of (S)-(+)neomenthyldiphenylphosphine [(S)-NMDPP] in phosphine-catalyzed annulations. For both cyanoallenes 1 and 8, this phosphine gave good to reasonable yields of the annulation products 7a (99%) and 9a (50%), but with an ee of only 5% for 7a and 28% for 9a (entries 1 and 5). Chiraphos gave good yields for both products, but with low or no ee (entries 2 and 6). In terms of yield, (-)-DIOP proved to be the most reliable catalyst, though no ee values higher than 12% were obtained (entries 3 and 7). For cyanoallene (1), DUANPhos gave 7a in a yield of 54% with slight excess of the other enantiomer (entry 4). For both substrates 1 and 8, the sterically very hindered DUANPhos gave a very slow conversion. After prolonged reaction times, 9a was isolated in 18% yield. Being the highest so far, the ee was determined to be 60%. Higher temperatures or a change in solvent did not lead to improvements for this specific case. catASium[®]D(R), bearing a tertiary nitrogen, gave a good yield (79%) but the ee did not reach significant values (entry 9). Most of the phosphines tested are diphosphines with the phosphorus atoms in different stereoconfigurations, therefore undesired complexity in the asymmetric induction cannot be excluded.

In conclusion, the use of cyanoallenes in phosphine-catalyzed [3+2] annulations successfully provided the cyanosubstituted dihydropyrroles. The use of a 3,3-dimethylsubstituted allene was demonstrated for the first time. Some initial results in the asymmetric phosphine-catalyzed [3+2] annulations with cyanoallenes were also established.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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chromatography (hexanes–EtOAc, 4:1–1:1). For further details, see the supplementary material.

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