Efficient Synthesis of 2-Pyridylenynes and Application in Cobalt-Catalysed Benzannulation Reactions

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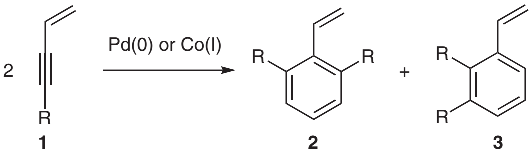
Abstract: The cobalt-catalysed benzannulation of 2-pyridine-substituted enynes gave 2,3-bis(2-pyridyl)styrenes in moderate yields. The reaction with dibromomethane as well as diiodomethane generated the corresponding planar-chiral bispyridinium salts in good yields. On the other hand, the transformations with reagents of the type $RCHBr_2$ to afford diastereomeric products led to the desired conversion. However, these products could not be obtained in pure form.

Key words: benzannulation, cobalt, enynes, pyridines, styrenes

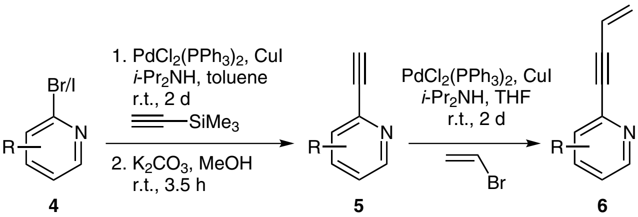
The benzannulation of enynes is a very facile reaction for the fast assembly of multiple functionalised styrene derivatives. Two transition-metal-catalysed methods have been described to realise this transformation efficiently. First, the well-documented palladium-catalysed benzallulation reported by Yamamoto and Gevorgyan which can be applied for the homo-benzannulation[1] as well as for the cross-benzannulation[2] utilising an enyne and an alkyne as starting materials. The second method is the cobalt-catalysed benzannulation described by us which has only been applied for the homo-benzannulation thus far.[3] The benzannulation of enynes **1** (Scheme 1) can lead to two regioisomers **2** and **3**. While in the palladium-catalysed reaction the products of type **2** are obtained exclusively, the cobalt-catalysed process is strongly solvent-dependent and in these reactions both regioisomers can be generated as major regioisomers.



Scheme 1

We were particularly interested in enynes bearing a 2-pyridyl substituent. The thereof generated bispyridyl products of type **3** could act as bidentate planar-chiral ligands, but also unprecedented diastereomers were envisaged when the bispyridyl derivatives were reacted with geminal dibromomethane derivatives (see below).

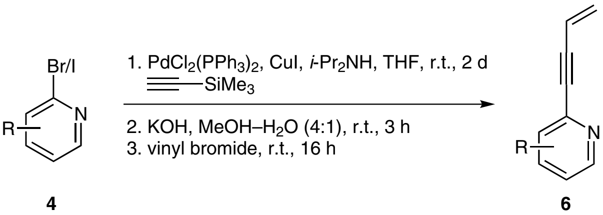
For the synthesis of the enynes commercially available 2-iodopyridine and 2-bromopyridine derivatives were selected. Following a more traditional stepwise reaction sequence for the synthesis of the enynes, a Sonogashira coupling with TMS acetylene, followed by a deprotection and isolation of the product, and a second Sonogashira coupling with vinyl bromide were conducted (Scheme 2).[4]



Scheme 2

The results of this two-step procedure are summarised in Table 1.

Inspired by the sequential one-pot procedure reported by Doye,[5] we also applied this sequence for the efficient synthesis of the desired 2-pyridyl enynes **6** (Scheme 3).



Scheme 3

The results of the one-pot reaction sequence are also incorporated in Table 1 (right column).[6] The comparison of the two reaction sequences reveals that the yields are considerably higher when the labile intermediates of type **5** are not isolated. The one-pot protocol has the high advantage of sustainability avoiding additional workup procedures, reducing the amount of palladium catalyst and reagents, and consuming less time. Only in a single case (Table 1, entry 4), for whatever unrevealed reason, the one-pot reaction sequence was not successful. Moreover, the electron-deficient pyridine derivatives applied in entries 7 and 8 (Table 1) could not be converted into the desired products. Also, when 2-bromo-4-aminopyridine was used (Table 1, entry 6) no desired product could be isolat-

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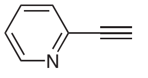
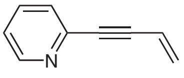
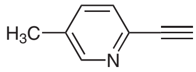
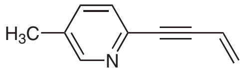
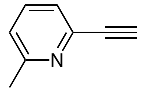
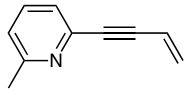
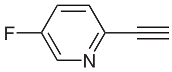
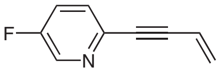
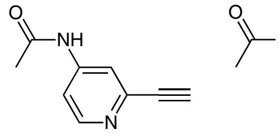
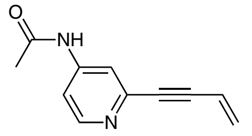
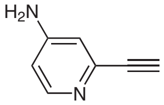
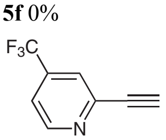
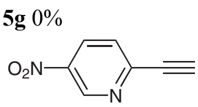
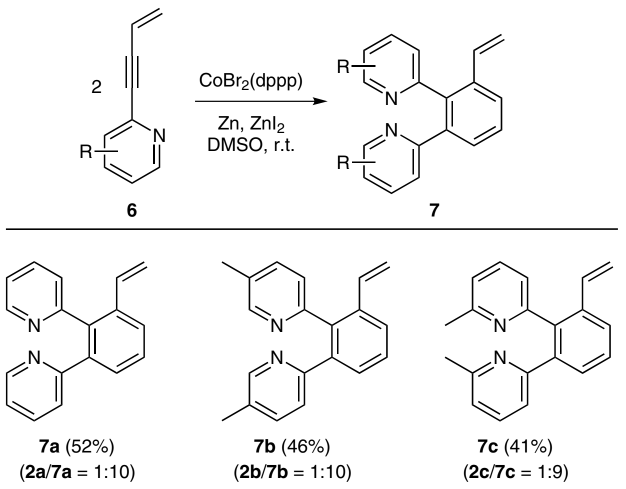
Table 1 Results of the Reaction Sequence for the Synthesis of Enynes of Type **6**

Entry	Alkyne **5** (single-step yield, %)	Enyne **6** (single-step yield, %)	One-pot yield (%)
1	 **5a** 85%	 **6a** 72%	74
2	 **5b** 74%	 **6b** 83%	89
3	 **5c** 72%	 **6c** 69%	87
4	 **5d** 65%	 **6d** 46%	–
5	 **5e** 72%	 **6e** 69%	83
6	 **5f** 0%	–	–
7	 **5g** 0%	–	–
8	 **5h** 0%	–	–

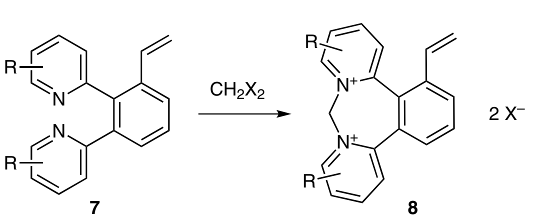


7a (52%) (**2a**/**7a** = 1:10) **7b** (46%) (**2b**/**7b** = 1:10) **7c** (41%) (**2c**/**7c** = 1:9)

Scheme 4

ed. Nevertheless, five enynes of type **6** could be obtained and used in the cobalt-catalysed benzannulation reaction (Scheme 4).[7] For three of the enynes **6a**–**c** the cobalt-catalysed benzannulation reaction led to the desired products in moderate yields. Although a number of reaction conditions and workup procedures were tested, the yield for the previously reported derivative **7a** could only be increased by about 12%.

For the enyne **6d** only traces of the desired product **7d** could be detected by GC–MS analysis while the conversion of **6e** to the corresponding product **7e** gave no conversion at all. The regioselectivities of the cobalt-catalysed benzannulation reactions are good and proved to be best when the reactions were performed in dimethylsulfoxide (DMSO) as solvent. After column chromatography the pure regioisomers **7a**–**c** were obtained in acceptable yields. Nevertheless, with these three bispyridyl derivatives in hand, we tested the reaction with dibromo- and diiodomethane under various conditions to generate bispyridinium salts of type **8** (Scheme 5).[8]



Scheme 5

Interestingly, the conversion into the products **8** generates planar chiral compounds (as racemates) which could be verified in the X-ray crystal structure analysis of compound **8a** (Figure 1).[9] Unfortunately, we were not successful in separation of the racemates by recrystallization with chiral carboxylates, such as D-tartrate.

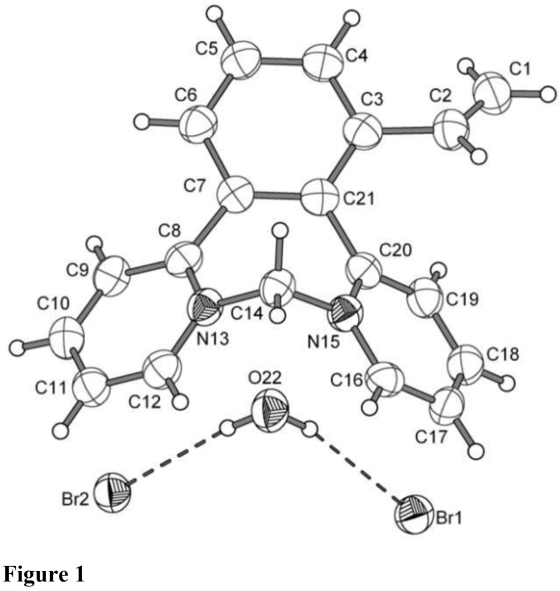


Figure 1

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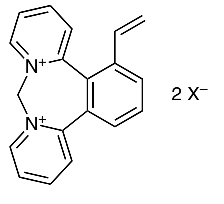
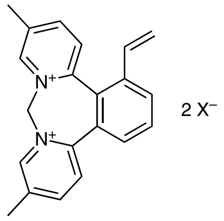
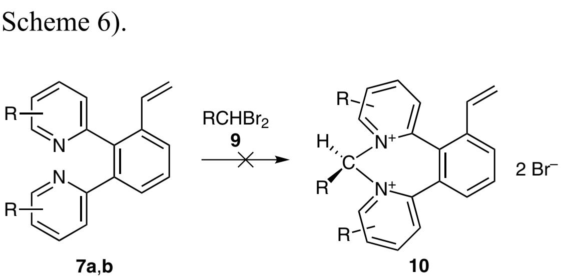
The results of the conversion of starting materials **7a** and **7b** with dibromomethane and diiodomethane are given in Table 2.[10]

Table 2 Results of the Reactions of **7a** and **7b** with CH_2Br_2 and CH_2I_2

Entry	Product **8**	Yield (%)
1		**8a** X = Br 85
2		**8b** X = I 85
3		**8c** X = Br 67
4		**8d** X = I 75

The reactions of **7c** with dibromo- and diiodomethane resulted not in the formation of the bispyridinium salts most likely caused by steric hindrance of the adjacent methyl substituents. Based on these partially encouraging results we envisaged the use of substituted dibromomethane derivatives **9** as these would result in the formation of diastereomers with a chiral centre and an axial chirality (**10**, Scheme 6).



Scheme 6

Unfortunately, the conversions of **7a** and **7b** with aryl-substituted dibromomethane derivatives (R = Ph, 4-$Me_2NC_6H_4$, 4-$F_3CC_6H_4$, and 2-BrC_6H_4) under various reaction conditions did not result in the formation of the desired products in pure form.

In summary, we have shown that an efficient one-pot process for the synthesis of 2-pyridyl-substituted enynes **6** can be realised and in most cases good yields were obtained. The enynes were then converted in a regioselective benzannulation utilising a cobalt catalyst to generate the products of type **7** in moderate yields. The conversion of the bispyridine derivatives **7** with dibromo- and diiodomethane could be realised to form the bispyridinium salts of type **8**. In the reactions with the dibromo derivatives $RCHBr_2$ the desired products of type **10** could not be isolated in pure form.

Acknowledgment

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

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(3) Pünner, F.; Hilt, G. *Chem. Commun.* **2012**, *48*, 3617.

(4) **General Procedure for the Stepwise Sonogashira Reaction of 2-Iodo- and 2-Bromopyridines of Type 4**
$PdCl_2(PPh_3)_2$ (42 mg, 2.0 mol%), CuI (11 mg, 2.0 mol%), and Ph_3P (32 mg, 4.0 mol%) were suspended in toluene (10 mL). To the suspension, degassed *i*-Pr_2NH (1.0 mL, 7.00 mmol, 2.3 equiv), 2-iodo- or 2-bromopyridine **4** (3.00 mmol, 1.0 equiv) and ethynyltrimethylsilane (0.5 mL, 3.60 mmol, 1.2 equiv) were added successively, and the reaction mixture was stirred at r.t. for 2 d. K_2CO_3 (2.90 g, 21.0 mmol, 7.0 equiv) and MeOH (20 mL) were added to the mixture and stirred at r.t. until complete conversion was observed by TLC or GC–MS analysis. The reaction mixture was concentrated under reduced pressure, H_2O was added followed by extraction with CH_2Cl_2, and dried over Na_2SO_4. The crude product was purified by column chromatography to give the desired product **5** [the same procedure was used for the second Sonogashira reaction with vinyl bromide (1 M in THF, 1.2 equiv) instead of ethynyltrimethylsilane].

(5) Severin, R.; Reimer, J.; Doye, S. *J. Org. Chem.* **2010**, *75*, 3518.

(6) **One-Pot Procedure for the Synthesis of 2-Pyridyl enynes of Type 6**
$PdCl_2(PPh_3)_2$ (42 mg, 2.0 mol%), CuI (11 mg, 2.0 mol%), and Ph_3P (32 mg, 4.0 mol%) were suspended in THF (10 mL). To the suspension, degassed *i*-Pr_2NH (1.0 mL, 7.00 mmol, 2.3 equiv), 2-iodo- or 2-bromopyridine **4** (3.00 mmol, 1.0 equiv), and ethynyltrimethylsilane (0.5 mL, 3.60 mmol, 1.2 equiv) were added successively, and the reaction mixture was stirred at r.t. for 2 d. KOH (1.18 g, 21.0 mmol, 7.0 equiv) in MeOH–H_2O (15 mL, 4:1 v/v) were added to the mixture and stirred at r.t. for 3.5 h. Then vinyl bromide [3.6 mL (1 M in THF), 3.60 mmol, 1.2 equiv] were added and stirred at r.t. for another 16 h. The reaction mixture was concentrated under reduced pressure, H_2O was added followed by extraction with CH_2Cl_2, and dried over Na_2SO_4. The crude

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product was purified by column chromatography to give the desired product **6**.

(7) **General Procedure for the Cobalt-Catalysed Benzannulation Reaction of 2-Pyridyl Enynes of Type 6**
$CoBr_2$(dppp) (126 mg, 20 mol%), Zn powder (26 mg, 40 mol%), and ZnI_2 (128 mg, 40 mol%) were dissolved in DMSO (1.5 mL), and the enynes of type **6** were added (1.00 mmol). The reaction mixture was stirred at r.t. until complete conversion was observed by TLC or GC–MS analysis. A solution of EDTA (584 mg, 2.00 mmol) in aq NH_3 buffer (20 mL, pH 10) was added followed by extraction with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, the solvent was evaporated, and the crude product was purified by column chromatography to give the desired styrene derivatives **7**.

(8) Almarzoqi, B.; George, A. V.; Isaacs, N. S. *Tetrahedron* **1986**, *42*, 601.

(9) The supplementary crystallographic data can be obtained free of charge from The Cambridge Crystallographic Data Centre; CCDC 924471.

(10) **Representative Procedure for the Synthesis of the Bispyridinium Salt 8a**
CH_2Br_2 (20 μL, 0.29 mmol, 1.45 equiv) was added to a solution of 2,3-bis(2-pyridyl)styrene **7a** (52 mg, 0.20 mmol, 1.0 equiv) in MeCN (1.0 mL) and was stirred at 70 °C for 3 d. The solvent was removed, the residue washed successively with 3.0 mL CH_2Cl_2, Et_2O, and pentane and dried under reduced pressure to give the desired product **8a**.

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