Synthesis of CF_3-Containing 1,2,3,4-Tetrahydroisoquinoline-3-Phosphonates via Regioselective Ruthenium-Catalyzed Co-cyclotrimerization of 1,7-Azadiynes

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Abstract: An efficient access to novel trifluoromethyl-substituted phosphonate analogues of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (TIC) derivatives based on regioselective ruthenium-catalyzed co-cyclotrimerization of functionalized 1,7-diynes with various alkynes has been developed using RuClCp*cod and preferably Grubbs second-generation catalysts.

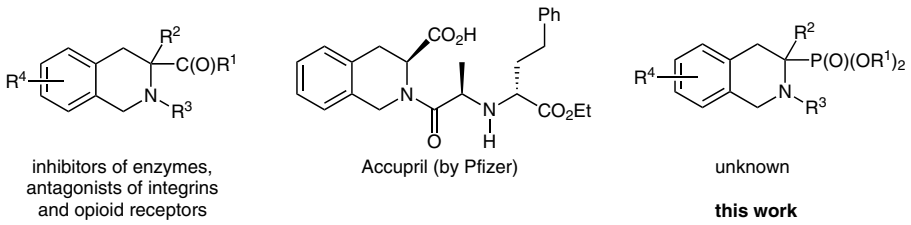
Key words: α-aminophosphonates, 1,7-azadiynes, alkynes, cyclotrimerization, ruthenium catalysis

α-Aminophosphonates and related α-aminophosphonic acids are structural analogues of the corresponding α-amino acids.[1–3] They contain a tetrahedral phosphonic acid moiety that mimics the transition state of nucleophilic substitution reactions at the carboxyl group of natural amino acids,[4] which makes them efficient competitors for the active sites of enzymes and other cell receptors. As a consequence, α-aminophosphonates have found a multitude of applications in medicinal, agricultural, and industrial chemistry.[1–8]

On the other hand, the 1,2,3,4-tetrahydroisoquinoline core is found in organic molecules that exhibit a wide array of biological activities, including antihypertensive,[9] antitumor,[10] and antimalarial[11] properties. Among them, the 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (TIC), being a constrained analogue of phenylalanine, attracts a special attention as an important building block to construct highly selective enzyme inhibitors,[12] antagonists of integrins,[13] and δ-opioid receptors[14] with a broad spectrum of remarkable pharmacological activity. The most successful example of the TIC core utilization in drug design is the discovery of angiotensin-converting enzyme inhibitor quinapril,[15] commercialized as Accupril, which is currently used for the treatment of hypertension and congestive heart failure (Figure 1).

On top of this, the introduction of CF_3 groups into biologically relevant compounds has nowadays become an important tool in drug discovery.[16] Indeed, many biologically active compounds, for example, the antidepressant Prozac and the anticancer agent Casodex, contain the CF_3 groups as an additional essential motif.[17] Therefore, the development of efficient methods for the preparation of new TIC analogues, especially their CF_3 derivatives, as potential enzyme inhibitors and unique building blocks for peptide modification, is of great importance.

An efficient protocol for the preparation of protected α-trifluoromethyl-substituted derivatives of tetrahydroisoquinoline-3-carboxylic acid (TIC) has been elaborated via [2+2+2] cycloaddition of α-CF_3-α-amino esters bearing two terminal alkyne chains with another alkyne. In the case of terminal alkynes the reaction led to the formation of an inseparable mixture in a ratio 1:1 of 5(7)-regioisomers.[18] We now report on a convenient and selective access to a hitherto unknown class of phosphonate analogues of TIC, based on N-propargylation of α-alkynyl-α-CF_3-α-aminophosphonates **1**[19] followed by co-cyclotrimerization[20] with terminal alkynes and for the first time via catalytic regioselective formation of the *meta*-arene isomer promoted by two types of ruthenium catalysts: RuClCp*COD and preferably the alkene-metathesis Grubbs second-generation catalyst (Grubbs II, Scheme 1).



inhibitors of enzymes, antagonists of integrins and opioid receptors

Accupril (by Pfizer)

unknown

this work

Figure 1 Bioactive TIC derivatives and their unknown phosphonate analogues

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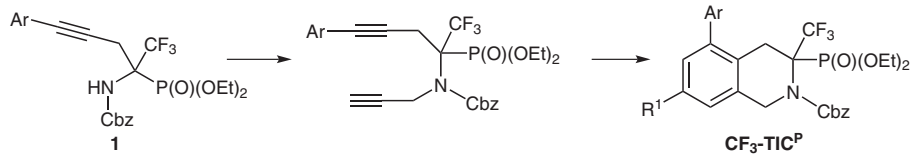


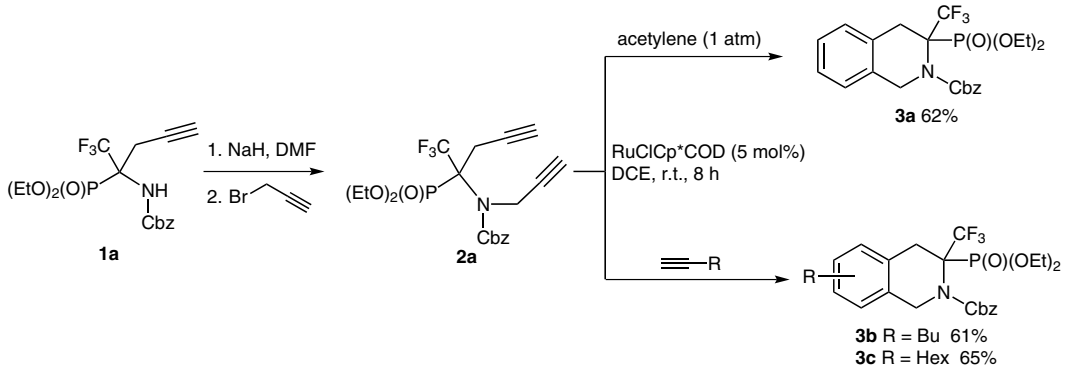
Scheme 1 Access to phosphonate analogues of TIC

The investigation of the catalytic alkyne cyclotrimerization[21] started with the reaction of terminal 1,7-diyne **2a** with acetylene. For this purpose, the N-alkylation of propargyl-containing α-CF_3-α-aminophosphonate **1a** with propargyl bromide has been initially performed. As a result, we found that the best conversion (91%) of aminophosphonate **1a** into 1,7-azadiyne **2a** can be achieved using 1.4 equivalents of NaH in DMF in the presence of a five-fold excess of propargyl bromide. The reaction has been monitored by ^{19}F NMR spectroscopy.

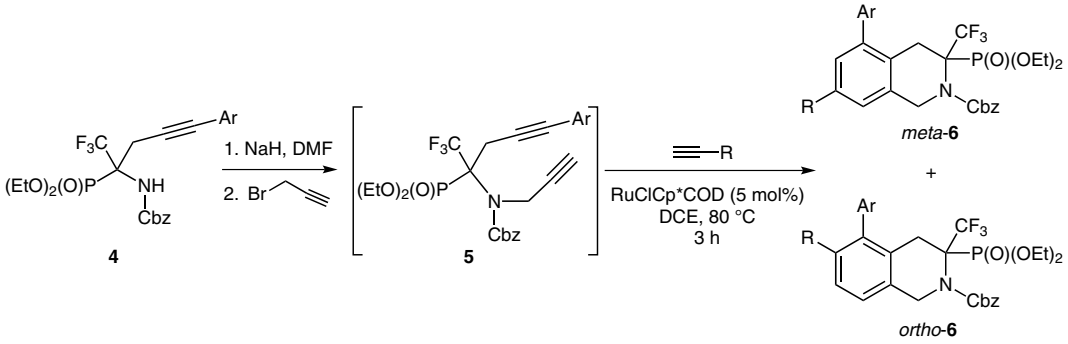
Taking into account the high NMR yield of **2a** and the difficulty of its purification, crude **2a** (>90% purity), quantitatively obtained by the standard workup procedure, has been further utilized for the cyclotrimerization steps. Thus, we found that [2+2+2] cycloaddition of **2a** with acetylene (1 atm) occurres at room temperature in dichloroethane after eight hours in the presence of 5 mol% RuClCp*COD affording the corresponding bicyclic phosphonate **3a** in 62% overall yield for the two steps (Scheme 2).

The same conditions have proved to be acceptable for the reaction of **2a** with 1-hexyne and 1-octyne. In both cases, the cyclotrimerization products **3b** and **3c** have been obtained in good yield as a mixture of their 6- and 7-alkylated regioisomers in a 1:1 ratio (Scheme 2).

In attempts to induce the regioselectivity of the [2+2+2]-cycloaddition process, we have investigated the reactions of 1,7-azadiynes **5**, containing an internal triple bond, with terminal alkynes such as hexyne, octyne, and phenylacetylene. The derivatives **5** (Scheme 3, Table 1) have been prepared starting from readily available aryl-containing aminophosphonates **4**,[19] and then crude compounds **5** (purity >90%) were used for ruthenium-catalyzed cyclotrimerization step. It turned out that the cycloaddition of 1,7-azadiynes **5** with hexyne-1 and octyne-1 proceeded at 80 °C in dichloroethane in the presence of 5 mol% of RuClCp*cod and led to reaction completion after three hours to afford the corresponding CF_3-substituted tetrahydroisoquinoline-3-phosphonic acid derivatives **6** in moderate yields. In all cases the *meta* isomers **6** were formed as major cyclotrimerization products with remarkable regioselectivity (*meta*/*ortho* from 92:8 to 94:6) (Scheme 3, Table 1).



Scheme 2 Synthesis of diyne **2a** and tetrahydroisoquinolines **3a–c**



Scheme 3 Synthesis of diynes **5a**,**b** and tetrahydroisoquinolines **6a–f**

Table 1 Synthesis of Tetrahydroisoquinolines **6a**–**f** via RuClCp*COD Catalysis

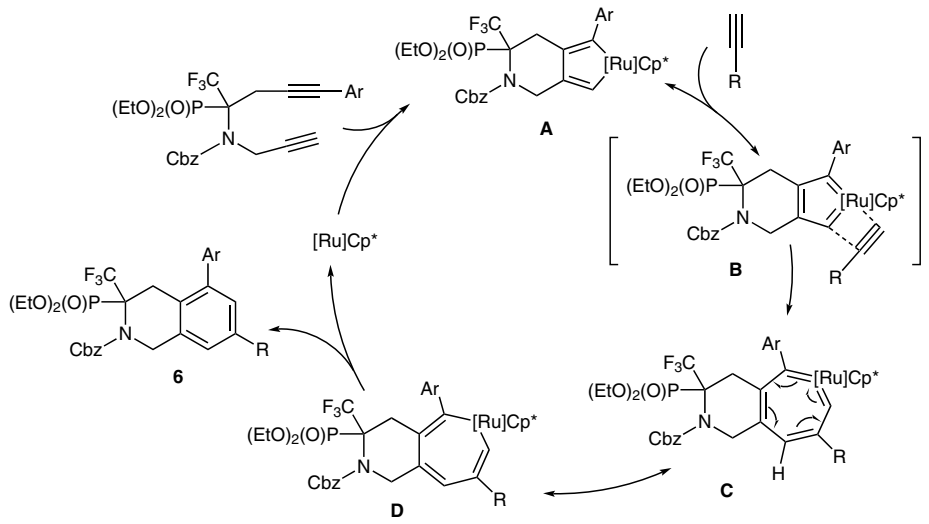
Entry	Ar	R	Yield of **6** (%)[a]	*meta*/*ortho*[b]
1	Ph	Bu	**6a** 60	93:7
2	Ph	C_6H_{13}	**6b** 57	92:8
3	Ph	Ph	**6c** 51	93:7
4	4-$MeOC_6H_4$	Bu	**6d** 42	94:6
5	4-$MeOC_6H_4$	C_6H_{13}	**6e** 39	93:7
6	4-$MeOC_6H_4$	Ph	**6f** 41	93:7

[a] Isolated yield for two steps after purification by chromatography on silica gel.
[b] Determined by ^{19}F NMR spectroscopy.

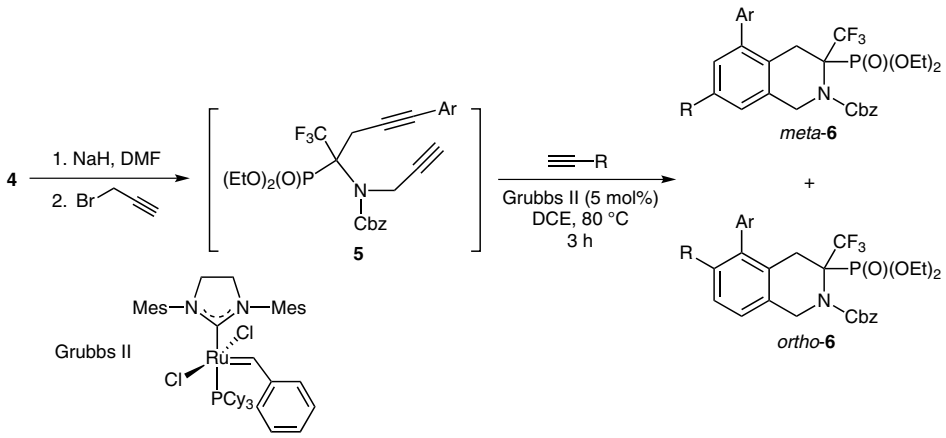
The action of precatalyst RuClCp*cod can be rationalized as described in Scheme 4. The first step corresponds to the oxidative coupling of the diyne to give the ruthenacyclopentadiene **A**, close to the transition state, leading to its more stable tautomer **B** with the carbene character of Ru=C bonds.[22] The less hindered Ru=C bond of **B** is expected to give a regioselective [2+2] cycloaddition with the alkyne triple bond, via a metathesis step, affording the less hindered adduct **C**, with the R group away from the bulky RuCp* group (Scheme 4).

The new biscarbene ruthenium intermediate **C** corresponds to the tautomer **D** closed to the transition state leading to the reductive elimination step. The different reactivity of the two Ru=C bonds in **B** is responsible for the observed regioselectivity and is due to both electronic and steric effects, as the Ar group in the Ar–C=Ru moiety is known to stabilize the Ru=C carbene bond[22b] and the alkyne couples with the less hindered C=Ru bond to avoid steric interaction with both RuCp* and Ar.

The Ru=C carbene bond character of intermediate **B** and **C** led us to evaluate a possible more active ruthenium–alkylidene catalyst, the Grubbs second-generation catalyst already shown to be efficient for enyne ring-closing metathesis, whereas the Grubbs first-generation (Grubbs I) catalyst could perform specific intramolecular cyclotrimerization of alkynes.[23] As the Grubbs first-generation catalyst was shown not to be the most efficient for the



Scheme 4 Proposed mechanism for regioselective cyclotrimerization catalyzed by RuClCp*COD



Scheme 5 Synthesis of Bicyclic Derivatives **6** from Alkynyl Phosphonates **4**

cyclotrimerization of terminal diynes containing the aminoester moiety,[18] the Grubbs second-generation catalyst, containing a bulky and an electron-rich NHC ligand, was evaluated in the search for regioselectivity of alkyne interactions. As a result, it was found that the 5 mol% of Grubbs second-generation catalyst smoothly proceeds at 60 °C for 3–4 hours to promote the cyclotrimerization leading to the desired phosphorylated TIC derivatives[24] in significantly better isolated yields (60–77%) with an excellent regioselectivity *meta*/*ortho* from 92:8 to 95:5 (Scheme 5, Table 2).

Table 2 Synthesis of Tetrahydroisoquinolines **6a**–**f** via Grubbs II Catalysis

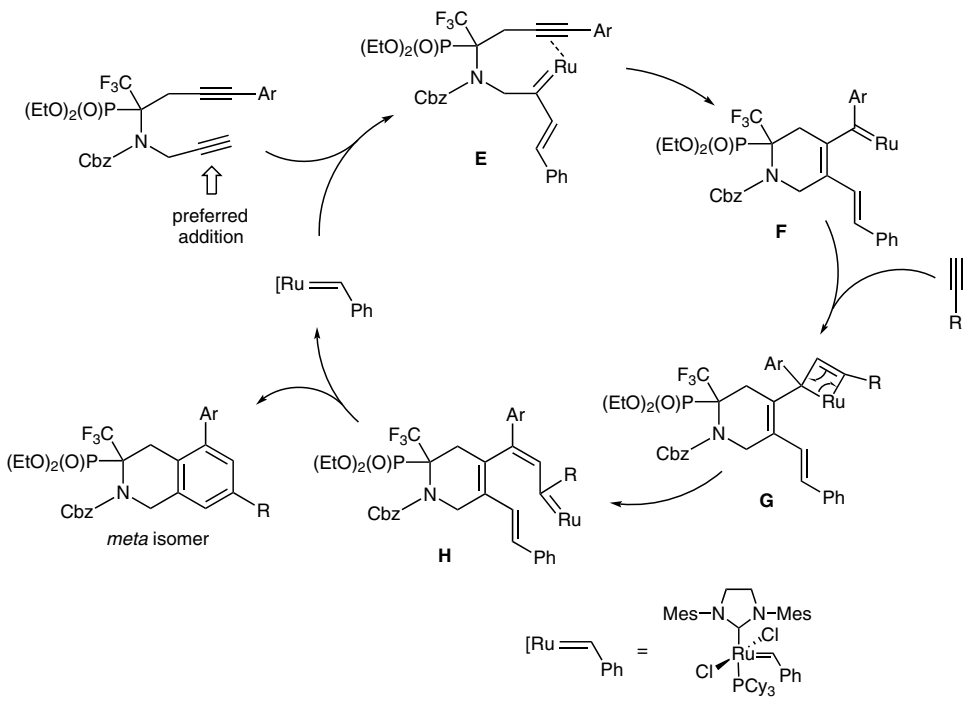
Entry	Ar	R	Yield of **6** (%)[a]	*meta*/*ortho*[b]
1	Ph	Bu	**6a** 77	93:7
2	Ph	C_6H_{13}	**6b** 68	94:6
3	Ph	Ph	**6c** 63	93:7
4	4-$MeOC_6H_4$	Bu	**6d** 72	92:8
5	4-$MeOC_6H_4$	C_6H_{13}	**6e** 75	95:5
6	4-$MeOC_6H_4$	Ph	**6f** 60	95:5

[a] Isolated yield for two steps after purification by chromatography on silica gel.
[b] Determined by ^{19}F NMR spectroscopy.

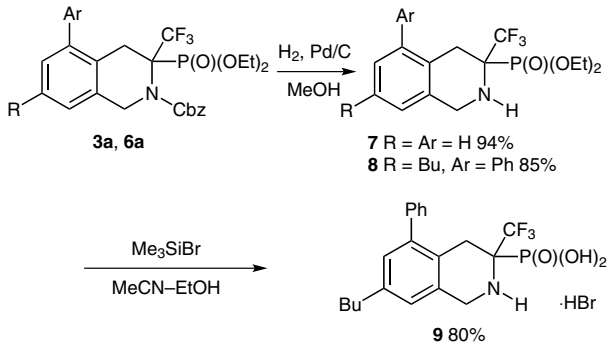
In this case, the preferred addition of ruthenium alkylidene bond to the less substituted alkyne moiety of the 1,7-diyne **5** should lead to the alkenyl alkylidene ruthenium moiety **E** then interacting intramolecularly with the other triple bond to form the first cycle and intermediate **F**.[23] A cascade of intra- and intermolecular, as well as ring-closing metathesis steps, which are related to the well-established enyne and olefin metathesis, would finally result in the liberation of the ruthenium benzylidene catalyst and in the preferred formation of the corresponding *meta* isomer (Scheme 6). The addition of the alkylidene bond to the external alkyne in **G** is expected to afford the alkenylidene **H** reacting intramolecularly to generate the *meta* isomer and the alkylidene ruthenium catalyst, thus causing the chemo- and regioselectivity of this process.

To obtain free cyclic aminophosphonates selective removal of protection groups from amino and phosphonic acid functions could be applied via standard protocols commonly used in peptide chemistry. Thus, the Cbz protective group could be easily removed by catalytic hydrogenation on 10% Pd/C in methanol at room temperature for two hours to afford NH-phosphonates **7** and **8** in good yields. Subsequent treatment of **8** with trimethylsilyl bromide led to the formation of the desired free amino phosphonic acid **9** as hydrogen bromine salt (Scheme 7).

In conclusion, we have developed a convenient method for crossed cyclotrimerization of phosphonate containing 1,7-azadiyne and terminal alkyne mediated by two ruthenium catalysts, RuClCp*cod, the precursor of biscarbene complex, and the Grubbs second-generation alkene metathesis catalyst which revealed the most efficient catalytic activity. This catalytic protocol offers an efficient access to a hitherto unknown family of functionalized phosphorus analogues of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (TIC) derivatives with the regioselective formation of the arene ring bearing *meta* substituents arising from diyne and terminal alkyne.



Scheme 6 Proposed mechanism for cyclotrimerization catalyzed by Grubbs second-generation catalyst



Scheme 7 The synthesis of free aminophosphonate

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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(24) **Typical Procedure for Compound 6**
A degased solution of dyine-containing aminophosphonate (0.39 mmol), alkyne (1.55 mmol, 4 equiv), and Grubbs II catalyst (0.02 mmol, 5 mol%) in dry CH_2Cl_2 (8 mL) was stirred under heating at 60 °C for 3 h. After cooling to r.t., the solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel (eluent: CH_2Cl_2–EtOAc) to afford the product.
Selected Data for Compound 6b
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.07 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.17 (t, *J* = 6.5 Hz, 3 H, CH_3), 1.32–1.45 (m, 2 H, CH_2), 1.61–1.71 (m, 2 H, CH_2), 2.68 (t, *J* = 7.6 Hz, 2 H, CH_2), 3.52–3.56 (m, 2 H, CH_2),

3.89–4.20 (m, 4 H, OCH_2), 4.76 (br s, 2 H, CH_2), 5.21 (d, J = 12.2 Hz, 1 H, OCH_2), 5.35 (d, J = 12.2 Hz, 1 H, OCH_2), 7.08–7.21 (m, 2 H, ArH), 7.32–7.52 (m, 10 H, ArH). ^{19}F NMR (282 MHz, $CDCl_3$): δ = 9.81 (s, 3 F, CF_3). ^{31}P NMR (161 MHz, $CDCl_3$): δ = 16.63 (q, J = 3.3 Hz). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 13.9, 15.8 (d, J = 6.6 Hz), 16.2 (d, J = 5.5 Hz), 22.4, 33.6, 35.3, 43.4, 47.3, 62.7 (d, J = 8.8 Hz), 64.0 (m), 64.8 (dq, J = 28.7, 154.8 Hz), 67.9, 124.7, 125.9 (qd, J = 12.8, 288.9 Hz), 127.1, 127.2 (d, J = 6.6 Hz), 128.1, 128.2, 128.3, 128.4, 129.2, 129.4, 136.2, 140.2, 140.6, 141.6, 155.7, 171.1. Anal. Calcd for $C_{32}H_{37}F_3NO_5P$: C, 63.67; H, 6.18; N, 2.32. Found: C, 63.28; H, 5.88; N, 2.54.

