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COMMUNICATION

Efficient [5 + 1]-strategy for the assembly of 1,8-naphthyridin-4(1*H*)-ones by domino amination/conjugate addition reactions of 1-(2-chloropyridin-3-yl) prop-2-yn-1-ones with amines†‡

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A facile synthetic approach for the synthesis of 1,8-naphthyridine-4(1*H*)-one derivatives *via* a catalyst free and Pd-supported tandem amination sequence is developed and described. In a case of aliphatic amines reaction proceeds in a catalyst free mode, however anilines demand Pd-supported reaction conditions.

Pyridine derivatives constitute an important class of azaheterocycles found in many natural products, pharmaceuticals, and functional materials.[1] Heteroannulated pyridines, namely naphthyridine derivatives, are of considerable pharmacological relevance. They represent important lead structures in medicinal chemistry (treatment of various human diseases) and agricultural chemistry (use as pesticides).[2] Among various isomeric pyridopyridines known, 1,8-naphthyridines[3–5] have been the by far most studied subclass (Fig. 1). There are a number of world-wide top selling drugs, such as nalidixic acid[5a] – a bacteriostatic agent and amfonelic acid[5b,c] – a highly selective dopamine reuptake inhibitor, containing 1,8-naphthyridin-4-one core.

For more than a century, chemists have been developing methodologies for the synthesis of annulated pyridines and it is unlikely that interest in the field will cease, because of the great importance of the pyridine core in both biological and chemical fields.[6] Pyridine syntheses are present in countless protocols elaborated during the 20th century, as well as in recent years. A number of [5 + 1]-protocols for the construction of the pyridine framework have been reported in the literature. In most cases, ammonia has served as the nitrogen source, for example, in pyridine syntheses starting from 1,5-dicarbonyl compounds,[7] 1,1-bis

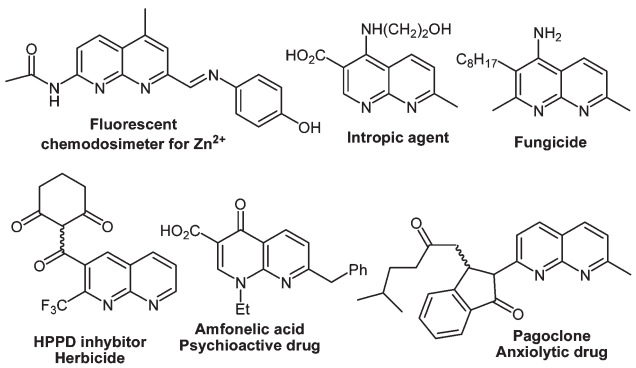

Fig. 1 Important 1,8-naphthyridines.

(alkylthio)-1,4-pentadienes,[8] and 1,6-dienes (by ozonolysis and subsequent condensation with ammonia).[7a] In recent years, several elegant transition metal-catalyzed domino amination [5 + 1]-cyclization protocols have been developed to afford functionalized quinolines.[9]

On the other hand, [4 + 1]- and [3 + 2]-cyclization protocols *via* the intramolecular and intermolecular cycloadditions have nowadays gained new applications for the synthesis of indole[10] and benzofurane[10a,b,11] frameworks as well as for the complex polycyclic systems with the mentioned subunits.[12] Nevertheless, recently, we have communicated the palladium-catalyzed reaction of 2-alkynyl-3-bromothiophenes with anilines which afforded thienopyrroles by a domino C–N coupling/hydroamination process. At the same time the reaction of 2-alkynyl-3-bromobenzothiophenes with anilines under identical conditions resulted in the formation of benzothienoquinolines by a domino C–N coupling/annulation process.[13]

Many quinoline[10a,b,14] and iso-quinoline derivatives,[10a,b] as well as fused pyridines have been synthesized following the intermolecular addition of the amino function onto the acetylene sub-unit. Nevertheless, the palladium-catalyzed the carbonylative Sonogashira coupling reaction[14] of *ortho*-halogen-anilines represents another synthetic strategy used to build up the 4-quinolone framework.

Continuing our research on the efficient synthesis[15] of drug-like heteroannulated pyridines, we have started a study directed

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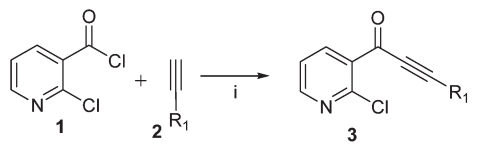
‡Dedicated to Professor Vyacheslav Ya. Sosnovskikh on the occasion of his 60th birthday.

to the development of a new method for the synthesis of 1,8-naphthyridines based on [5 + 1]-cyclizations of 1-(2-chloropyridin-3-yl)prop-2-yn-1-ones **3** with a set of aromatic and aliphatic amines. The alkynones **3** are easily accessible by Sonogashira coupling of 2-chloropyridine-3-carboxylic acid chloride (**1**) with terminal alkynes (Table 1), for this reaction we have used a standard Sonogashira acylation conditions.[9i,16] The reactions proceed with excellent regioselectivity, which was proved.

1-(2-Chloropyridin-3-yl)-3-phenylprop-2-yn-1-one (**3a**) was chosen as a model compound for the optimization of the Pd-catalysed reaction with aniline to give 1,8-naphthyridin-4(1*H*)-one **5a**. After the optimization of the reaction conditions with regard to the type of catalyst and solvent, we have found that the use of $Pd(PPh_3)_4$ (10 mol%) as the catalyst, 2 equiv. of K_2CO_3, and DMF as a solvent (150 °C) was essential to get good yield of **5a** (Table 2, entry 6).

Encouraged by these findings, we examined the reaction of other 1-(2-chloropyridin-3-yl)prop-2-yn-1-ones **3** with a range of commercially available aromatic and aliphatic amines under the optimized reaction conditions. As illustrated in Table 3,

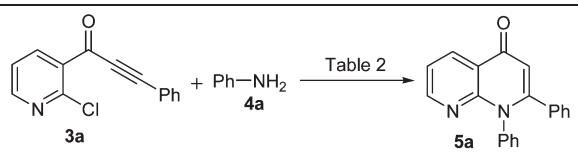
Table 1 Synthesis of 1-(2-chloropyridin-3-yl)prop-2-yn-1-ones **3**. *Reaction conditions*: (i) $PdCl_2(PPh_3)_2$ (2 mol%), CuI (4 mol%), THF under dry argon



	3	R_1	Yield[a]
1	**a**	Ph	93
2	**b**	4-(*t*-Bu)-Ph	79
3	**c**	n-Pr	81
4	**d**	TMS (**3e**) → H (**3d**)[c]	18[b]
5	**e**	TMS	72

[a] Yields related to pure compounds. [b] Product is unstable. [c] TMS-group was cleaved by KF.

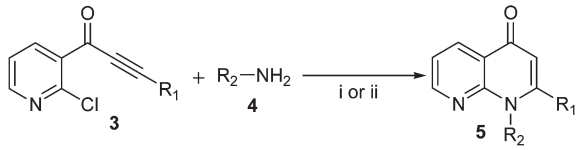
Table 2 Synthesis of 1,8-naphthyridin-4(1*H*)-one **5a**. Optimization of the reaction conditions



	Catalyst	Solvent	Base	*T* (°C) and time	Yield[a] (**5a**)
1	No catalyst	DMF	K_2CO_3	150 °C, 16 h	22
2	$Pd(dba)_2/PPh_3$[b]	DMF	K_2CO_3	150 °C, 16 h	16
3	$Pd(dba)_2/PPh_3$[b]	MeCN	K_2CO_3	Reflux, 16 h	11
4	$Pd(dba)_2/PPh_3$[b]	Toluene	K_2CO_3	Reflux, 16 h	4
5	$Pd(OAc)_2$[c]	DMF	K_2CO_3	150 °C, 16 h	19
6	$Pd(PPh_3)_4$[d]	DMF	K_2CO_3	150 °C, 16 h	60

[a] Yields related to pure compounds. [b] 5 mol% $Pd(dba)_2$/10 mol% PPh_3. [c] 10 mol% X-Phos. [d] 10 mol% $Pd(PPh_3)_4$.

Table 3 Synthesis of 1,8-naphthyridin-4(1*H*)-ones **5**. *Reaction conditions*: (i) $Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (2 equiv.), DMF 150 °C, under dry argon, 16 h. (ii) K_2CO_3 (2 equiv.), DMF 150 °C (100 °C if R_1 = TMS), under dry argon, 16 h



	N	R_1	R_2	Yield[ab]
1	**5b**	Ph	Benzyl	98[ii]
2	**5c**	Ph	2-Chlorobenzyl	84[ii]
3	**5d**	Ph	Cyclopentyl	96[ii]
4	**5e**	Ph	Cyclohexyl	98[ii] (91)[c]
5	**5f**	Ph	2-Phenylethyl	92[ii] (84)[c]
6	**5g**	Ph	2-Ethanol	61[ii]
7	**5h**	Ph	n-Heptyl	96[ii]
8	**5i**	Ph	*t*-Butyl	(58)[ii]
9	**5j**	Ph	Allyl	74[ii]
10	**5k**	Ph	H	71[ii]
11	**5l**	Ph	3,5-Dimethylphenyl	41[i] (20)[ii] (52)[d]
12	**5m**	Ph	3-Methoxyphenyl	62[i] (29)[ii]
13	**5n**	Ph	2,4-Dimethoxyphenyl	62[i] (23)[ii]
14	**5o**	Ph	*p*-Chlorophenyl	58[i] (24)[ii]
15	**5p**	Ph	*p*-Bromophenyl	45[i] (18)[ii]
16	**5q**	Propyl	Benzyl	93[ii]
17	**5r**	Propyl	Cyclohexyl	97[ii]
18	**5s**	4-(*t*-Bu)Ph	2-Phenylethyl	98[ii]
19	**5t**	4-(*t*-Bu)Ph	Cyclohexyl	94[ii]
20	**5u**	4-(*t*-Bu)Ph	Phenyl	63[i] (24)[ii]
21	**5v**	TMS	Benzyl	81[ii] (R^1 = H)
22	**5w**	TMS	2-Phenylethyl	65[ii] (R^1 = H)
23	**5x**	Ph	3-CF_3-phenyl	61 (60)[d]

[a] Yields related to pure compounds. [b] Yields of isolated products in the presence of Pd catalyst (conditions i) or in the absence of a catalyst (conditions ii). [c] Starting from **11** reaction conditions i. [d] Starting from **11** reaction conditions ii.

compounds **3** readily reacted with various aniline derivatives to give the corresponding products in moderate to good yields. Aliphatic amines are considerably more nucleophilic than aromatic amines. While aromatic amines required the employment of a Pd catalyst, reactions of aliphatic amines proceeded smoothly under catalyst free conditions (DMF, K_2CO_3, 150 °C) to deliver the correspondent 1,8-naphthyridin-4(1*H*)-ones **5** in excellent yields (Table 3). However, to illustrate the advantage of Pd-supported reaction conditions for anilines regarding yields, we have conducted parallel cyclization with the same anilines without catalyst. Results are summarised in Table 3 (yields are in brackets with correspondent notes).

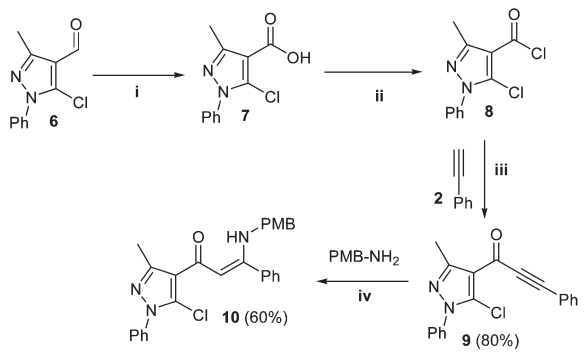
In a case of aliphatic amines, when the reactions were carried out in the presence of a Pd catalyst, the yields and reactions times were similar to the catalyst-free conditions. When a methanolic solution of ammonia was used, product **5k** was obtained in 71% yield. Interestingly, the same product was formed by Pd-catalyzed reaction of *tert*-butylamine with **3a**. This can be explained by cleavage of the *tert*-butyl group under the reaction conditions employed. However, under the catalyst free condition the correspondent *tert*-butyl derivative **5i** was obtained.

The structures of 1,8-naphthyridin-4(1*H*)-ones **5b**, **5f** and **5k** were unambiguously confirmed by X-ray crystal structure

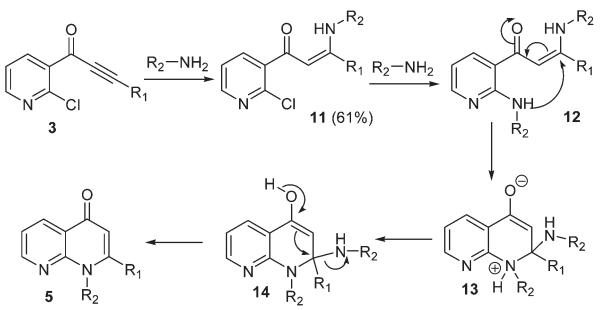
analyses (Fig. 2–4, ESI†).[17] Molecule **5f** crystallized as a hydrate and possesses a plane structure; the corresponding torsion angle N(2)C(8)–C(9)C(14) is 87.1°. An intermolecular hydrogen bond O(1)–H–O(2) is observed to a water molecule.

With these results in hand, we were interested in the extension of the method with regard to the new heterocycles bearing an *ortho*-halogen. With the purpose of assembling a 1*H*-pyrazolo[3,4-*b*]pyridin-4(7*H*)-one ring system by the Pd-supported reaction with amines and using **9** as a starting material we have followed the synthetic route depicted in Scheme 1. Compound **9** was synthesised in three steps from commercially available 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **6** and subsequently was used under our reaction conditions in the reaction with the *p*-methoxybenzylamine taken as a model compound. To our great disappointment the main product isolated was the correspondent adduct **10**. Its constitution was established by X-ray structure analysis (Fig. 5, ESI†). The optimization of the reaction conditions by changing solvent (1,4-dioxane, DMA, xylene) or taking other catalysts ($Pd(OAc)_2$, Pd_2dba_3, $PdCl_2(PPh_3)_2$) as well as ligands (BINAP, XantPhos, DavePhos, XPhos, SPhos), and increasing the temperature, did not succeed in the formation of the desired products.

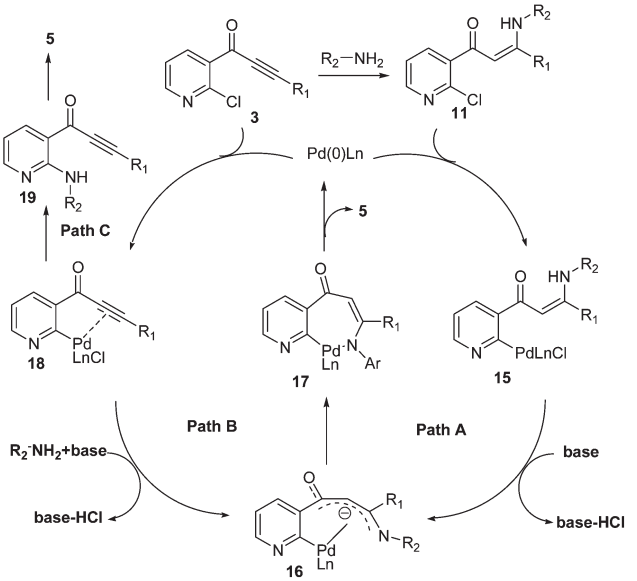
For the synthesis of products **5**, we propose two possible reaction mechanisms depending on the reaction conditions, namely a catalyst free pathway (Scheme 2) and a Pd-catalyzed pathway (Scheme 3). We believe that the catalyst free cyclization proceeds



Scheme 1 Unsuccessful synthesis of 1*H*-pyrazolo[3,4-*b*]pyridin-4(7*H*)-one ring system. *Reaction conditions*: (i) acetone, $KMnO_4$, r.t., 12 h. (ii), $SOCl_2$, reflux 3 h. (iii) $PdCl_2(PPh_3)_2$ (2 mol%), CuI (4 mol%), 1,4-dioxane, 70 °C, under dry argon, 3 h. (iv) $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (2 equiv), DMF 150 °C, under dry argon, 16 h.



Scheme 2 Possible reaction mechanism for the catalyst free pyridine ring formation.



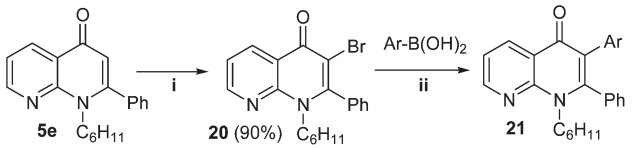
Scheme 3 Possible mechanism for the Pd-supported pyridine ring formation.

via intermediate **11** which is formed by Michael-addition of the amine onto position 3 of the ynone system. In the case of aromatic amines, when the reaction was carried out without catalyst, we were able to isolate the intermediate **11** (R_2 = 3-CF_3-Ph, yield is 61%) and to establish its structure by means of 1D and 2D NMR techniques. Subsequently, intermediate **11** undergoes a nucleophilic aromatic substitution by amine on the pyridine ring to form intermediate **12**. The following cyclization *via* **13** and **14** gives 1,8-naphthyridin-4(1*H*)-ones **5**.

A possible mechanism for the Pd-catalysed cyclization is depicted in Scheme 3. In this case, several mechanistic paths are possible. The reaction might proceed by formation of intermediate **11** by conjugate addition of the amine to the ynone moiety. Oxidative addition of the Pd(0) to **11** results in the formation of organopalladium species **15** (path A). The reaction with base gives intermediate **16**, which undergoes an intramolecular Buchwald–Hartwig reaction *via* organopalladium species **17** and reductive elimination of Pd(0) to give product **5**. On the other hand, intermediate **16** can be alternatively formed by a slightly different path. Initial oxidative addition of Pd to the halide **3** may result in the formation of intermediate **18**. The addition of the amine might deliver intermediate **16** (path B). Intermediate **18** can also be directly attacked by the amine (Buchwald–Hartwig reaction) to deliver intermediate **19**. The latter can undergo a cyclization by intramolecular Michael addition giving rise to products **5** (path C). Isolation of intermediates **11** and **10** in a related reaction suggests that the reaction proceeds *via* path A. Analysing the literature, we have found some controversial arguments[9i,j] for some of the paths of the mechanism presented in this communication.

To be sure that the intermediate type **11** is indeed a part of the reaction chain in both catalyst free and Pd-supported 4-pyridone ring formation we have undertaken a mechanistic study. As it was discovered the compound **11** reacts with the correspondent aniline (2 equiv.) under reaction condition (i) (Table 3) to deliver the corresponding product **5z**. The synthesis of **5l** was achieved

Table 4 Synthesis of 1,8-naphthyridin-4(1*H*)-ones **21**. *Reaction conditions*: (i) Bromine (1.5 equiv.), Na_2CO_3 (6 equiv.), THF, 20 °C, 6 h. (ii) $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (2 equiv.), DMF, 120 °C, under dry argon, 16 h



21	Ar	Yield[a] (%)
a	Phenyl	60
b	4-Ethylphenyl	60
c	4-Trifluoromethylphenyl	43

[a] Yields related to pure compounds.

under the same conditions by the reaction of **11** with 2 equiv. of 3,5-dimethylaniline, however compound **5z** (9%) was detected as a by-product. At the same time, when the aliphatic amines (cyclohexylamine and 2-phenylethylamine) were investigated under reaction condition (ii), we have observed formation of 1,8-naphthyridine-4(1*H*)-ones **5e** and **5f** in the yields of 91% and 84% respectively (Table 3). This indeed delivers a strong support for compounds of type **11** to be intermediates in the reaction cascade described.

To further functionalize the heterocyclic scaffold, we have synthesized 3-bromo-1-cyclohexyl-2-phenyl-1,8-naphthyridin-4(1*H*)-one (**20**) by bromination of **5e** with molecular bromine in the presence of Na_2CO_3 in THF. The Suzuki–Miyaura cross-coupling reaction of **20** with a set of arylboronic acids afforded 1,8-naphthyridines **21** (Table 4). The best yields were obtained when $Pd(PPh_3)_4$ was used as the catalyst in the presence of 2 equiv. of K_2CO_3 as the base (THF, 20 °C).

Fluorescence methods are powerful tools for investigating biomolecular interactions. There is notably a strong demand for the development of new fluorescent probes.[18] 1,8-Naphthyridine derivatives have found an important application as fluorescent labels and emitters.[3] In this regard, the absorption and emission properties of 1,8-naphthyridin-4(1*H*)-ones **5e**, **20**, and **21a–c** were studied. The results obtained during this study are summarized in the ESI,† Table 1.

To conclude, we have developed a new and efficient approach for the synthesis of 1,8-naphthyridin-4(1*H*)-ones from commercially available starting materials based on a domino amination/conjugate addition protocol. Scope and limitations of the reaction are currently being studied. Further studies related to the application of the methodology to the synthesis of other nitrogen-based heterocycles are currently under way.

Experimental section

General comments

The dry solvents DMF and THF were purchased directly from ACROS as AcroSeal bottles. Other solvents were purified by destination. All reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane) or electrospray ionization (ESI). For preparative scale chromatography silica gel 60 (0.063–0.200 mm, 70–230 mesh) was used. The absorption spectra were measured on a Perkin Elmer UV/VIS Spectrometer Lambda 2 in dichloromethane ($c = 2.5 \times 10^{-5}$ mol l^{-1}). The fluorescence spectra were recorded on a Hitachi F-4010 fluorescence spectrometer in dichloromethane ($c = 10^{-4}$ mol l^{-1}; excitation wavelength: 350 nm). The solvent was distilled before use. Compound **1** was obtained starting from commercially available 2-chloropyridine-3-carboxylic acid by the method described previously.[19] Acetylenes **2** and amines **4** are commercially available compounds.

Procedure A – general procedure 1-(2-chloropyridin-3-yl)prop-2-yn-1-ones (3)

1 g (6.35 mmol) of 2-chloronicotinic acid was refluxed in an excess of $SOCl_2$. After 3 h the $SOCl_2$ was removed *in vacuo* and the crude white residue used without further purification.

1.05 equiv. of the corresponding acetylene, 0.02 equiv. (2 mol %) of $PdCl_2(PPh_3)_2$, 0.04 equiv. (4 mol%) of CuI and 1.0 equiv. of the chlorinated 2-chloropyridine-3-carboxylic acid chloride (**1**) are added to dry THF under argon atmosphere in a pressure tube. The mixture is cooled to 0 °C, 1.05 equiv. NEt_3 are added and the mixture is stirred at room temperature. After 3 h the reaction mixture is washed with water and extracted with ethylacetate. The combined phases are dried over Na_2SO_4, the solvent is removed *in vacuo* and the residue purified by column chromatography (eluent: n-heptane–ethylacetate).

Procedure B – general procedure for alkylamines (5b–k, 5q–t, 5v, 5w)

2.0 equiv. of the corresponding alkylamine, 2.0 equiv. of K_2CO_3 and 1.0 equiv. of the corresponding 1-(2-chloropyridin-3-yl) prop-2-yn-1-one are heated at 150 °C (100 °C if a TMS group is present in the molecule) in dry DMF under argon atmosphere in a pressure tube. After 16 h the solvent is removed *in vacuo* and the crude product is purified by column chromatography (eluent: n-heptane–ethylacetate).

Procedure C – general procedure for anilines (5a, 5l–p, 5u, 5x)

2.0 equiv. of the corresponding aniline, 2.0 equiv. of K_2CO_3, 0.1 equiv. (10 mol%) of $Pd(PPh_3)_4$ and 1.0 equiv. of the corresponding 1-(2-chloropyridin-3-yl)prop-2-yn-1-one are heated at 150 °C in dry DMF under argon atmosphere in a pressure tube. After 16 h the solvent is removed *in vacuo* and the crude product is purified by column chromatography (eluent: n-heptane–ethylacetate).

Procedure D – general procedure for bromination (20)

1.0 equiv. of the starting material, 1.5 equiv. of bromine and 6.0 equiv. of Na_2CO_3 in THF are stirred at room temperature for 6 h. The solvent is removed *in vacuo* and the crude product purified by column chromatography (eluent: n-heptane–ethylacetate).

Procedure E – general procedure for Suzuki-coupling (21a–c)

1.0 equiv. of the starting material, 1.1 equiv. of the boronic acid, 0.05 equiv. (5 mol%) $Pd(PPh_3)_4$ and 2.0 equiv. K_2CO_3 are heated in DMF for 16 h at 120 °C. The solvent is removed *in vacuo* and the crude product is purified by column chromatography (eluent: n-heptane–ethylacetate).

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