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A straightforward synthesis of 1,3-dichloro-5,8-dihydroisoquinoline by consecutive Stille cross-coupling and metathesis reactions

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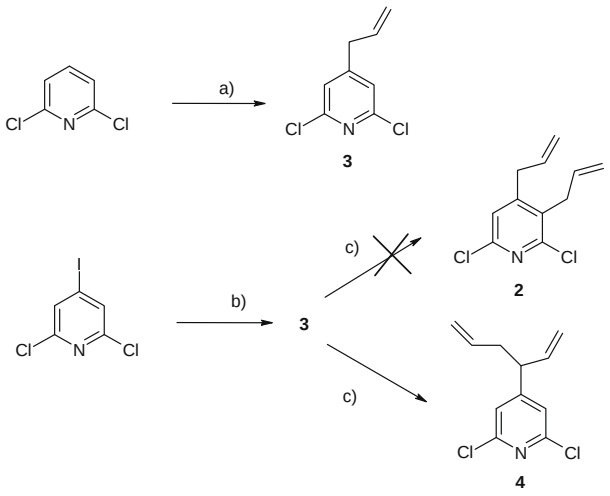
ABSTRACT

An efficient three-step synthetic route from 2,6-dichloro-4-iodopyridine to 1,3-dichloro-5,8-dihydroisoquinoline is described. A ring-closing-metathesis reaction constitutes the key step in this synthetic sequence. The reactivity of both chloro atoms is demonstrated in a Suzuki arylation reaction.

Organometallic chemistry is of significant importance for the synthesis of a variety of chemical entities. Applications of lithiation,[1] modern Grignard,[2] transition metal catalysed cross-coupling[3] and metathesis chemistry[4] have resulted in the synthesis of many new drug-like compounds which are often hard to prepare by classical chemistry methods. In addition, organometallic chemistry applications in large-scale production have gained more importance.[5] In the course of our research endeavours, we became interested in the synthesis of 1,3-dichloro-5,8-dihydroisoquinoline (**1**) as a novel starting material for Suzuki cross-coupling. Although there were some initial doubts about the stability of compound **1** and its Suzuki derivatives (potential oxidation by air to the corresponding heteroaromatic 1,3-dichloroisoquinoline), it was decided to devise a synthetic route towards **1**. We envisaged that this might be possible by application of mild reaction conditions utilising organometallic chemistry, an area in which we have been active.[6]

Consequently, efforts were undertaken towards the synthesis of the novel key intermediate, 2,6-dichloro-3,4-diallylpyridine **2**. Initially, a strategy was selected based on a regioselective direct Grignard reaction developed by Knochel and co-workers,[7] followed by a lithiation reaction (Scheme 1). Disappointingly, treatment of 2,6-dichloropyridine with in situ prepared 2,2,6,6-tetramethylpiperidine-MgCl·LiCl, followed by transmetallation with CuCN·2LiCl and addition of allyl bromide resulted in a low yield of 2,6-dichloro-4-allylpyridine (**3**). This result prompted the use of commercially available 2,6-dichloro-4-iodopyridine as starting material for the synthesis of **2**. After a sequence involving Grignard exchange with *i*PrMgCl·LiCl, transmetallation with CuCN·2LiCl and again trapping the obtained reaction mixture with allyl bromide, the desired 2,6-dichloro-4-allyl-pyridine (**3**)[8] was isolated in a satisfactory yield of 75% (Scheme 1). It should be mentioned that running the reaction with *n*-BuLi at −78 °C instead of *i*PrMgCl·LiCl at −10 °C led to a complex reaction mixture. The subsequent step was the selective introduction of the second allyl group on **3**. Thus, from our experience,[9] direct lithiation with LiTMP, in situ transmetallation with CuCN·2LiCl and addition of allyl bromide were studied. Surprisingly, compound **4**[10] was isolated in a moderate yield of 40%, instead of the desired diallylpyridine **2** (Scheme 1). Apparently, the allyl-CH_2 group is easily deprotonated under these reaction conditions. Therefore, it was decided to switch attention



Scheme 1. Reagents and conditions: (a) (i) 1 mol equiv 2,6-dichloropyridine, 1.2 mol equiv TMPMgCl·LiCl, THF, 0–15 °C, 5 h; (ii) 1.2 mol equiv CuCN·2LiCl, −60 °C to 0 °C, 1 h; (iii) 1.2 mol equiv allyl bromide, −60 °C to rt, 16 h,15%; (b) (i) 1 mol equiv 2,6-dichloro-4-iodopyridine, 1.25 mol equiv *i*-PrMgCl.LiCl, THF, −50 °C, 30 min; (ii) 1.25 mol equiv CuCN·2LiCl, −60 °C to 0 °C, 1 h; (iii) 1.25 mol equiv allyl bromide, −60 °C to rt, 16 h, 75%; (c) (i) 1 mol equiv **3**, 3.2 mol equiv LiTMP, THF, −70 °C, 3 h; (ii) 3.2 mol equiv CuCN·2LiCl, −70 °C to 0 °C, 1 h; (iii)1.3 mol equiv allyl bromide, −70 °C to rt, 16 h, 40% **4**.

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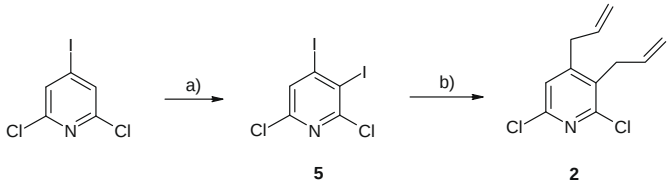
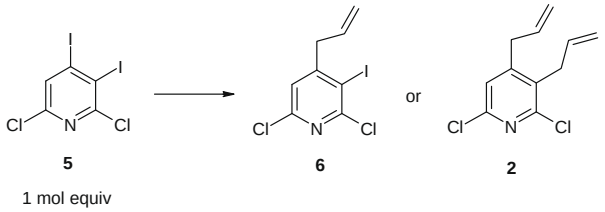
to a direct lithiation/cross-coupling strategy for the preparation of **2**, as outlined in Scheme 2. After a brief survey of the reaction conditions, novel 2,6-dichloro-3,4-diiodopyridine (**5**) was prepared in a reasonable yield of 70% via lithiation at the 3-position of 2,6-dichloro-4-iodopyridine with LiTMP at low temperature, followed by treatment with a solution of iodine in THF.[11]

With compound **5** in hand, cross-coupling reactions were investigated to prepare 2,6-dichloro-3,4-diallylpyridine (**2**). The results are summarised in Table 1. The first approach was based on the published work of Kotha et al.[12] who converted aryl halides into the corresponding allyl compounds by a $Pd(PPh_3)_4$-mediated Suzuki cross-coupling reaction with allyl boronic pinacol ester and CsF in refluxing THF. Interestingly, this method was also suitable for the conversion of 1,2-diodo arenes into the corresponding 1,2-diallyl compounds, which subsequently were applied in ring-closing metathesis reactions resulting in unstable 1,4-dihydronaphthalenes. Unfortunately, in our hands this Suzuki reaction failed using **5** as starting material (Table 1, entry 1). This prompted the application of Stille cross-coupling methodology. Reaction of **5** with tributylallylstannane and $Pd(PPh_3)_4$ in DMF at 110 °C[13] resulted in the formation of **2** in a moderate yield, with some concomitant formation of triallyl chloropyridine (Table 1, entry 2). Lowering the temperature to 85 °C and switching from DMF to dioxane as the solvent resulted in the mono-allyl compound **6** (Table 1, entry 3).[14] Fortunately, repeating this reaction at an elevated temperature (110 °C) led to the desired compound **2** in a yield of 48% (Table 1, entry 4). Finally, by running the reaction under modified Fu conditions [$Pd(PPh_3)_4$, CsF, dioxane, 110 °C],[15] compound **2** was isolated in a satisfactory yield of 70% (Table 1, entry 5).[16] Scaling up this particular reaction (1–9 mmol) had no negative impact on the observed yield.



Scheme 2. Reagents and conditions: (a) (i) 1 mol equiv 2,6-dichloro-4-iodopyridine,1.2 mol equiv LiTMP, THF, −78 °C, 2 h; (ii) 1.2 mol equiv iodine, −78 °C, 70%; (b) see conditions described in Table 1.

Table 1



Entry	Reaction conditions	Product	Yield[a] (%)
1	2.2 mol equiv $H_2C{=}CHCH_2Bpin$, 2.2 mol equiv CsF, 10 mol % $Pd(PPh_3)_4$, THF, 18 h reflux	**5**	
2	2.2 mol equiv $H_2C{=}CHCH_2Sn(Bu)_3$, 10 mol % $Pd(PPh_3)_4$, DMF, 110 °C, 2 h	**2**	30[b]
3	2 mol equiv $H_2C{=}CHCH_2Sn(Bu)_3$, 5 mol % $Pd(PPh_3)_4$, dioxane, 85 °C, 2 h	**6**	22
4	2 mol equiv $H_2C{=}CHCH_2Sn(Bu)_3$, 5 mol % $Pd(PPh_3)_4$, dioxane, 110 °C, 2 h	**2**	48
5	2.1 mol equiv $H_2C{=}CHCH_2Sn(Bu)_3$, 4.2 mol equiv CsF, 8 mol % $Pd(PPh_3)_4$, dioxane, 110 °C, 3 h	**2**	70

[a] Isolated yield of pure compound.
[b] Contaminated with a trace of triallyl chloropyridine.

The ring-closing metathesis reaction (RCM) was evaluated as the next step. The application of RCM for the synthesis of azamacrocycles, heterocycles, natural compounds and cyclic peptides has been extensively documented in the literature,[17] and we have also gained some experience in this area.[18] Intriguingly, the synthesis of carbocycles by ring-closing metathesis is relatively less explored in comparison with heterocycles. Our first attempt to react compound **2** in the presence of 5 mol % Grubbs' 2nd generation catalyst[19] (Fig. 1) over 2.5 h at room temperature in dichloromethane resulted in an inseparable mixture of the regioisomeric 5,8-, 7,8- and 5,6-dihydro-1,3-dichloroisoquinolines in a combined yield of 76% and a molar ratio of 2:3:4 (Scheme 3). This observation can be rationalised by invoking the initial formation of **1**, followed by partial isomerisation of the double bond due to some degradation of the catalyst to Ru–H. The Ru–H is able to attack the double bond via a non-selective hydrometallation, followed by a non-selective ruthenium hydride elimination reaction.[20]

A number of precedents have been reported to overcome isomerisation in RCM. Fustero described the use of Grubbs' 1st generation catalyst (Fig. 1)[21] and Stevens[20] has reported the application of a catalytic amount of $RuClH(CO)(PPh_3)_3$ as an additive to Grubbs' 2nd generation catalyst. Another way to tackle this isomerisation reaction is described by Grubbs and co-workers. They tested a number of additives in the presence of Grubbs' 2nd generation catalyst and found that the addition of a catalytic amount of 1,4-benzoquinone was very effective in preventing isomerisation.[22] These conditions resulted in a clean conversion into compound **1** within 45 min with an isolated yield of 75%[23] (Scheme 3). Neither isomerisation nor oxidation into the corresponding isoquinoline was observed, which is in contrast with the related synthetic route to functionalised 5,8-dihydronaphthalenes as reported by Kotha.[12] It is interesting to note that our initial concerns about the potential lack of stability of **1** were unfounded, because after storage of compound **1** for three months under air in a refrigerator at 5 °C, no trace of degradation was observed by NMR analysis.

In order to test **1** as the starting material for Suzuki cross-coupling chemistry, the replacement of both chloro atoms with phenyl groups was explored. A brief survey of the reaction conditions led to conversion into 1,3-diphenyl-5,8-dihydroisoquinoline (**7**) by treatment of **1** with 3 mol equiv of $PhB(OH)_2$, 9 mol equiv of $K_3PO_4{\cdot}H_2O$, 3 mol % of $Pd(OAc)_2$ and 6 mol % of S-Phos (Fig. 1) in degassed toluene at 90 °C for 30 min. Compound **7** was obtained as a colourless oil in high yield (85%)[24] (Scheme 4). In contrast with the observed stability of compound **1**, small impurities were visible in the NMR spectrum of **7** after a three-month storage period under air in a refrigerator at 5 °C.

In conclusion, starting from commercially available 2,6-dichloro-4-iodopyridine, a straightforward three-step reaction procedure has been devised for the preparation of novel 1,3-dichloro-5,8-dihydroisoquinoline (**1**). The key step is the RCM of

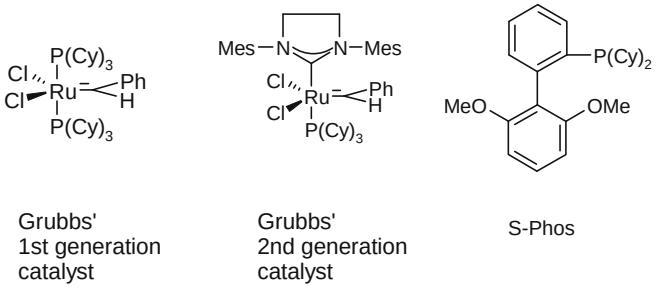
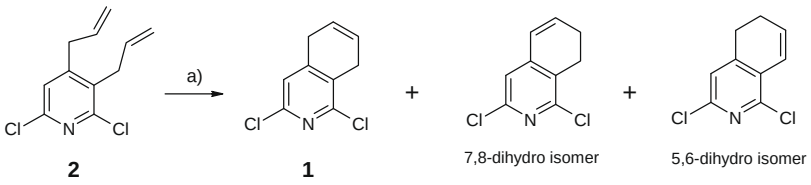
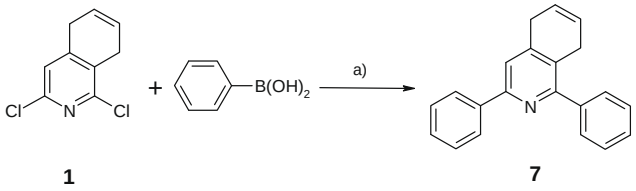


Figure 1.



Scheme 3. Reagents and conditions: (a) 1 mol equiv **2**, 5 mol % Grubbs' 2nd generation catalyst, 20 mol % 1,4-benzoquinone, dichloromethane, 25 °C, 75%: compound **1** is formed as the sole product. In the absence of 1,4-benzoquinone all three isomers are formed (ratio = 2:3:4). See the detailed description in the text.



Scheme 4. Reagents and conditions: (a) 1 mol equiv **1**, 3 mol equiv PhB(OH)2, 9 mol equiv $K_3PO_4 \cdot H_2O$, 3 mol % $Pd(OAc)_2$, 6 mol % S-Phos, toluene, 90 °C, 30 min, 85%.

diallylpyridine **2** into **1** under mild conditions. The two novel intermediates **2** and **5** which are disclosed herein may serve as versatile synthetic building blocks. Both chlorine atoms in **1** are able to undergo a Suzuki arylation reaction. Additional functionalisation reactions of **1** are in progress. As a note of interest, besides the key compounds **1**, **2** and **5**, compounds **3**, **4**, **6** and **7** are, to the best of our knowledge, not described in the literature.

Acknowledgements

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10. *Selected analytical data for compound* **4**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40–2.54 (m, 2H), 3.31–3.38 (m, 1H), 5.10–5.21 (m, 4H), 5.60–5.71 (m, 1H), 5.81–5.92 (m, 1H), 7.10 (s, 2H).
11. *Typical procedure for the preparation of compound* **5**: An oven-dried 250-ml, three-necked reaction vessel was charged with anhydrous THF (50 ml) and 2,2,6,6-tetramethylpiperidine (1.7 g, 12 mmol) under a nitrogen atmosphere. The resulting magnetically stirred solution was cooled to −78 °C followed by dropwise addition of *n*-BuLi (4.8 ml, 2.5 M in *n*-hexane, 12 mmol). The temperature was allowed to rise to 0 °C and the reaction mixture was stirred for 30 min. After cooling again to −78 °C, a solution of 2,6-dichloro-4-iodopyridine (2.74 g, 10 mmol) in anhydrous THF (15 ml) was added dropwise and the reaction mixture was stirred for 1.5 h at −78 °C, followed by dropwise addition of iodine (3.05 g, 10 mmol) in anhydrous THF (15 ml). The resulting mixture was reacted for 1 h at −78 °C. Subsequently, the reaction was quenched with a saturated aqueous solution of NH_4Cl and diethyl ether was added. The organic layer was successively separated, extracted with aqueous $NaHSO_3$, dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained crude **5** was dissolved in a minimum of CH_2Cl_2 and purified by flash chromatography [silica gel 60 (0.040–0.063 mm, Merck)] with CH_2Cl_2–petroleum ether, 1:1 (v/v), to give 2.8 g of pure **5** (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 108.30, 123.67, 132.72, 150.04, 153.60. HRMS (ES+): calcd for $C_5H_2NCl_2I_2$ $(M+H)^+$ 399.7654; found: 399.7658.
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14. *Selected analytical data for compound* **6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.45 (d, J = 6 Hz, 2H), 5.09–5.16 (m, 1H), 5.19–5.25 (m, 1H), 5.78–5.86 (m, 1H), 7.01 (s, 1H).
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16. *Typical procedure for the preparation of compound* **2**: An oven-dried 250-ml three-necked reaction vessel was charged with degassed dioxane (100 ml), followed by addition of **5** (2 g, 5 mmol), tributylallylstannane (3.48 g, 10.5 mmol), CsF (3.19 g, 21 mmol) and $Pd(PPh_3)_4$ (0.46 g, 0.4 mmol). The mixture was magnetically stirred under a nitrogen atmosphere in a pre-heated oil bath at 110 °C. After 3 h, compound **5** was fully converted into compound **2** (LC–MS monitoring). After cooling to room temperature, the reaction mixture was diluted with diethyl ether, filtered and concentrated in vacuo. The obtained crude **2** was further purified by flash chromatography [silica gel 60 (0.040–0.063 mm, Merck)] with CH_2Cl_2–petroleum ether, 1:3 (v/v), to give 0.78 g of **2** (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.40 (br d, J = 6 Hz, 2H), 3.53 (br d, J = 6 Hz, 2H), 4.93 (br d, J = 18 Hz, 1H), 5.06–5.12 (m, 2H), 5.21 (dd, J = 11 Hz and 2 Hz, 1H), 5.81–5.94 (m, 2H), 7.11 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ

32.91, 36.75, 116.64, 118.53, 123.78, 130.97, 133.04, 133.59, 147.93, 150.99, 153.45. HRMS ES+: calcd for $C_{11}H_{12}NCl_2$ $(M+H)^+$ 228.0347; found: 228.0340.

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23. *Typical procedure for the preparation of compound* **1**: An oven-dried 250-ml three-necked reaction vessel was charged with anhydrous degassed CH_2Cl_2 (50 ml), followed by addition of **2** (650 mg, 2.85 mmol), Grubbs' 2nd generation catalyst (120 mg, 0.14 mmol) and 1,4-benzoquinone (60 mg, 0.55 mmol). After magnetic stirring under a nitrogen atmosphere for 45 min at room temperature [LC–MS, HPLC, TLC (CH_2Cl_2–petroleum ether, 1:2) monitoring] the black-coloured reaction mixture was filtered and concentrated in vacuo. Pure **1** was obtained by flash chromatography [silica gel (0.040–0.063 mm, Merck)] with CH_2Cl_2–petroleum ether, 1:2 (v/v), to give 430 mg of **1** (75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.29–3.35 (m, 2H), 3.37–3.43 (m, 2H), 5.79–5.86 (m, 1H), 5.89–5.96 (m, 1H), 7.04 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.04, 29.47, 122.25, 122.58, 124.00, 128.07, 147.09, 149.09, 150.14. HRMS (ES+): calcd for $C_9H_8NCl_2$ $(M+H)^+$ 200.0034; found: 200.0038.
24. *Typical procedure for the preparation of compound* **7**: An oven-dried 100-ml three-necked reaction vessel was charged with degassed toluene (10 ml) followed by addition of **1** (100 mg, 0.5 mmol), phenylboronic acid (183 mg, 1.5 mmol), $K_3PO_4{\cdot}H_2O$ (1.03 g, 4.5 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol) and S-Phos (12.4 mg, 0.03 mmol). After magnetic stirring for 30 min under a nitrogen atmosphere in a pre-heated oil bath at 90 °C [LC–MS, TLC (CH_2Cl_2) monitoring], the reaction was complete. The reaction mixture was allowed to attain room temperature and diluted with diethyl ether, filtered and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography [silica gel (0.040–0.063 mm, Merck)] with CH_2Cl_2 delivered 110 mg of **7** (85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.29–3.35 (m, 2H), 3.46–3.51 (m, 2H), 5.87–5.95 (m, 2H), 7.34–7.49 (m, 7H), 7.54–7.58 (m, 2H), 8.01–8.07 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.00, 30.25, 118.97, 123.46, 125.55, 126.76, 126.88, 127.86, 128.09, 128.48, 128.57, 129.13, 139.53, 140.87, 144.87, 154.08, 158.17. HRMS (ES+): calcd for $C_{21}H_{18}N$ $(M+H)^+$ 284.1439; found: 284.1426.