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Elaboration of a novel effective approach to enantiopure functionalised 2,2′-dialkyl-1,1′-binaphthyls by stereoconservative cross-couplings at positions 2 and 2′ ☆

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Abstract—The yield and the stereochemical outcome of methylations of 1,1′-binaphthyl-2,2′-dielectrophiles (ditriflate and diiodide) clearly depend on the reactivity of the organometallics used. It was found that only the Negishi reaction of a diiodide allows direct effective synthesis of non-racemic functionalised C_2-symmetric 2,2′-dialkyl-1,1′-binaphthyls.

The unique stereochemical properties of axially chiral 2,2′-substituted 1,1′-binaphthyl derivatives are the reason for the enhanced interest in their synthesis and applications. As a result of this interest they have become one of the most important groups of artificial chiral-pool compounds. Many applications of 1,1′-binaphthyl derivatives have been found especially C_2-symmetric examples having heteroatom based groups in positions 2 and 2′ (N, P, As, O, S). Only a limited number of applications of 1,1′-binaphthyl derivatives bearing carbon groups at positions 2 and 2′ have been reported[1–7] and these derivatives almost exclusively have C(sp^3)-monocarbon groups at the above-mentioned positions. However, their reported applications in stereoselective synthesis (as chiral catalysts,[1,2] ligands,[3,4] reagents,[5] additives[6] and auxiliaries[7]) are promising. A reason for their limited application is that their synthesis in nonracemic form has not been properly investigated. Their synthesis is most often based on the preparation of the enantiopure 2,2′-dimethyl derivative **1a** or 1,1′-binaphthyl-2,2′-dicarboxylic acid as key intermediates followed by functionalisation. Enantiopure 1,1′-binaphthyl-2,2′-dicarbonitrile[8] or 2,2′-bis(4-alkyloxazolin-2-yl) derivatives[6,9] can be used as alternative intermediates.

Non-racemic 2,2′-dimethyl-1,1′-binaphthyl (**1a**) has been prepared by stereoselective Grignard coupling from 1-bromo-2-methylnaphthalene.[10] The former was also obtained by a stereoselective Suzuki coupling.[11] Currently, **1a** is prepared exclusively by effective stereoconservative nickel catalysed methylation of easily accessible enantiopure 2,2′-ditriflate **2a** with methylmagnesium halides, a method, which has been reported independently by several research groups.[1,3,12]

The direct introduction of functionalised alkyl groups would be of interest for the efficient synthesis of functionalised derivatives. However, Grignard reagents are intolerant of many functional groups under cross-coupling reaction conditions (at the boiling point of the solvent used), so functionalisation is only possible after the cross-coupling reaction. Therefore we performed a systematic study on the methylations of 1,1′-binaphthyl-2,2′-dielectrophiles **2** (the ditriflate **2a** and the diiodide **2b**) via cross-coupling reactions with a variety of organometallic reagents. These reactions are also interesting from a stereochemical point of view because they take place at positions 2 and 2′, where nonbonding interactions between substituents play a crucial role in the configurational stability of the 1,1′-binaphthyl derivatives and hence there is a risk of racemisation during the

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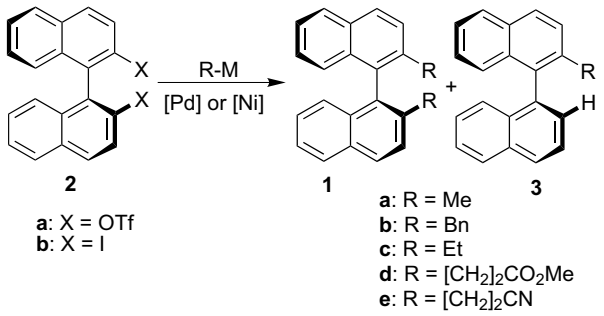
reaction.[13] 1,1′-Binaphthyl-2,2′-dielectrophiles **2** should be considered as moderately electron rich but highly strained substrates (seeing that there is a bulky 1-naphthyl substituent adjacent to the site of the cross-coupling reaction).

For methylations of binaphthyl dielectrophiles with various organometallic reagents we examined a variety of catalysts (Pd and Ni complexes with PPh_3, P(2-furyl)$_3$, P(*o*-tolyl)$_3$, dppe, dppp, dppf ligands), solvents (Et_2O, THF, dioxane, DME, NMP, toluene) and additives (K_2CO_3, K_3PO_4 and CsF for the Suzuki coupling, LiCl for Stille coupling) analogous to the conditions for effective methylations of aryl triflates and aryl iodides described in literature. The best results under optimised conditions are presented (Table 1, Scheme 1).

Firstly, we examined methylations of the more easily accessible ditriflate **2a**. The reactivity of the organometallic reagent was found to be crucial for the efficiency of the reaction. The desired product **1a** was obtained in high yields only in the case of the most reactive reagents—methylmagnesium halides and trimethylaluminium (Table 1, entries 1–4). A good yield of **1a** was also obtained from the Negishi reaction, however, the methylzinc reagent had to be used in higher excess (Table 1, entries 5 and 6), otherwise, the monomethylated derivative **3a** was found to be the main product. In all these cases, **1a** was isolated in enantiopure form—with complete conservation of configuration—from the ditriflate **2a**. The use of less reactive organometallics (B, Sn) did not result in the formation of a detectable amount of the desired product **1a**.

In the case of the more reactive diiodide **2b** (already commercially available), the desired product **1a** was isolated from each type of cross-coupling reaction and in excellent yields from the more reactive organometallics. Also traces of partially stannylated and butylated



Scheme 1. Alkylations of 1,1′-binaphthyl-2,2′-dielectrophiles **2**.

binaphthyl derivatives were obtained from the Stille reaction. The stereochemical result of the reaction was found to be dramatically dependent on the reactivity of the organometallic reagent used. Only two extreme results were observed: either complete conservation (in the case of Mg, Al and Zn; Table 1, entries 9–12) or almost complete loss (racemisation in the case of B and Sn; Table 1, entries 13–15) of configuration from the substrate (diiodide **2b**). Similar stereochemical results were also observed in our study on the synthesis of 1,1′-binaphthyl-2,2′-diyl bridged ferrocene by cross-coupling reactions from the diiodide **2b**.[14] The different stereochemical results are most probably caused by differences in mechanistic pathways, which have been reported elsewhere.[14]

The Negishi reaction of the diiodide **2b** with alkylzinc halides, the method with the highest potential for the synthesis of homochiral functionalised 2,2′-dialkylated 1,1′-binaphthyls **1**, was tested on a few examples (Table 2). It was found that the yields of the desired products **1** were slightly lower if the alkyl groups, which were introduced contained hydrogen on the β-carbon atom (Table 2, entries 2, 4 and 5). As a result of β-hydrogen elimination, small amounts of monoalkylated, hydro-

Table 1. Methylations of 1,1′-binaphthyl-2,2′-dielectrophiles **2**[15]

Entry	**2**	Equiv. of Me–M[a]	Cat. (5 mol %)[a]	Solvent	Yield of **1a**[b] (%)	Ee of **1a**[c] (%)
1[3,12]	(*R*)-**2a**[d]	2 Me–MgBr	$NiCl_2$dppp	Et_2O	99	>98
2[1]	(*S*)-**2a**[d]	2 Me–MgI	$NiCl_2(PPh_3)_2$	Et_2O	89	>98
3	(*S*)-**2a**	2 Me–MgI	$NiCl_2$dppe	Et_2O	89	>98
4	(*S*)-**2a**	2 Me–$AlMe_2$	$PdCl_2$dppf	PhMe	85	>98
5	(*S*)-**2a**	2 Me–ZnI	$Pd(PPh_3)_4$	THF	20	>98
6	(*S*)-**2a**	3 Me–ZnI	$Pd(PPh_3)_4$	THF	62	>98
7	(*S*)-**2a**	2 $(MeBO)_3$[e]	[Pd]	Various	0	—
8	(*S*)-**2a**	2 Me–SnR_3(Me, Bu)[f]	[Ni] or [Pd]	Various	0	—
9	(*R*)-**2b**	2 Me–MgI	$NiCl_2$dppe	Et_2O	90	>98
10	(*R*)-**2b**	2 Me–$AlMe_2$	$PdCl_2$dppf	PhMe	87	>98
11	(*R*)-**2b**	2 Me–ZnI	$Pd(PPh_3)_4$	THF	92	>98
12	(*R*)-**2b**	2 Me–ZnI	$NiCl_2$dppe	THF	93	>98
13	(*R*)-**2b**	2 $(MeBO)_3$[e]	$Pd(PPh_3)_4$	Dioxane–THF	65	5
14	(*R*)-**2b**	2 Me–$SnMe_3$[f]	Pd[P(2-furyl)$_3$]$_4$	THF	70	0
15	(*R*)-**2b**	2 Me–$SnBu_3$[f]	Pd[P(2-furyl)$_3$]$_4$	THF	56	0

[a] With respect to Ar–I or Ar–OTf.
[b] Isolated yield.
[c] Determined by HPLC on (+)-poly(triphenylmethyl) methacrylate/silica.
[d] Including 3,3′-diarylated **2a**.
[e] +3 equiv K_2CO_3 (with respect to Ar–I or Ar–OTf).
[f] +3 equiv LiCl (with respect to Ar–I or Ar–OTf).

Table 2. Alkylations of 1,1′-binaphthyl-2,2′-dielectrophiles **2**[15]

Entry	2	Equiv of R–M[a]	Cat. (5 mol %)[a]	Solvent	Yield of **1**[b] (%)	Ee of **1** (%)	Yield of **3**[b] (%)
1	(*S*)-**2b**	2 Bn–ZnBr	$Pd(dba)_2$, dppf (1:1)[d]	THF	**1b**, 85	>98[c]	**3b**, traces
2	(*S*)-**2b**	2 Et–ZnEt	$Pd(PPh_3)_4$	THF	**1c**, 60	n.d.[f]	**3c**, 20
3	(*S*)-**2a**	3 $MeO_2CCH_2CH_2$–ZnI	[Ni] or [Pd]	THF[e]	**1d**, 0	—	**3d**, 0
4	(*R*)-**2b**	2 $MeO_2CCH_2CH_2$–ZnI	$Pd(PPh_3)_4$	THF[e]	**1d**, 68	>98[c]	**3d**, 12
5	(*R*)-**2b**	2 $NCCH_2CH_2$–ZnI	$Pd(PPh_3)_4$	THF[e]	**1e**, 62	>96[g]	**3e**, 21

[a] With respect to Ar–I or Ar–OTf.
[b] Isolated yield.
[c] Determined with HPLC on (+)-poly(triphenylmethyl) methacrylate/silica (**1b**) or Chiralcel Daicel OD-RH column (**1d**).
[d] +3 equiv Bu_4NI (with respect to Ar–I).
[e] THF contains 0.2 mL of DMA and 1 mL of benzene originating from the synthesis of the zinc reagent. Reaction was performed at 40 °C.
[f] Not determined.
[g] Determined by comparison of the specific rotations of the diacid **1f** ($R = CH_2CH_2CO_2H$) obtained by hydrolysis of **1d** and **1e**.

dehalogenated products **3** were obtained from the reaction mixture in these cases. Nevertheless, the desired products **1** were obtained in reasonable yields and very efficiently with respect to the number of required reaction steps and moreover, in enantiopure form.

A control experiment with ditriflate **2a** (Table 2, entry 3) showed that alkylation with a more complex alkylzinc halide does not give, in contrast to the methylation under analogous conditions, even traces of the dialkylated product **1d**.

In conclusion, our study on the methylation of 1,1′-binaphthyl-2,2′-dielectrophiles **2** showed that the Negishi cross-coupling reaction of the more reactive diiodide **2b** is the most convenient synthetic approach for the effective direct synthesis of enantiopure 1,1′-binaphthyl derivatives bearing functionalised alkyl groups at positions 2 and 2′. Monoalkylated hydro-dehalogenated products **3** were isolated, besides the desired dialkylated ones **1**, if the alkyl groups introduced contained hydrogen on the β-carbon atom. Our study on the synthesis and applications of functionalised 2,2′-dialkylated 1,1′-binaphthyls is currently in progress.

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15. General procedure: A solution of 2 mmol (if not given otherwise) of organometallic reagent in about 2 mL of solvent was added dropwise to a solution of 285 mg (0.5 mmol) **2a** or 253 mg (0.5 mmol) **2b**, 0.05 mmol of catalyst and additive in 5 mL of dried solvent and the reaction mixture was heated to reflux (if not given otherwise) overnight under a nitrogen atmosphere. After cooling to 0 °C, the reaction mixture was poured into a 10% aqueous cooled solution of HCl. The organic layer was washed twice with water and brine, dried over anhydrous $MgSO_4$ and the solvent was removed in vacuo. The product was isolated by flash chromatography on silica, using hexane or hexane–dichloromethane from 9:1 up to 4:1 as eluents.

1b: White crystalline solid. ^{1}H NMR ($CDCl_3$, δ): 7.86 (d, $^3J = 8.7$ Hz, 4H, Ar-*H*), 7.38 (d, $^3J = 8.3$ Hz, 2H, Ar-*H*), 7.35 (dd, $J = 2.1$, 8.6 Hz, 2H, Ar-*H*) 7.17 (ddd, $J = 1.9$, 5.6, 6.3 Hz, 2H, Ar-*H*), 7.15–7.08 (m, 8H, Ar-*H*), 6.82 (m, 4H, Ar-*H*), 3.62 (d, $^2J = 15.3$ Hz, 2H, CH_2), 3.45 (d, $^2J = 15.3$ Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$, δ): 140.37, 137.84, 134.78, 133.01, 132.32, 129.30, 128.10, 127.88, 126.24, 126.15, 125.80, 125.35, 38.57. (*S*)-**1b**: Mp 172–173 °C. $[\alpha]_D^{19.5}$ +14.4 (*c* 1.0, $CHCl_3$). (*RS*)-**1b**: Mp 114–116 °C.

1c: Colourless oil. ^{1}H NMR ($CDCl_3$, δ): 7.88 (d, $^3J = 8.2$ Hz, 2H, Ar-*H*), 7.87 (d, $^3J = 8.3$ Hz, 2H, Ar-*H*), 7.51 (d, $^3J = 8.5$ Hz, 2H, Ar-*H*), 7.40 (ddd, $J = 1.1$, 7.0 8.0 Hz, 2H, Ar-*H*), 7.21 (ddd, $J = 1.3$, 7.0, 8.5 Hz, 2H, Ar-*H*), 7.03 (d, $^3J = 8.5$ Hz, 2H, Ar-*H*), 2.41–2.25 (m, 4H, CH_2), 1.02 (dd, 6H, CH_3). ^{13}C NMR ($CDCl_3$, δ): 135.78, 134.65, 133.49, 132.31, 128.26, 127.78, 127.11, 126.30, 126.02, 125.42, 29.85, 15.56.

(*R*)-**1d**: White oil. $[\alpha]_D^{24}$ −9.8 (*c* 0.83, $CHCl_3$). ^{1}H NMR ($CDCl_3$, δ): 7.93 (d, $^3J = 8.5$ Hz, 2H, Ar-*H*), 7.89 (d, $^3J = 8.1$ Hz, 2H, Ar-*H*), 7.53 (d, $^3J = 8.5$ Hz, 2H, Ar-*H*), 7.41 (ddd, $J = 1.2$, 7.6, 8.3 Hz, 2H, Ar-*H*), 7.20 (ddd, $J = 1.3$, 7.3, 8.2 Hz, 2H, Ar-*H*), 6.98 (d, $^3J = 8.4$ Hz, 2H, Ar-*H*), 3.52 (s, 6H, OCH_3), 2.25–2.80 (m, 8H, CH_2). ^{13}C NMR ($CDCl_3$, δ): 173.41, 136.88, 134.66, 133.32, 132.62, 128.54, 128.18, 127.18, 126.50, 126.33, 125.66, 51.68, 34.71, 29.08. IR ($CHCl_3$, cm^{-1}): 1705, 1230, 1005.

(*R*)-**1e**: Yellowish solid. Mp 83–86 °C. $[\alpha]_D^{24}$ −51.4 (*c* 1.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$, δ): 8.02 (d, $^3J = 8.6$ Hz, 2H, Ar-*H*), 7.88 (d, $^3J = 8.2$ Hz, 2H, Ar-*H*), 7.51 (d, $^3J = 8.6$ Hz, 2H, Ar-*H*), 7.40 (ddd, $J = 1.1$, 7.0, 8.5 Hz, 2H, Ar-*H*), 7.19 (ddd, $J = 1.2$, 6.9, 8.3 Hz, 2H, Ar-*H*), 6.96 (d, $^3J = 8.6$ Hz, 2H, Ar-*H*), 2.80–2.60 (m, 4H, CH_2) 2.33–2.23 (m, 4H, CH_2). ^{13}C NMR ($CDCl_3$, δ): 134.39, 134.11, 132.92, 132.82, 129.17, 128.35, 127.01, 126.78, 126.25, 125.81, 118.97, 29.56, 17.75. IR ($CHCl_3$, cm^{-1}): 2225.

(*R*)-**1f**: White solid. Mp 240–245 °C. $[\alpha]_D^{24}$ +38.5 (*c* 0.35, $CHCl_3$). ^{1}H NMR ($CDCl_3$, δ): 7.92 (d, $^3J = 8.4$ Hz, 2H, Ar-*H*), 7.87 (d, $^3J = 8.0$ Hz, 2H, Ar-*H*), 7.52 (d, $^3J = 8.4$ Hz, 2H, Ar-*H*), 7.39 (ddd, $J = 1.2$, 6.9, 8.3 Hz, 2H, Ar-*H*), 7.18 (ddd, $J = 1.4$, 6.9, 8.2 Hz, 2H, Ar-*H*), 6.95 (d, $^3J = 8.4$ Hz, 2H, Ar-*H*), 2.40–2.80 (m, 8H, CH_2). ^{13}C NMR ($CDCl_3$, δ): 178.08, 134.83, 133.60, 131.83, 131.36, 127.34, 127.04, 125.38, 124.68, 124.64, 124.40, 32.17, 26.91.