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Stereoconservative Negishi arylation and alkynylation as an efficient approach to enantiopure 2,2′-diarylated 1,1′-binaphthyls†

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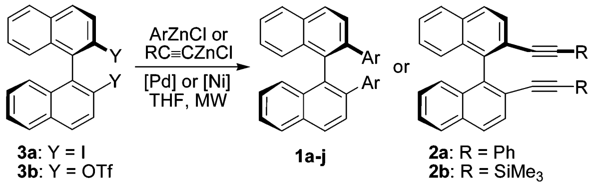
Negishi arylation and alkynylation of easily synthesized chiral 2,2′-diodo-1,1′-binaphthyl rapidly proceeds in refluxing THF utilizing controlled microwave irradiation, affording enantiopure 2,2′-diarylated 1,1′-binaphthyls in good to excellent yields.

Configurationally stable 2,2′-substituted 1,1′-binaphthyl derivatives[1] represent one of the most investigated groups of chiral compounds because of their stereochemical peculiarity – axial chirality. They have found widespread applications[2] in stereoselective synthesis,[2a–d] for the separation and recognition of chiral compounds,[2d–f] and in material science.[2d,g]

However, due to the absence of general and efficient methods for the preparation of non-racemic binaphthyls bearing aryl groups at positions 2 and 2′, there is only a limited number of reports on their application. Metallocene,[3] bisphenanthroline[4] and dipyridyl[5] derivatives of type **1**, for example, have been described as ligands in stereoselective catalysis, whereas dithienyl derivatives have been utilized for the synthesis of conductive polymers.[6] Cyclophane binaphthyls of type **2** with aryls attached *via* ethynyl spacers were considered in respect to applications in material science.[7]

The available synthetic pathways to non-racemic diaryls **1** were reviewed recently.[8a] A direct approach, *i.e.* stereoconservative arylation at positions 2 and 2′ utilizing cross-coupling of suitable enantiopure binaphthyl precursors would be of particular importance. Recently, we have shown that the Suzuki reaction of arylboronic acids with diiodide **3a** proceeds with significant racemization of the binaphthyl moiety.[8,9] A stereoconservative pathway in the Suzuki arylation at positions 2 and 2′ was achieved by "umpolung" – *via* the coupling of 1,1′-binaphthyl-2,2′-diboronic acid and aryl iodides.[8] This approach allowed us to prepare enantiopure diarylated products **1** in moderate yields (<56%).[8a] However, arylation with electron rich and more sterically demanding *ortho*-substituted aryl halides gave predominantly the undesired monoarylated products.

In the Negishi cross-coupling approach described herein, we first examined the use of commercially available bistriflate **3b** as a binaphthyl substrate by screening a variety of nickel and palladium catalysts.[10] Reaction of **3b** with *p*-tolylzinc chloride provided the desired diarylated product **1a** only in moderate yield even at high catalyst loadings (44% yield of **1a** using 6 equiv. of *p*-tolylzinc chloride and 0.15 equiv. of Ni(dppe)Cl_2).



Based on our previous experience[9,11] we next tried to use the less conveniently available – but more reactive – diiodide **3a** (see below) as binaphthyl source. Gratifyingly, the Pd(PPh_3)$_4$-catalyzed (5 mol%) Negishi arylation with *p*-tolylzinc chloride was found to be very effective – after 1 min of reflux in THF it afforded the desired product **1a** in excellent 99% yield! Moreover, starting from non-racemic diiodide **3a** this reaction proved to be stereoconservative. The complete conversion of diiodide **3a** at room temperature required 12 h.

There are only a few reports on microwave-enhanced Negishi cross-coupling reactions.[12] Carrying out the reaction mentioned above starting from **3a** under controlled microwave irradiation[13] at 120 °C for 40 s in THF allowed the isolation of product **1a** in quantitative yield. Lowering the catalyst loading from 5 mol% to 0.5 mol% (0.25% per Ar–I bond) resulted in only a minor decrease of the isolated yield (93%) after 18 min of irradiation at 120 °C (required for completion, turnover frequency 6×10^4 h^{-1}). Usage of either lower or higher amount of arylzinc chloride than threefold excess, resulted in a slight decrease in the yield of **1**, in the latter case due to losses during work-up (more complicated separation from the homocoupling product of the arylzinc chloride).

Investigations with respect to the stereoconservativity of this reaction under microwave irradiation conditions demonstrated that this bis-Negishi cross coupling reaction was completely stereoconservative in the range from 80 to 150 °C. In control experiments it was further demonstrated that both, the starting diiodide **3a** and the product **1a**, do not racemize upon irradiation in THF solution at temperatures up to 150 °C.

We next applied our optimized procedure using sealed vessel microwave irradiation[13] (120 °C) for the preparation of a set of enantiopure diarylated derivatives **1** (Table 1). This protocol allowed to prepare diarylated products **1** with electron neutral and electron-rich aryl groups within 1 min in excellent yields (87–99%). The even more strained *ortho*-substituted product **1e** was prepared in almost quantitative yield. Arylations with less reactive, electron-poor arylzinc chlorides proceeded slightly slower (5–20 min) but still afforded the corresponding products **1h–j** in very good yields (75–92%). The reactions performed under thermal heating (reflux, *ca.* 67 °C) proceeded more slowly and afforded the desired products in somewhat lower yields (up to 24%, see ESI†). All Negishi couplings performed with enantiopure **3a** provided the corresponding diarylated products **1a–j** without loss of enantiomeric purity (±0.2% ee).

The *ortho*- and *meta*-methoxy derivatives **1e** and **1d** are valuable precursors for the synthesis of new ligands for asymmetric catalysis. On the other hand, the spatial arrangement of the nitrogen donor atoms in the 3-pyridyl derivative **1j** does not allow intramolecular bidentate coordination to a metal center, while it can serve as a supramolecular synthon for the formation of helical self-assemblies. The properties and applications of diaryls **1** are currently under investigation and will be reported in due course.

The first synthesis of racemic 2,2′-bis(arylethynyl) derivative **2a** was reported by thermal Stephen–Castro alkynylation of diiodide

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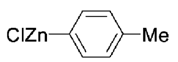
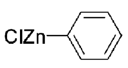
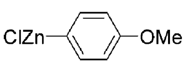
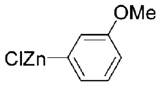
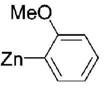
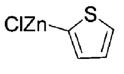
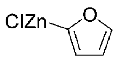
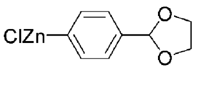
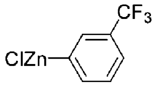
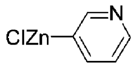
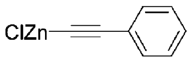
† Electronic Supplementary Information (ESI) available: Experimental procedures, spectral data and chiral chromatography data. See http://www.rsc.org/suppdata/cc/b4/b410185e/

Table 1 Set of (*R*)-**1** and (*R*)-**2** prepared by the Negishi reaction of (*R*)-**3a**[a]

ArZnCl or RC≡CZnCl	Product	Time[b]/min	Yield[c] (%)
	**1a**	0.6	99
	**1b**	0.6	99
	**1c**	0.6	94
	**1d**	0.6	87
	**1e**	1	99
	**1f**	1	99
	**1g**	1	99
	**1h**[d]	20	75
	**1i**	5	92
	**1j**	5	88
	**2a**	3	90
ClZn—≡—SiMe$_3$	**2b**	3	81

[a] *Reaction conditions*: 0.2 mmol (*R*)-**3a**, 1.2 mmol ArZnCl or RC≡CZnCl, 0.01 mol Pd(PPh$_3$)$_4$, THF, single-mode microwave irradiation[13] at 120 °C. [b] Time required for complete conversion of **3a**. [c] Isolated yield, 99.1 ± 0.2% ee (HPLC on Daicel Chiralcel OD-H column). [d] Bis(4-formylphenyl) derivative **1h**.

3a with copper phenylacetylide in 31% yield,[14] while attempts to apply classical Sonogashira conditions resulted in the formation of undesired product of tandem reactions.[14] Being encouraged by the results obtained for the Negishi arylations described above, we next applied a Negishi protocol for the alkynylation of enantiopure diiodide (*R*)-**3a** (99.1% ee) with zinc phenylacetylide. After 40 min of thermal heating to reflux (*ca.* 65 °C), the desired dialkynylated product **2a** was isolated in 66% yield without racemization. When the same reaction was performed with controlled microwave irradiation at 120 °C, (*R*)-**2a** was obtained in excellent 90% yield within 3 min (Table 1). In contrast, all alkynylation attempts of bistriflate **3b** were met with no success.

Similarly, we found that microwave assisted Negishi alkynylation of diiodide (*R*)-**3a** with zinc trimethysilylacetylide gave the corresponding silylated diethyne (*R*)-**2b** (81% yield, Table 1), which can be easily deprotected (K$_2$CO$_3$, MeOH–THF, r.t.) to the corresponding diethyne (*R*)-**2c** (R = H, 91% yield), a valuable intermediate for the synthesis of various diarylated derivatives **2**.

The ready availability of the enantiopure precursor – diiodide **3a** – is crucial for the general applicability of the reported synthesis of diaryls **1** and **2**. There is only a single procedure published in the literature for the preparation of diiodide **3a** in enantiopure form.[15] This is based on diazotation of enantiopure 2,2′-diamino-1,1′-binaphthyl (**4**) in conc. sulfuric acid, precipitation of the corresponding diazonium salt with triiodomercurate and final pyrolysis, affording enantiopure **3a** in 50–60% yield. The classical diazotation of racemic **4** in dilute HCl and subsequent addition of KI provided the product **3a** only in 18% yield.[16] Replacement of dilute HCl by trifluoroacetic acid (TFA) as a water-free medium afforded racemic **3a** in 62% yield.[17] We found that the reaction in TFA proceeds completely stereoconservatively. This procedure is significantly less time consuming and avoids the use of toxic mercury salts.[18]

In summary, we have developed a rapid, high yielding procedure for stereoconservative Negishi arylation and alkynylation of diiodide **3a**. This procedure, in combination with the improved preparation of enantiopure precursor **3a**, provides ready access to novel C_2-symmetric 2,2′-diarylated 1,1′-binaphthyls **1** and **2**.

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Notes and references

1 M. Putala, *Enantiomer*, 1999, **4**, 243.
2 (*a*) Reviews or representative examples: K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013; (*b*) R. Noyori, *Aymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994; (*c*) C. Rosini, L. Franzini, A. Raffaelli and P. Salvadori, *Synthesis*, 1992, 503; (*d*) L. Pu, *Chem. Rev.*, 1998, **98**, 2405; (*e*) D. J. Cram, *Science*, 1988, **240**, 760; (*f*) S. G. Telfer and R. Kuroda, *Coord. Chem. Rev.*, 2003, **242**, 33; (*g*) V. Ostroverkhov, R. G. Petschek, K. D. Singer and R. J. Twieg, *Chem. Phys. Lett.*, 2001, **340**, 109.
3 R. L. Halterman and T. M. Ramsey, *J. Organomet. Chem.*, 1997, **530**, 225.
4 K. Judice, S. J. Keipert and D. J. Cram, *J. Chem. Soc., Chem. Commun.*, 1993, 1323.
5 J. P. H. Charmant, N. J. Hunt, G. C. Lloyd-Jones and T. Nowak, *Collect. Czech. Chem. Commun.*, 2003, **68**, 865.
6 J. Li, A. Rajca and S. Rajca, *Synth. Met.*, 2003, **137**, 1507.
7 (*a*) D. L. An, T. Nakano, A. Orita and J. Otera, *Angew. Chem., Int. Ed.*, 2002, **41**, 171; (*b*) A. Orita, D. L. An, T. Nakano, J. Yaruva, N. Ma and J. Otera, *Chem. Eur. J.*, 2002, **8**, 2005.
8 (*a*) H. Brath, M. Dubovská, M. Juríček, P. Kasák and M. Putala, *Collect. Czech. Chem. Commun.*, 2004, **69**, 1517; (*b*) P. Kasák, H. Brath, M. Dubovská, M. Juríček and M. Putala, *Tetrahedron Lett.*, 2004, **45**, 791.
9 P. Kasák, R. Mikláš and M. Putala, *J. Organomet. Chem.*, 2001, **637–639**, 318.
10 Example of a Ni-catalyzed Negishi arylation of aryl triflates: P. A. Blomgren, S.-K. Kim and B. H. Lipshutz, *Tetrahedron Lett.*, 1999, **40**, 197.
11 P. Kasák and M. Putala, *Tetrahedron Lett.*, 2004, **45**, 5279.
12 (*a*) L. Öhberg and J. Westman, *Synlett*, 2001, 1893; (*b*) P. Stanetty, M. Schnürch and M. D. Mihovilovic, *Synlett*, 2003, 1862; (*c*) P. Walla and C. O. Kappe, *Chem Commun.*, 2004, 564; (*d*) I. Mutule and E. Sune, *Tetrahedron Lett.*, 2004, **45**, 3909.
13 Emrys Synthesiszer (Biotage AB, Uppsala), for details, see: A. Stadler and C. O. Kappe., *J. Comb. Chem.*, 2001, **3**, 624 . For a recent review on controlled microwave chemistry, see: C. O. Kappe, *Angew. Chem., Int. Ed.*, 2004, **43**, in press.
14 W. Baidosi, H. Schumann and J. Blum, *Tetrahedron*, 1996, **52**, 8349.
15 K. J. Brown, M. S. Berry and J. R. Murdoch, *J. Org. Chem.*, 1985, **50**, 4345.
16 M. P. Cava and J. F. Stucker, *J. Am. Chem. Soc.*, 1955, **77**, 6022.
17 V. Sokolov, N. Khrushchova, B. M. Foxman and M. Rosenblum, *Organometallics*, 1993, **12**, 4805.
18 Enantiopure **3a** is commercially available at a price similar to the less reactive **3b**. Current supplier: Ivy Chemicals Corporation, www.ivychem.com.