DOI: 10.1002/adsc.201000350

A Direct Synthesis of Symmetrical (*E*,*E*)-1,4-Diaryl-1,3-butadienes by Wenkert Arylation of Thiophene

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Received: May 5, 2010; Revised: July 28, 2010; Published online: September 14, 2010

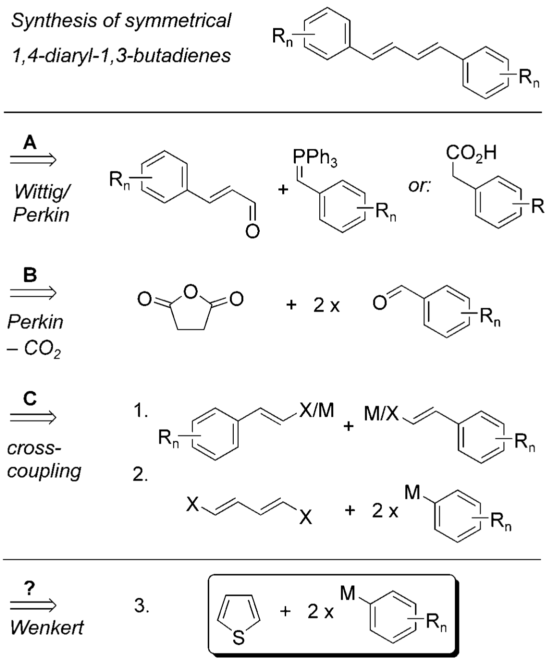
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000350.

Abstract: The nickel-catalyzed coupling of thiophene with aryl Grignard reagents (Wenkert reaction) is accelerated by N-heterocyclic carbene or trialkylphosphane ligands, providing a general, scalable direct synthesis of symmetrical 1,4-diarylbutadienes.

Keywords: alkenes; cross-coupling; homogeneous catalysis; nickel; sulfur heterocycles

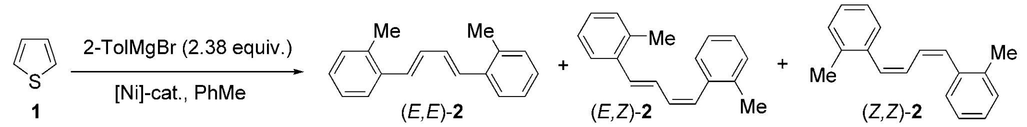
Symmetrical 1,4-diaryl-1,3-butadienes are photoactive materials[1] and find use as starting materials in Diels–Alder reactions,[2,3] photo- or thermocyclizations,[4] or the McCormack reaction.[5] Their established preparations (Scheme 1) by Wittig (**A**),[3,6] Horner (**A**),[1b,4b] or *via* Perkin (**A**, **B**) reactions[7] display low atom-economy or yields, and ask for multistep syntheses of the precursor reagents. Catalytic couplings of styryl-metals and/or halides (**C**, 1.),[8] or of butadienyl-dimetals with aryl halides,[9] or of aryl nucleophiles with 1,4-diiodobutadiene (**C**, 2.)[10] are known, but since the coupling partners are expensive or not readily available themselves, those routes are limited to small-scale preparations.[10c] Thus, when we recently wished to access a variety of symmetrical 1,4-diaryl-1,4-butadienes, we concluded that a scalable one-step synthesis for those was still elusive. Interestingly, Wenkert and co-workers had elegantly obtained 1,4-diphenylbutadiene from thiophene (**1**) and phenylmagnesium bromide in the presence of a nickel catalyst.[11] Low activity and stereoselectivity appear to have prevented applications, let alone a generalization of this approach (**C**, 3.). We now find that suitable ligands including trialkylphosphanes and N-heterocyclic carbenes (NHC) turn the Wenkert arylation of thiophene into a general and superior synthetic method. This is somewhat surprising, because trialkylphosphanes are not typical ligands in Wenkert reactions,[12] and NHC/nickel systems have not found previous use in thioether cross-couplings at all, to the best of our knowledge.

Our studies on the extension of the Wenkert arylation of thiophene set off with 2-tolylmagnesium bromide as moderately bulky test nucleophile and nickel catalysts at the 3 mol% level (Table 1). Standard catalysts for Wenkert reactions[12] which contain triaryl- or diarylphosphane ligands {$NiCl_2(PPh_3)_2$, $NiCl_2[Ph_2P\text{-}(CH_2)_nPPh_2]$} displayed low activity (entries 1, 6, 7). However, the electron-rich trialkylphosphane (entries 2–5, 8–10) and N-heterocyclic carbene (NHC) li-



Scheme 1. Synthetic pathways to symmetrically substituted 1,4-diaryl-1,3-butadienes.

Table 1. Screening of conditions for the Ni-catalyzed Wenkert arylation of thiophene with 2-tolylmagnesium bromide.[a]



Entry	Catalyst	[mol%]	T [°C]	Solvent[b]	**2** after 12 h [%][c]		**2** after 36 h [%][c]	
					total	*E,E*:*E,Z*:*Z,Z*	total	*E,E*:*E,Z*:*Z,Z*
1	$NiCl_2(PPh_3)_2$	3	80	THF	40	43:16:41	43	54:14:32
2	$NiCl_2(PCy_3)_2$	3	80	THF	42	77:11:12	62	82:10:8
3[d]	$NiCl_2(PCy_3)_2$	3	80	THF	59	62:15:23	82	73:13:14
4	$NiCl_2[P(n\text{-}Bu)_3]_2$	3	80	THF	47	88:9:3	72	89:9:2
5	$NiCl_2(PMe_3)_2$	3	80	THF	46	88:10:2	72	92:7:1
6	$NiCl_2$(dppe)	3	100	THF	37	41:15:44	41	50:13:37
7	$NiCl_2$(dppp)	3	100	THF	12	68:12:20	15	75:11:14
8	$Ni(acac)_2+PCy_3$	3+7.5	80	THF	38	75:11:14	56	82:10:8
9	$NiCl_2(PCy_3)_2$	3	80	Et_2O	93	19:20:61	90	38:26:36
10	$NiCl_2[P(n\text{-}Bu)_3]_2$	3	80	Et_2O	55	10:7:83	71	16:8:76
11	$Ni(acac)_2$+IMes·HCl	3+7.5	80	THF	73	65:16:19	75	90:9:1
12[d]	$Ni(acac)_2$+IMes·HCl	3+6	80	THF	80	33:22:45	89	40:21:39
13	$Ni(acac)_2$+IPr·HCl	3+7.5	80	THF	67	56:22:22	77	68:20:12
14	$Ni(acac)_2$ + ICy·HCl	3 + 75	80	THF	29	86:9:5	42	90:9:1
15	$Ni(acac)_2$+IMes·HCl	3+6	80	Et_2O	4	28:35:37	6	86:8:6
16	$Ni(acac)_2$+IPr·HCl	3+6	80	Et_2O	5	33:33:34	6	33:32:35

[a] *Reaction conditions:* thiophene (1.26 mmol), 2-TolMgBr (3 mmol, 2.38 equiv.; 2 $mol L^{-1}$ in THF or Et_2O), toluene (2 mL), catalyst, internal standard dodecane (100 μL).

[b] Co-solvent from the Grignard reagent.

[c] Yields and product ratios determined by GC/FID against internal standard.

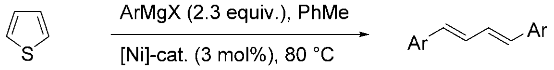
[d] Reaction diluted with additional toluene (10 mL). Abbreviations: Cy = cyclohexyl; Tol = tolyl; dppe/dppp = $Ph_2P(CH_2)_nPPh_2$ (n = 2, 3); IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolylidene, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazolylidene, ICy = 1,3-dicyclohexylimidazolylidene.[15]

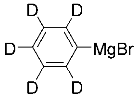
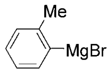
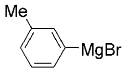
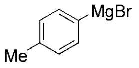
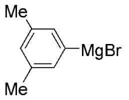
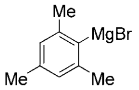
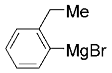
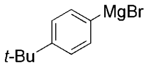
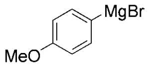
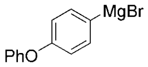
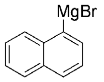
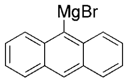
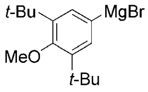
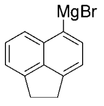
gands (entries 11–16) provided high catalytic activity and yields of up to 90% of diene isomers **2**.

Electronic ligand effects are critical (compare entries 1, 6, 7 *vs.* 2–5), but steric ligand effects are not pronounced (compare the trialkylphosphane series, entries 2–5). The isomer composition was ligand-dependent, with preference for either (*E,E*)- or (Z,Z)-, but not (*E,Z*)-**2** as the major product. From the time-dependency of the isomer ratio it is clear that isomerization from (*Z,Z*)- *via* (*E,Z*)- to (*E,E*)-**2** occurs under the reaction conditions; however, the isomerization is relatively slow, thus the high (*E,E*)-selectivity of certain entries after 12 h appears to be intrinsic rather than a consequence of isomerization. While Wenkert reactions require apolar bulk solvents,[11] the stereoselectivity of the reaction also depends on the etheral co-solvent introduced with the Grignard reagent: THF generally favors the (*E,E*)-**2** isomer, whereas the combinations of phosphane ligands and Et_2O as co-solvent show a marked initial selectivity for (*Z,Z*)-**2** (entries 9, 10). The combination of NHC ligands and Et_2O as co-solvent is inefficient (entries 15, 16).[13] In general, higher conversions were achieved by diluting the reaction mixture with additional toluene (entries 3, 12).

Concluding from Table 1, favorable reaction conditions are defined by use of trialkylphosphane ligands with either THF or Et_2O as co-solvent, or carbene ligands and THF as co-solvent.[14] These conditions were tested with a range of Grignard reagents (Table 2). The butadiene isomer fraction was isolated as a stereoisomer mixture and quantified after 20 h of reaction time to identify the most active catalysts, irrespective of isomer selectivity (Table 2, column "mix").[15] Next, the most promising catalyst/cosolvent combination was applied in the synthesis of the (*E,E*)-isomer [Table 2, column (*E,E*)]. The proportion of (*E,E*)-isomer in the crude product was increased either by applying extended reaction times or by performing an iodine-catalyzed photoisomerization on the initial crude product isomer mixture. A range of (*E,E*)-1,4-diaryl-1,3-butadienes were prepared by the new methodology, some for the first time, in fair to high yields (Table 2). Phenyl or *ortho*- and *para*-substituted aryl nucleophiles often gave yields in excess of 60%. *meta*-Substituted aryl reagents were saliently lower yielding (entries 5, 7, 15). The reaction was successful with annelated aromatic Grignard reagents (13, 14, 16). The use of thiophene and aryl Grignard reagents allows for a simple upscaling of the reaction.

Table 2. Synthesis of 1,4-diaryl-1,3-butadienes from thiophene.[a]



Entry	ArMgX	Ligand	Solvent	Yield [%][b] mix	*E,E*
1	PhMgCl	IMes	THF	70	61[c]
2	PhMgCl	IPr	THF	68	
3		PCy_3	Et_2O		62
4		IMes	THF	90	74[c]
5		IMes PCy_3	THF THF	32 29	24[c]
6		IMes IPr	THF THF	73 73	62[c]
7		PCy_3 PBu_3	THF Et_2O	28 19	19
8		PBu_3 PBu_3	THF Et_2O	76 37	71
9		IPr IMes PCy_3	THF THF Et_2O	72 98 94	- 75[c] –
10		IPr PBu_3	THF THF	70 51	62[c] –
11		PCy_3 IMes	THF THF	65 49	54 –
12		PBu_3	Et_2O	56	43
13		PCy_3	Et_2O Et_2O	85 –	64 57[d]
14		PCy_3	Et_2O	–	46
15		IMes IMes	THF THF	– –	56 (76)[e]
16		IMes	THF	–	49

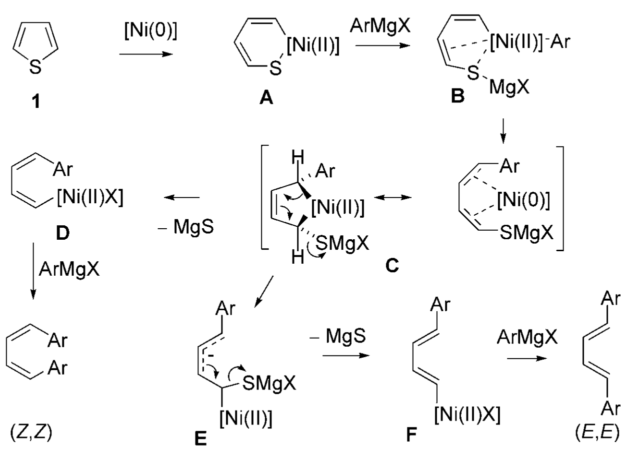
[a] *Reaction conditions:* thiophene (1 equiv.), 3 mol% $NiCl_2(PR_3)_2$ or 3 mol% $Ni(acac)_2$ + 7.5 mol% NHC·HCl, ArMgX (2.3 equiv.), toluene (5 mL mmol^{-1}).

[b] The term "mix" refers to the yield of butadiene stereoisomer mixture, at a 2-mmol scale, 80 °C, 20 h; "*E,E*" refers to yield of (*E*,*E*)-isomer at a 10-mmol scale, 80 °C, 36 h.

[c] Yield after iodine isomerization, see text.

[d] 0.25-molar scale.

[e] Yield of 1,4-diarylbutane after hydrogenation of the diene isomer mixture.[15]



Scheme 2. Proposed reaction mechanism, see text.

In the case of (*E,E*)-di-1-naphthyl-1,3-butadiene, a 0.25-molar scale reaction was performed and the product obtained with only a slight reduction in yield (entry 13).

The role of both thiolate and sulfide as leaving groups in this cross-coupling reaction is notable. Based on experimental observations and literature precedents, we propose the following mechanism (Scheme 2) *via* metallacyclic intermediates to explain both the absence of monoarylated intermediates,[11] and the stereoselectivity for either (*Z*,*Z*)- or (*E*,*E*)-isomeric products seen in our study (Table 1).

Insertion of Ni(0) into a C–S bond of thiophene (**1**→**A**),[16,17] transmetallation to **B** and reductive elimination will generate a η^4-Ni(0)-diene-thiolate, mesomeric to metallacycle **C**, which undergoes 1,4-elimination of magnesium sulfide to butadienyl-nickel species **D**.[18]

Alternatively, dissociation from **C** and stereoisomerization of open-chain species **E** produces **F**. Depending on the configuration of the butadienyl-nickel(II) intermediate (**D** or **F**), either (*Z*,*Z*)- or (*E*,*E*)-diene is eventually formed. Spectator ligands at nickel will affect the relative rates to **D** and **F**, and polar co-solvents will favor dissociation to **E**, increasing the amount of (*E*,*E*)-diene.

In conclusion, we have shown that trialkylphosphane and NHC complexes of nickel are superior catalysts in the Wenkert arylation of thiophene with aryl Grignard reagents. A direct and scalable synthesis of (*E*,*E*)-1,4-diaryl-1,3-butadienes is thus available.

Experimental Section

(*E,E*)-1,4-Dimesityl-1,3-butadiene

To a Schlenk vessel containing $NiCl_2[P(n\text{-}Bu_3)]_2$ (0.160 g, 0.30 mmol, 3 mol%) under argon, dry toluene (50 mL) was added, followed by thiophene (0.80 mL, 10.0 mmol) and mesityl-magnesium bromide (2 M in THF; 11.5 mL, 23.0 mmol). The reaction mixture was heated to 80 °C with stirring. After 36 h, the reaction mixture, which had turned into a thick suspension, was cooled, diluted with 2–4 volumes of toluene, and quenched by careful addition of an equal volume of saturated aqueous NH_4Cl. [***Caution:*** *Work-up must be carried out in a well-ventilated hood, because H_2S is released upon hydrolysis.*] The organic phase was washed with equal volumes of aqueous HCl (2.4 $mol L^{-1}$), aqueous NaOH (2 $mol L^{-1}$), and water. After drying ($MgSO_4$), the solution was filtered and evaporated. Chromatographic purification (SiO_2/hexanes) of the crude gave the product as a colorless solid; yield: 2.062 g (71%)

See the Supporting Information for full experimental details, characterization of products and copies of product ^1H and ^{13}C NMR spectra.

Acknowledgements

We thank DFG for funding, and Prof. C. Bolm, RWTH Aachen University, for support.

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[15] See the Supporting Information for additional screening results.

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[17] For a related mechanism in the nickel-catalyzed desulfurization of benzothiophene with Grignard reagents: J. Torres-Nieto, A. Arévalo, J. J. García, *Organometallics* **2007**, *26*, 2228.

[18] For a similar elimination of a 2-alkoxy-zirconacyclopentene to a butadienyl-zirconium species, see: N. Chinkov, S. Majumdar, I. Marek, *J. Am. Chem. Soc.* **2003**, *125*, 13258.