Tetrahedron Letters 50 (2009) 3985–3987

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient synthesis of 3,3′-dipyridyl BINOL ligands

Anna Goldys, Christopher S. P. McErlean *

School of Chemistry, University of Sydney, NSW 2006, Australia

ARTICLE INFO

Article history:
Received 16 March 2009
Revised 6 April 2009
Accepted 24 April 2009
Available online 3 May 2009

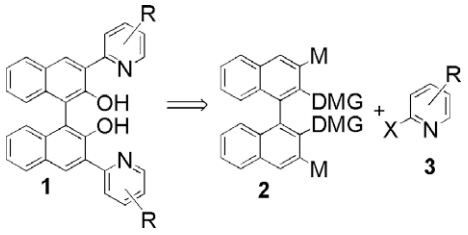
ABSTRACT

Microwave-assisted Suzuki cross-coupling between 2,2′-bis(methoxymethyl)-3,3′-bis(potassium trifluoroboronato)BINOL and a series of 2-bromo- or 2-chloropyridines provides efficient access to 3,3′-dipyridyl BINOL ligands.

The class of BINOL-derived ligands occupies a privileged position in the arena of synthetic organic chemistry.[1] Of particular importance in this respect is the subset of ligands based on the 3,3′-disubstituted BINOL scaffold. With an appropriate choice of sterically demanding substituent at these flanking positions, impressive levels of enantio- and diastereocontrol have been realised over a wide range of transformations.[2]

Gao and co-workers were the first to report 3,3′-dipyridyl-substituted BINOL variants.[3] Recently, Snieckus and co-workers have reported a general synthesis of this class and have employed these compounds in highly enantioselective additions of alkyl zinc reagents to aldehydes.[4] Those authors present evidence that the coordinating nitrogen atom on the pyridine ring leads to the formation of a bi-functional catalyst coordinating more than one metal centre.[5] This is not the only mode of action available to such ligands. It can be envisaged that the pendant nitrogen donor could function as a Lewis acid, co-coordinating to a bound single metal centre.[6] We became interested in utilising this class of 3,3′-dipyridyl-substituted BINOL ligand for organocatalytic applications and set about developing an efficient synthesis of these compounds.

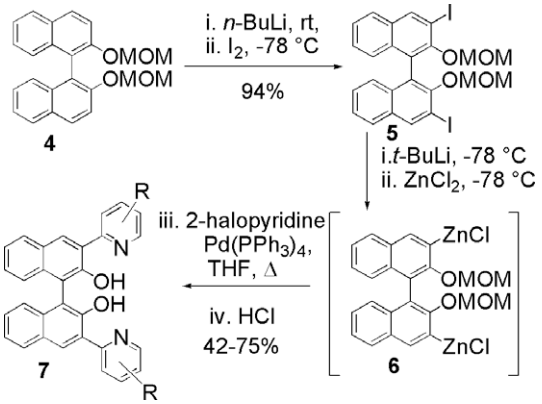
The synthesis of 3,3′-substituted BINOL **1** compounds can be envisaged to arise through a palladium-mediated cross-coupling between a metalated BINOL unit **2** and an aryl or heteroaryl halide **3** (Scheme 1). The metalated BINOL unit can be efficiently generated employing directed metalation groups (DMGs) such as an OMOM, OMe or $OCONEt_2$. However, the introduction of pyridyl units in this way has proved troublesome due to the unwillingness of halopyridines to participate in palladium-mediated reactions. The initial attempts of Jørgensen and co-workers to couple BINOL bis-boronic acid with halopyridines were unprofitable.[7] In the first reported synthesis of these compounds, Gao and co-workers used a Suzuki cross-coupling between a bis-boronic pinacol ester and a halopyridine to install the desired unit in yields ranging from 79 to 84%.[3] Extended reactions times (24 h in refluxing toluene) were



Scheme 1. Retrosynthetic analysis.

required to effect the coupling which suffered from narrow scope. Unfortunately, the synthesis of the bis-boronic pinacol ester has proven capricious in our hands, with the compound being prone to hydrolysis and consequently giving disappointing results in the cross-coupling reactions with 2-bromopyridine.

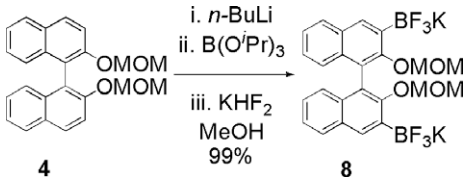
After surveying alternatives, Snieckus settled upon the Negishi coupling as the most efficient method to generate these compounds.[4] The readily available bis-MOM compound **4** underwent



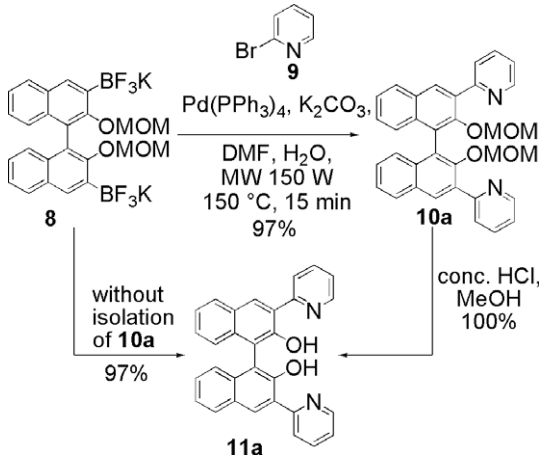
Scheme 2. Snieckus' route to 3,3′-dipyridyl BINOL ligands.

* Corresponding author. Tel.: +61 2 9351 3970; fax: +61 2 3951 3329.
E-mail address: C.McErlean@chem.usyd.edu.au (C.S.P. McErlean).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.04.092



Scheme 3. Synthesis of **8**.



Scheme 4. Suzuki coupling reaction of **8**.

a double *ortho*-lithiation–iodination sequence. The purified bis-iodo compound **5** underwent lithium–halogen exchange with *tert*-butyllithium and transmetalation with $ZnCl_2$ to give compound **6**. Palladium-mediated cross-coupling with a range of 2-halopyridines in refluxing THF then delivered the desired 3,3′-dipyridyl-substituted BINOL ligands **7** in yields ranging from 42 to 75%. Attempts to generate the organo-zinc species **6** directly from the initial doubly *ortho*-lithiated compound resulted in reduced yields (Scheme 2).

We decided that a more operationally simple procedure was required, which would deliver the ligands in higher overall yield. As such, we explored the synthesis and microwave-assisted cross-coupling reactions of the bis(potassium trifluoroboronato)BINOL compound **8**.

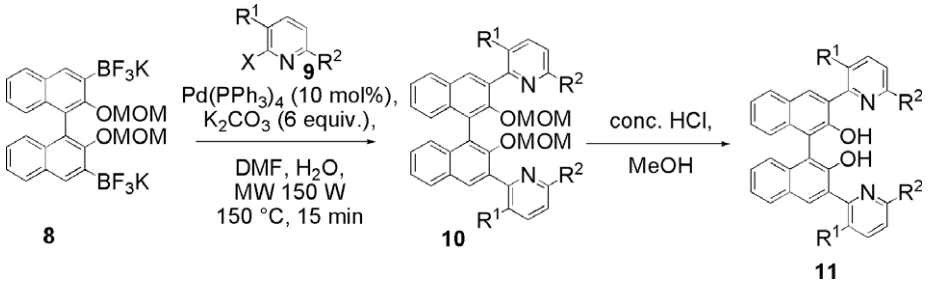
Aryl, alkenyl and alkyl trifluoroborates have found increasing use in synthesis as boron coupling partners in Suzuki reactions.[8] Aryltrifluoroborates possess a number of properties that make them very practical reagents. Unlike the corresponding boronic acids, trifluoroborates exist as discrete species, avoiding complicated acid-boroxine equilibria. They are inert towards many of the standard reagents used by the synthetic chemist, acting as protected boronic acids under oxidative,[9] alkylative[10] and a variety of other conditions.[11] They are a much more atom economical source of boron than pinacol or related esters, and they readily participate in Suzuki coupling reactions without additives and in air. Importantly for our purposes, these solid compounds can be made in an operationally simple manner following the procedure of Vedejs.[11]

Our synthesis began with the *ortho*-lithiation of the bis-MOM compound **4**, in the absence of TMEDA. Reaction with triisopropyl borate delivered the readily hydrolysable boronic ester which was converted into the corresponding bis(potassium trifluoroboronato) complex by the action of KHF_2. Simple filtration then delivered the desired 2,2′-bis(methoxymethyl)-3,3′-bis(potassium trifluoroboronato) BINOL compound **8** as a bench-stable, colourless solid in 99% yield from **4** (Scheme 3).

Having achieved a simple and reliable synthesis of the boronate coupling partner,[12] we proceeded to investigate the Suzuki coupling with 2-bromopyridines. Pleasingly, our initial attempt at effecting a union between compound **8** and 2-bromopyridine **9** was successful. Irradiating a mixture of **8**, **9**, $Pd(PPh_3)_4$ (10 mol %) and K_2CO_3 in DMF/water to 150 °C in a sealed microwave reactor,[13] gave the desired adduct **10a** as the sole product in 97% yield and in just 15 min. Acid hydrolysis delivered the desired 3,3′-dipyridyl-BINOL **11a**, quantitatively. To simplify the procedure further, the MOM-protecting group could be removed during the reaction work-up by treatment with acid. This simple protocol delivered the desired 3,3′-dipyridylBINOL **11a** in an identical yield (Scheme 4).

We next sought to explore the scope of the pyridyl coupling partner. Snieckus had used 3-substituted-2-iodopyridines to illustrate the Negishi coupling methodology.[4] We were confident that

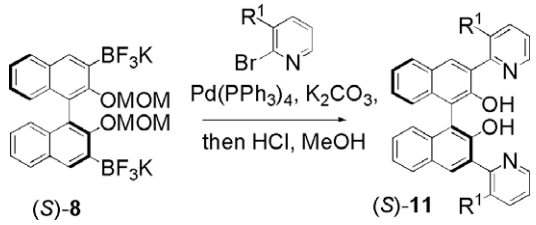
Table 1
Synthesis of ligands **11a–h**



Entry	Substrate **9**	R^1	R^2	X	Yield of **10**[a] (%)	Yield of **11**[a] (%)
1	**a**	H	H	Br	97	100
2	**b**	OBn	H	Br	51	90
3	**c**	OC_6H_{13}	H	Br	64	95
4	**d**	OC_4H_9	H	Br	56	95
5	**f**	OTs	H	Br	27	96
6	**g**	OH	H	Br	n.d.[b]	—
7	**h**	H	OMe	Cl	63	92

[a] Isolated yield after chromatography.
[b] Not detected.

Table 2
Synthesis of enantiomerically enriched ligands **11a–d**



Entry	Compound	ee[a]	Observed $[\alpha]_D^{20}$
1	**11a**	—	−45.8
2	**11b**	>98%	−48.9
3	**11c**	>98%	−37.0
4	**11d**	>98%	−34.5

[a] Determined on a Diacel AD-H column, eluting with 50% hexane–*iso*propanol.

the less reactive 2-bromopyridines would participate in the microwave-assisted Suzuki couplings. Gratifyingly, 3-benzyloxy,[14] 3-hexyloxy and 3-butyloxy-2-bromopyridine[15] reacted under the conditions listed above to give the desired compounds in 51%, 64% and 56% yields, respectively (Table 1, entries 2–4). The use of readily available bromopyridines represents a significant improvement to the current methods.

The bifunctional coupling partner 3-tosyl-2-bromo-pyridine[16] also underwent coupling with the bis-boronate, albeit in a much reduced yield (entry 5). The reaction was not restricted to bromopyridines. 2-Chloro-5-methoxypyridine could be utilised effectively as the coupling partner to give the desired product in 63% yield (entry 7). In each case, acid-catalysed removal of the MOM-protecting group was uneventful and delivered the free diol in a straightforward manner. As the reaction was conducted in aqueous media, we thought that alcohol-protecting groups on the pyridine core may be superfluous. However, attempts to couple the parent 2-bromo-3-pyridinol under the standard conditions were uniformly unsuccessful (entry 6).

Whilst these initial reactions defined the scope of the pyridyl coupling partner, they were performed on racemic BINOL substrates. We next sought to ascertain whether or not the microwave conditions were suitable for the generation of a single enantiomeric series. As such, (*S*)-**4** was converted into the corresponding bis(potassium trifluoroboronato)BINOL (*S*)-**8** in the manner described above. The bis(potassium trifluoroboronato)BINOL (*S*)-**8** was then subjected to the microwave-assisted Suzuki coupling–deprotection protocol. Enantioselective HPLC analysis of the product 3,3′-dipyridyl BINOL compounds **11b–d** and **11h** demonstrated unambiguously that the stereochemical integrity of the biaryl bond was not compromised during the coupling protocol (Table 2).

In summary, we have disclosed an efficient route to 3,3′-dipyridyl-substituted BINOL ligands based on a microwave-assisted Suzuki coupling reaction between the bis(potassium trifluoroboronato)BINOL compound **8** and a series of 2-halopyridines. Applications of these ligands in catalytic settings will be reported in due course.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.092.

References and notes

1. Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857–897.
2. Examples include, hydrogenation: Minnaard, A. J.; Feringa, B. L.; Lefort, L.; De Vries, J. G. *Acc. Chem. Res.* **2007**, *40*, 1267–1277; halocyclisation of polyprenoids: Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900–903; organo-zinc additions to aldehydes: Harada, T.; Hiraoka, Y.; Kusukawa, T.; Marutani, Y.; Matsui, S.; Nakatsugawa, M.; Kanda, K. *Org. Lett.* **2003**, *5*, 5059–5062; cycloaddition reactions: Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626–9627; conjugate addition reactions: Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 4908–4909; reductive aminations: Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84–86.
3. Jin, R.-Z.; Bian, Z.; Kang, C.-q.; Guo, H.-q.; Gao, L. Z. *Synth. Commun.* **2005**, *35*, 1897–1902.
4. Milburn, R. R.; Hussain, S. M. S.; Prien, O.; Ahmed, Z.; Snieckus, V. *Org. Lett.* **2007**, *9*, 4403–4406.
5. Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187.
6. Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920.
7. Simonsen, K. B.; Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 7536–7538.
8. Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286; Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302–4314.
9. Molander, G. A.; Petrillo, D. E. *J. Am. Chem. Soc.* **2006**, *128*, 9634–9635; Molander, G. A.; Ribagorda, M. *J. Am. Chem. Soc.* **2003**, *125*, 11148–11149; Molander, G. A.; Figueroa, R. *Org. Lett.* **2006**, *8*, 75–78.
10. Molander, G. A.; Ellis, N. *J. Org. Chem.* **2006**, *71*, 7491–7493.
11. Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020–3027.
12. This reaction has been carried out several times on gram scale.
13. The microwave-assisted reactions were conducted in quartz reactor vessels using a Milestone MicroSYNTH laboratory microwave.
14. Genin, M. J.; Poel, T. J.; Yagi, Y.; Biles, C.; Althaus, I.; Keiser, B. J.; Kopta, L. A.; Friis, J. M.; Reusser, F.; Adams, W. J.; Olmsted, R. A.; Voorman, R. L.; Thomas, R. C.; Romero, D. L. *J. Med. Chem.* **1996**, *39*, 5267–5275.
15. Matondo, H.; Baboulène, M.; Rico-Lattes, I. *Appl. Organomet. Chem.* **2003**, *17*, 239–243.
16. Hodgson, R.; Kennedy, A.; Nelson, A.; Perry, A. *Synlett* **2007**, 1043–1046.