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Synthesis of Atropisomeric Analogues of DMAP

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Abstract

A method for the preparation of 7-aryl derivatives of *N*-methyl-5-azaindoline involving Suzuki cross-coupling is described. Certain biaryls prepared in this manner exhibit atropisomerism. In particular, azaindoline **11** is shown to be configurationally stable at room temperature and to catalyse efficiently the esterification of 1-methylcyclohexanol with Ac_2O.

Keywords: atropisomerism; biaryls; Suzuki reactions; catalysis.

Since the independent work of Litvinenko [1] and Steglich [2], 4-dimethylaminopyridine (DMAP) and closely related compounds have been widely used as nucleophilic catalysts in acylations and related transformations [3-5]. Recently, considerable effort has been directed towards the design and synthesis of chiral nucleophilic catalysts with the goal of developing systems displaying levels of selectivity and efficiency comparable to or exceeding those of enzymes [6]. To this end, Vedejs [7,8], Fuji [9], and Fu [10-14] have employed chiral derivatives of DMAP, 4-pyrrolidinopyridine, and 4-dimethylaminopyrindine, respectively, as catalysts for kinetic resolution of racemic alcohols.

We have focused our efforts on the preparation of atropisomeric biaryl nucleophilic catalysts with 1-methyl-2,3-dihydro-1*H*-pyrrolo[3,2-c]pyridine (*N*-methyl-5-azaindoline) **1** as the nucleophilic unit in the biaryl system. In contrast to the systems referred to above, rotation about the C_{Ar}-N bond is rendered impossible in this bicycle. Moreover, it has been recently reported that in certain acylation reactions azaindoline **1** exhibits catalytic activity comparable to that of DMAP itself [15].

Since the previously reported synthetic routes leading to *N*-methyl-5-azaindoline **1** are both multi-step and low-yielding [16-18], we developed an expedient four-step protocol starting with commercially available 4-aminopyridine **2**. This involved its initial derivatisation as *t*-butyl carbamate **3** (Boc_2O), followed by one-pot *o*-lithiation (*t*-BuLi) and alkylation (ethylene oxide) to give alcohol **4**. Mesylation and *in situ* cyclisation (MsCl, Et_3N) furnished *N*-Boc azaindoline **5**, which was reduced (DIBAL) to give 1-methyl azaindoline **1**. Clean bromination (NBS in DMF) [19] produced bromide **6**. Suzuki cross-coupling [20] of bromoarene **6** with a variety of relatively unhindered arylboronic acids under standard conditions [Na_2CO_3, $Pd(PPh_3)_4$ (cat.), PhMe, EtOH, H_2O; reflux] furnished 7-aryl derivatives **7a-e** and **8a-e** in good to excellent yields. The structure of the key intermediate **8e** (*vide infra*) was unequivocally confirmed by single-crystal x-ray crystallographic analysis (**Figure 1**).

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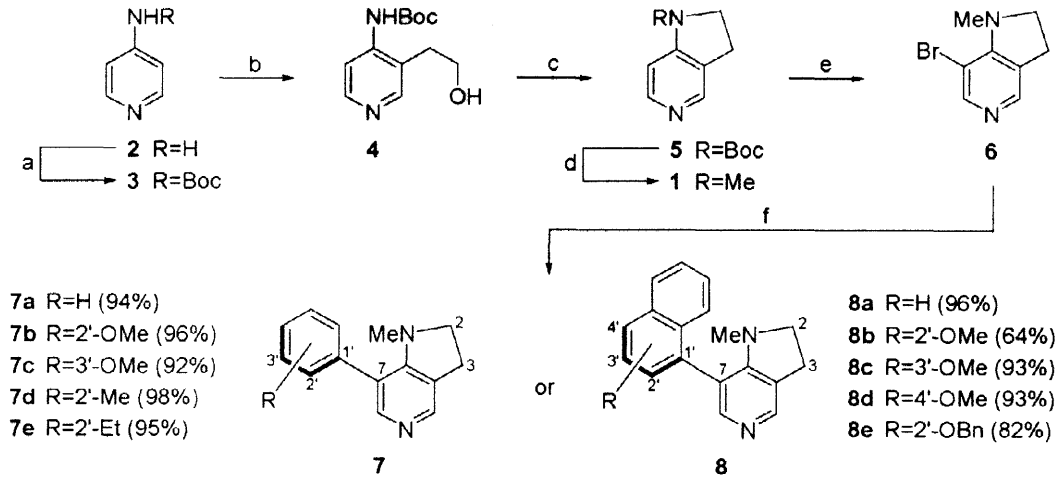


Scheme 1

Reagents and conditions: (*a*) Boc_2O, DCM, rt, 1 hr; >95%; (*b*) *i*. *t*-BuLi, THF, −78 → −15 °C, 3 hr; *ii*. ethylene oxide, −78 °C → rt, 2 hr; 75%; (*c*) MsCl, Et_3N, DCM, −10 °C → rt, 2 hr; >95%; (*d*) DIBAL, DCM, reflux, 20 hr; 55%; (*e*) NBS, DMF, 0 °C, 90 min; 81%; (*f*) $ArB(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, PhMe, H_2O, EtOH, reflux, 5-24 hr.

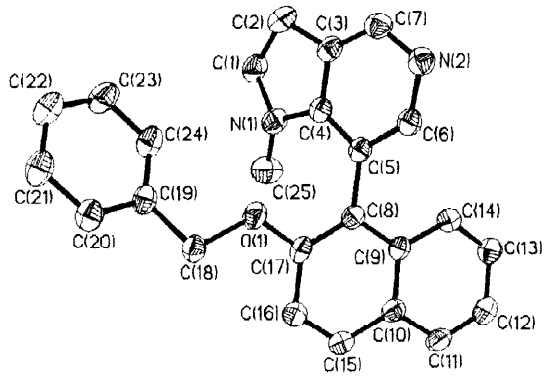


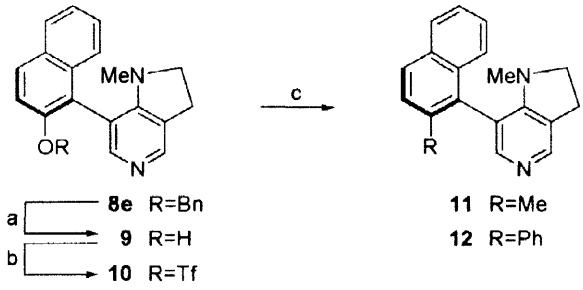
Figure 1. ORTEP drawing of biaryl **8e**

As the result of axial dissymmetry about the biaryl axis, the protons of each of the two CH_2 groups (at C_2 and C_3) in 5-azaindoline derivatives **7b-e** and **8a-e** are diastereotopic. ^{1}H NMR (250 MHz, $CDCl_3$, rt) studies showed that in biaryls **7c** and **8b,e** these protons are isochronous, i.e. appear as a pair of triplets, as in symmetrical biaryl **7a**. In contrast, the methylene protons in biaryls **7b,d,e** and **8a,c,d** are anisochronous and show more complex splitting patterns, which unequivocally confirms slow rotation about the central C_{Ar}-C_{Ar} axis due to steric hindrance. For 7-(1-naphthyl) derivative **8a** no coalescence was observed even at 100 °C. The rotational energy barrier for biaryl **8a** was calculated to be 85.9 ± 0.3 kJ/mol (20 °C) by computer simulation of the plateau-shaped elution profile obtained by chiral HPLC [21,22][2]. This corresponds to a half-life for racemisation of ~1.9 min at 20 °C which is significantly shorter than the arbitrarily set threshold of 1000 s considered the minimum requirement for chemical separation of optical antipodes [23]. Consequently, preparation of more hindered biaryls was required.

Since various attempts to perform direct Suzuki cross-coupling of aryl bromide **6** with 2-methyl-1--naphthaleneboronic acid were unsuccessful, an indirect synthesis of the 2'-methyl analogue of biaryl

[2] Computer program: Hochmuth DH. 'Mimesis 2.0 for Windows 95'.

8a was attempted (**Scheme 2**). Thus, catalytic hydrogenolysis of benzyl ether **8e** gave phenol **9**, which was converted to triflate **10** with Tf_2O/pyridine. Both Pd-mediated Me_4Sn [24] and Ni-mediated MeMgBr [25] couplings with triflate **10** were successful and gave biaryl **11** in good yield. Similarly, 2'-phenyl derivative **12** was obtained *via* Suzuki coupling of triflate **10** with phenylboronic acid.



Scheme 2

Reagents and Conditions: (*a*) H_2 (1 atm), Pd/C, EtOH, rt, 5 hr; (*b*) Tf_2O, pyridine, 0 °C → rt, 5 hr; 93% from **8e**; (*c*) MeMgBr, $NiBr_2(PPh_3)_2$, Et_2O, reflux, 15 hr; 85% (**10** → **11**); Me_4Sn, $Pd(PPh_3)_2Cl_2$, PPh_3, LiCl, 2,6-di-*t*-butyl-4--methylphenol, DMF, 120 °C, 20 hr; 73% (**10** → **11**); $PhB(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, DME, reflux, 18 hr; 53% (**10** → **12**).

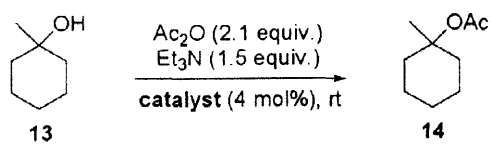
A sample of racemic biaryl **11** was separated into its enantiomers using analytical chiral HPLC (Chiralcel OD, hexane:isopropanol, 96:4) and the atropisomerisation of the individual enantiomers studied in benzene in the temperature range 120-180 °C (sealed-tube experiments). Kinetic parameters were obtained from the Arrhenius and Eyring plots [26] (**Table 1**). Extrapolation of both the Arrhenius and Eyring plots indicated that an enantiomerically pure sample of biaryl **11** would lose less than 1% of its optical purity over one year in solution at room temperature (298 K).

T/K	$10^7 k_{racem}/s^{-1}$	**Arrhenius parameters**	
		E_a/kJ mol^{-1}	107±3
393	8.93±0.22	ln(A/s^{-1})	18.8±1.0
413	45.4±2.0	**Eyring functions**	
433	185±3	$\Delta H^{\#}$/kJ mol^{-1}	103±4
453	682±16	$\Delta S^{\#}$/J mol^{-1} K^{-1}	-100±8

Table 1

Rate constants of racemisation k_{racem}, the Arrhenius parameters (E_a, A) and transition-state functions ($\Delta H^{\#}$, $\Delta S^{\#}$) for atropisomerisation of biaryl **11**.

Biaryls **8a** and **11** were shown to be active catalysts in acylation of a hindered alcohol, 1-methylcyclohexanol **13**, with Ac_2O in the presence of triethylamine (**Scheme 3**); the test previously used by others to assess the catalytic activity of DMAP and its analogues [2].



	13:14	
catalyst	**after 10 hr**	**after 24 hr**
no catalyst	99:1	98:2
DMAP	13:87	5:95
1	21:79	10:90
8a	36:64	18:82
11	22:78	13:87

Scheme 3

From the results obtained it is apparent that introduction of a 7-aryl substituent into azaindoline **1** has little detrimental effect on catalytic activity (**1** vs. **11**). It is also interesting to note that **11** is a superior catalyst to **8a** in the acylation studied. The increased nucleophilicity of the pyridyl nitrogen in biaryl **11** relative to that of biaryl **8a** presumably reflects the decreased degree of conjugation across the biaryl system with increased rotational restriction.

In conclusion, a simple route to 7-aryl-5-azaindolines involving Suzuki cross-coupling has been developed which can provide biaryls that are configurationally stable at room temperature and are efficient nucleophilic acylation catalysts. Work is currently in progress to evaluate the potential of enantiomerically pure analogues as catalysts for asymmetric transformations.

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