Pushing the limits of steric demand around a biaryl axis: synthesis of tetra-*ortho*-substituted biaryl naphthalenes†‡

Adam C. Glass, Sam Klonoski, Lev N. Zakharov§ and Shih-Yuan Liu*

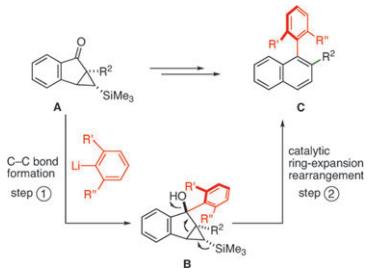
Received 29th June 2010, Accepted 27th July 2010
DOI: 10.1039/c0cc02170a

The synthesis of tetra-*ortho*-substituted biaryl naphthalenes, including examples bearing multiple *ortho*-isopropyl groups, has been developed *via* a catalytic rearrangement process.

Substituted biaryls are important substructures of many biologically active compounds,[1] organic materials,[2] and ligands in metal catalysts.[3] The development of methods for the synthesis of biaryls has mostly been dominated by metal-mediated coupling chemistry (*i.e.*, cross-coupling,[4] direct arylation,[5] and oxidative coupling[6]) due to its versatility. However, the assembly of highly substituted biaryls, in particular tetra-*ortho*-substituted derivatives, has generally been challenging for coupling-based strategies.[7,8] This is arguably due to the steric demand imposed by the coupling of two bis-*ortho*-substituted biaryl precursors. Alternative approaches toward the construction of tetra-*ortho*-substituted biaryls have recently been developed that include annulation-based strategies, *e.g.*, Diels–Alder[9] and [2 + 2 + 2] cycloadditions.[10]

Despite the significant advances that have been made to date, novel strategies for the generation of tetra-*ortho*-substituted biaryls are still highly desired. We have been pursuing a rearrangement-based approach for the synthesis of substituted biaryl naphthalenes.[11–13] Scheme 1 illustrates our strategy in which the addition of an arene nucleophile to the starting material **A** is followed by a ring-expansion rearrangement to furnish the desired biaryl naphthalene **C** *via* a cyclopropyl carbinol intermediate **B**. The distinguishing feature of our approach is that the key C–C bond-forming step is accomplished through a simple addition of a nucleophile to a carbonyl.[14] Given the strong thermodynamic driving force for this nucleophilic addition,[15] we envision that our method could serve as a potential method for the construction of tetra-*ortho*-substituted biaryl naphthalenes. In this communication, we demonstrate that a range of tetra-*ortho*-substituted biaryl naphthalenes can be produced *via* our method, including a very hindered tetra-*ortho*-substituted biaryl naphthalene bearing three isopropyl groups in the *ortho* positions.

We first investigated the feasibility of the nucleophilic addition to starting material **A** (Step 1 in Scheme 1). We chose



Scheme 1 Ring-expansion rearrangement strategy for the synthesis of tetra-*ortho*-substituted biaryl naphthalenes.

cyclopropyl carbonyl compound **1** (Table 1) as a representative electrophile for our survey. As can be seen from Table 1, the isolated yields of the addition products **2** are relatively independent of the electronic nature (entries 1–5) as well as the steric demand (entry 1 *vs.* entry 8, and entries 5–7) of the nucleophiles. A consistent yield of ~70% yield was observed. Somewhat surprisingly, the highest isolated yield (81%) for the generation of **2** resulted from the addition of the largest nucleophile, 2,4,6-triisopropylphenyllithium (entry 7).

This nucleophilic addition reaction is highly diastereoselective. Only one single diastereomer was observed for each of the products **2** (as analyzed by ^{1}H NMR). We have structurally characterized the adduct between **2** and 2-methoxy-1-naphthyllithium, *i.e.*, **2c**, *via* single crystal X-ray crystallography. The relative stereochemistry of the structure is consistent with an approach of the nucleophile opposite the blocking silylcyclopropane group (see Table 1). Interestingly, compound **2c** adopts a conformation in the solid state where the carbinol proton H(1) engages in hydrogen bonding with the oxygen O(2) of the methoxynaphthalene (O(2)–H(1) = 1.83(2) Å, sum of van der Waals radii = 2.72 Å).[16]

Having established the synthesis of an array of rearrangement precursors **2**, we turned our attention to the catalytic ring-expansion rearrangement. We determined that the rearrangement of cyclopropyl carbinol **2a** in the presence of a catalytic amount of Lewis acid furnished the desired tetra-*ortho*-substituted biaryl **3a**, however as a 73 : 27 mixture with its undesired tri-*ortho*-substituted isomer **4a** (Table 2, entry 1).[11] We discovered that the choice of solvent has a dramatic influence on regioselectivity. When the reaction is performed in toluene instead of 1,2-dichloroethane, the ratio of **3a** to **4a** improves to 93 : 7 (Table 2, entry 2). Other solvents that we screened did not improve the yield and/or the regioselectivity significantly (Table 2, entries 3–8). Interestingly, a reversal of regioselectivity was observed when acetonitrile was used as the solvent (Table 2, entry 8). We also screened a number of Lewis acids (Table 2, entries 9–12) and found europium triflate (entry 2) to be the most efficient catalyst under our conditions.

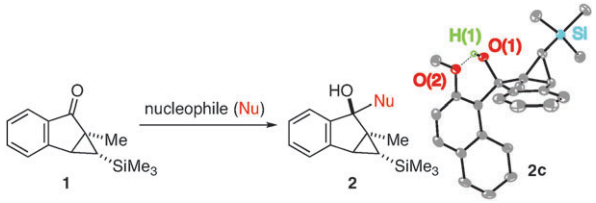
Department of Chemistry, University of Oregon, Eugene, Oregon 97403, USA. E-mail: lsy@uoregon.edu; Fax: +1 (541) 346-0487; Tel: +1 (541) 346-5573

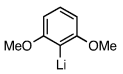
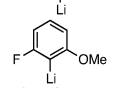
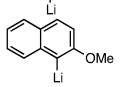
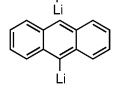
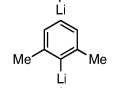
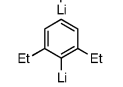
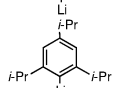
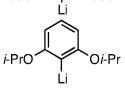
† This article is part of the 'Emerging Investigators' themed issue for ChemComm.

‡ Electronic supplementary information (ESI) available: Experimental procedures, compound characterization data. CCDC 778408 and CCDC 778409 contain the supplementary crystallographic data for complex **2c** and **7d**, respectively. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc02170a

§ Correspondence concerning X-ray crystallography should be directed to Lev Zakharov (E-mail: lev@uoregon.edu).

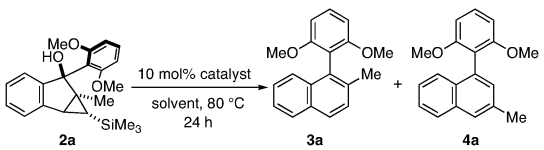
Table 1 Nucleophilic addition to **1**



Entry	Li–Nu	Product	Yield %[a]
1		**2a**	70
2		**2b**	71
3		**2c**	67
4		**2d**	70
5		**2e**	68
6		**2f**	67
7		**2g**	81
8		**2h**	68

[a] Isolated yield, average of two runs.

Table 2 Optimization survey for the regioselective synthesis of **3a**

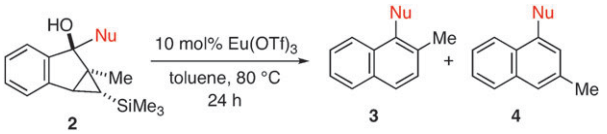


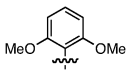
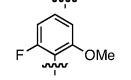
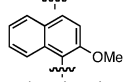
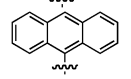
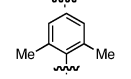
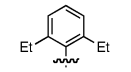
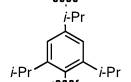
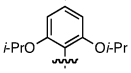
Entry	Catalyst	Solvent	Yield %[a]	**3a** : **4a**[b]
1	$Eu(OTf)_3$	1,2-Dichloroethane	68	73 : 27
2	**$Eu(OTf)_3$**	**Toluene**	**78**	**93 : 7**
3	$Eu(OTf)_3$	THF	54	92 : 8
4	$Eu(OTf)_3$	DMF	29	76 : 24
5	$Eu(OTf)_3$	*t*-BuOH	42	82 : 18
6	$Eu(OTf)_3$	PhCl	53	96 : 4
7	$Eu(OTf)_3$	1,3-Dichlorobenzene	52	93 : 7
8	$Eu(OTf)_3$	MeCN	15	25 : 75
9	$Sm(OTf)_3$	Toluene	76	85 : 15
10	$Er(OTf)_3$	Toluene	79	81 : 19
11	$SnCl_4$	Toluene	31	40 : 60
12	$BF_3{\cdot}Et_2O$	Toluene	29	35 : 65

[a] GC yield (**3a** + **4a**) *vs.* a calibrated internal standard, average of two runs. [b] Determined by GC.

With an optimized rearrangement protocol established, we subjected the various rearrangement precursors **2** from Table 1 to these conditions to test the scope of our method. We were pleased to see that a variety of substrates rearranged to furnish the desired biaryl naphthalenes in moderate to good yields (Table 3). With the exception of entry 1 (Nu = 2,6-dimethoxyphenyl),

Table 3 Rearrangement of **2** under optimized conditions



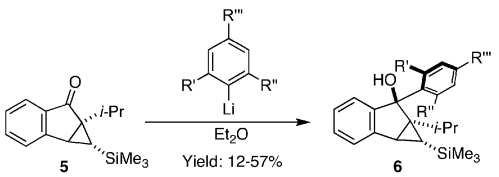
Entry	Precursor	Nu	Yield %[a]	**3** : **4**[b]
1	**2a**		71	93 : 7
2	**2b**		43	> 95 : 5
3	**2c**		63	> 95 : 5
4	**2d**		55	> 95 : 5
5	**2e**		79	> 95 : 5
6	**2f**		78	> 95 : 5
7	**2g**		86	> 95 : 5
8	**2h**		79	> 95 : 5

[a] Isolated yield, average of two runs. [b] Determined by ^{1}H NMR.

which gave a 93 : 7 mixture of regioisomers, all other substrates that we tested gave the tetra-*ortho*-substituted isomer exclusively. Noteworthy is the rearrangement of **2g**, which produced a tetra-*ortho*-substituted biaryl bearing two *ortho*-isopropyl groups in 86% yield.

Encouraged by these results, we sought to push the limits of steric demand around the biaryl axis by replacing the α-methyl group in **1** with an isopropyl group. The corresponding precursor **5** (Scheme 2) can be synthesized in a few steps from commercially available indanone.[17] Scheme 2 shows that a series of bis-*ortho*-substituted phenyllithium nucleophiles add to the carbonyl electrophile **5** in modest yield.

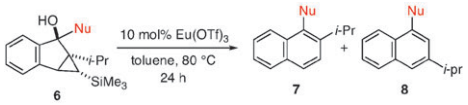
We were very pleased to observe that intermediates **6a–6d** underwent catalytic ring opening rearrangement under our optimized conditions to yield hindered tetra-*ortho*-substituted biaryl naphthalenes. As can be seen from Table 4, the isolated yields are independent of the steric demand around the biaryl axis. "Nucleophiles" (Nu in Table 4) containing methoxy, methyl, ethyl, and isopropyl groups in the 2,6-positions rearrange to produce the desired biaryl in reasonable yield (entries 1–4). We were also very pleased to see that the



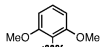
6a (R',R'' = OMe; R''' = H); **6b** (R',R'' = Me; R''' = H);
6c (R',R'' = Et; R''' = H); **6d** (R',R'',R''' = *i*-Pr)

Scheme 2 Nucleophilic addition to **5**.

Table 4 Rearrangement of **6** under optimized conditions

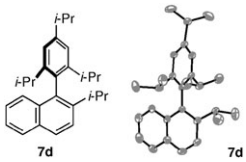


6 7 8

Entry	Precursor	Nu	Yield %[a]	7 : 8[b]
1	**6a**		63	> 95 : 5
2	**6b**		73	> 95 : 5
3	**6c**		73	> 95 : 5
4	**6d**		76	> 95 : 5

[a] Isolated yield, average of two runs. [b] Determined by ^{1}H NMR.

undesired regioisomer **8** is not observed under our reaction conditions. Noteworthy is the synthesis of **7d**, which is a tetra-*ortho*-substituted biaryl containing three *ortho*-isopropyl substituents. To the best of our knowledge, it is the most sterically encumbered biaryl naphthalene that has been synthesized to date. We have structurally characterized **7d** *via* single crystal X-ray diffraction, thus unambiguously establishing its identity.

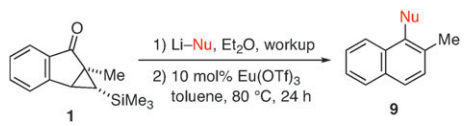


7d 7d

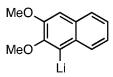
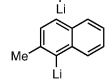
In order to improve the utility of our synthetic method, we attempted the rearrangement without isolating the cyclopropyl carbinol intermediate (Compound **B** in Scheme 1). When **1** was treated with organolithium reagents followed by catalytic ring expansion rearrangement, we observed the formation of the desired biaryl naphthalenes **9** in up to 65% yield over two steps (Table 5). The undesired tri-*ortho*-substituted biaryl was not observed under these conditions.

We have initiated preliminary studies toward an asymmetric version of this process. To this end, we successfully isolated optically pure **1** *via* semi-preparatory chiral HPLC. Treatment of optically pure **1** with 2-methoxynaphthyllithium and subsequent catalytic rearrangement with $Eu(OTf)_3$ furnished the desired tetra-*ortho*-substituted biaryl naphthalene **3c** in 54% isolated yield (over two steps) in 52% ee. Current efforts are geared toward optimizing the efficiency of this asymmetric process and developing a better understanding of its mechanism.

Table 5 Biaryl naphthalene synthesis without isolation of intermediates



1 9

Entry	Li–Nu	Product	Yield %[a]
1		**9a**	61
2		**9b**	65

[a] Isolated yield, average of two runs.

Support has been provided by the University of Oregon. This material is based upon work supported by the National Science Foundation under Grant No. DGE-0742540 (A.C.G.).

Notes and references

1 For examples, see: G. Bringmann and D. Menche, *Acc. Chem. Res.*, 2001, **34**, 615–624.
2 For recent examples, see: (*a*) K. Takaishi, M. Kawamoto and K. Tsubaki, *Org. Lett.*, 2010, **12**, 1832–1835; (*b*) Y. Ueno, S. Komatsuzaki, K. Takasu, S. Kawai, Y. Kitamura and Y. Kitade, *Eur. J. Org. Chem.*, 2009, 4763–4769.
3 For an overview of biaryl phosphine, BINAP, and BINOL ligands in catalysis applications, see: (*a*) D. S. Surry and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2008, **47**, 6338–6361; (*b*) M. Berthod, G. Mignani, G. Woodward and M. Lemaire, *Chem. Rev.*, 2005, **105**, 1801–1836; (*c*) J. M. Brunel, *Chem. Rev.*, 2005, **105**, 857–897.
4 For an overview, see: *Modern Arylation Methods*, ed. L. Ackermann, Wiley-VCH, Weinheim, Germany, 2009.
5 For an overview, see: (*a*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174–238; (*b*) G. P. McGlacken and L. M. Bateman, *Chem. Soc. Rev.*, 2009, **38**, 2447–2464.
6 For an overview, see: (*a*) M. C. Kozlowski, B. J. Morgan and E. C. Linton, *Chem. Soc. Rev.*, 2009, **38**, 3193–3207; (*b*) J. A. Ashenhurst, *Chem. Soc. Rev.*, 2010, **39**, 540–548.
7 For recent successful examples, see: (*a*) M. G. Organ, S. Calimsiz, M. Sayah, K. H. Hoi and A. J. Lough, *Angew. Chem., Int. Ed.*, 2009, **48**, 2383–2387; (*b*) L. Ackermann, H. K. Potukuchi, A. Althammer, R. Born and P. Mayer, *Org. Lett.*, 2010, **12**, 1004–1007.
8 For pioneering work in the synthesis of tetra-*ortho*-substituted biaryls *via* cross-coupling, see: (*a*) S. Miyano, S. Okada, T. Suzuki, S. Handa and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 2044–2046; (*b*) C. Dai and G. C. Fu, *J. Am. Chem. Soc.*, 2001, **123**, 2719–2724; (*c*) A. F. Littke, L. Schwarz and G. C. Fu, *J. Am. Chem. Soc.*, 2002, **124**, 6343–6348; (*d*) J. Yin, M. P. Rainka, X. X. Zhang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 1162–1163; (*e*) J. E. Milne and S. L. Buchwald, *J. Am. Chem. Soc.*, 2004, **126**, 13028–13032.
9 For leading references, see: (*a*) J. R. Perkins and R. G. Carter, *J. Am. Chem. Soc.*, 2008, **130**, 3290–3291; (*b*) M. Hapke, A. Gutnov, N. Weding, A. Spannenberg, C. Fischer, C. Benkhäuser-Schunk and B. Heller, *Eur. J. Org. Chem.*, 2010, 509–514.
10 For leading references, see: (*a*) K. Tanaka, *Chem.–Asian J.*, 2009, **4**, 508–518; (*b*) G. Nishida, K. Noguchi, M. Hirano and K. Tanaka, *Angew. Chem., Int. Ed.*, 2007, **46**, 3951–3954.
11 A. C. Glass, B. B. Morris, L. N. Zakharov and S.-Y. Liu, *Org. Lett.*, 2008, **10**, 4855–4857.
12 For a comprehensive review on the synthesis of substituted naphthalenes, see: C. B. de Koning, A. L. Rousseau and W. A. L. van Otterlo, *Tetrahedron*, 2003, **59**, 7–36.
13 For leading referencesof biaryl naphthalene synthesis using rearrangement-based methods, see: (*a*) Y. Nishii, T. Yoshida, H. Asano, K. Wakasugi, J. Morita, Y. Aso, E. Yoshida, J. Motoyoshiya, H. Aoyama and Y. Tanabe, *J. Org. Chem.*, 2005, **70**, 2667–2678; (*b*) G. S. Viswanathan, M. Wang and C.-J. Li, *Angew. Chem., Int. Ed.*, 2002, **41**, 2138–2141; (*c*) T. Shibata, Y. Ueno and K. Kanda, *Synlett*, 2006, 411–414; (*d*) T. Hamura, T. Suzuki, T. Matsumoto and K. Suzuki, *Angew. Chem., Int. Ed.*, 2006, **45**, 6294–6296; (*e*) Z. B. Zhu, Y. Wei and M. Shi, *Chem.–Eur. J.*, 2009, **15**, 7543–7548; (*f*) A. Padwa, U. Chiacchio, D. J. Fairfax, J. M. Kassir, A. Litrico, M. A. Semones and S. L. Xu, *J. Org. Chem.*, 1993, **58**, 6429–6437. To the best of our knowledge, there were no examples of tetra-*ortho*-substituted biaryl naphthalenes in these reports.
14 M. Hatano, T. Miyamoto and K. Ishihara, *Curr. Org. Chem.*, 2007, **11**, 127–157.
15 For example, the enthalpy of the addition of MeMgBr to di-*t*-butyl ketone has been determined to be −150 kJ mol^{-1}, see: T. Holm, *Acta Chem. Scand., Ser. B*, 1976, **30**, 985–990.
16 A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441–451.
17 See Supporting Information for details.

