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# Synthesis of Substituted Naphthalenes via a Catalytic Ring-Expansion Rearrangement

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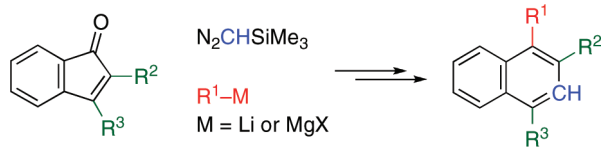
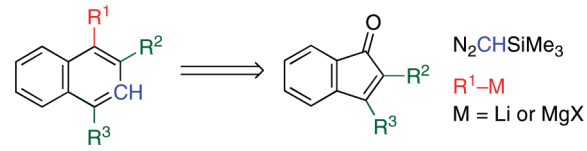
## ABSTRACT




**A new methodology for the preparation of substituted naphthalenes starting from readily available indenones, organometal reagents, and trimethylsilyldiazomethane via a catalytic rearrangement process is described. Hindered biaryl naphthalenes, including triortho-substituted biaryls, can be accessed through our method. Our results are consistent with a mechanism involving a benzobenzvalene intermediate.**

The naphthalene unit constitutes an important structural motif in biologically active molecules, in materials science, and in organic synthesis (e.g., in chiral ligands).[1] Correspondingly, substantial effort has been devoted to the development of synthetic methodologies for its construction. In addition to metal-mediated coupling-based strategies,[2,3] which furnish substituted naphthalene derivatives from an existing naphthalene core, a number of alternative approaches have been developed. These include cyclization/annulation-based syntheses (e.g., Diels−Alder cyclization,[1] Dötz reaction,[4] ring-closing metathesis,[5] annulations using alkynes,[6] intramolecular Lewis acid-catalyzed cyclizations)[1,7] and rearrangements of strained rings.[8] Despite significant advances made to date, novel methods for the synthesis of naphthalenes employing unprecedented synthons are still highly desirable. In this communication, we present a new methodology for the preparation of substituted naphthalenes starting from readily available indenones, organolithium/Grignard reagents, and trimethysilyldiazomethane via a catalytic rearrangement process (Scheme 1).

**Scheme 1.** Synthesis of Naphthalenes from Indenones




We have been engaged in developing synthetic methods that rearrange easily accessible precursors into valuable target structures. In particular, we sought to provide alternative routes toward naphthalene biaryls that might address some of the limitations of conventional cross-coupling technologies.[9]

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(1) For a comprehensive review, see: de Koning, C. B.; Rousseau, A. L.; van Otterlo, W. A. L. *Tetrahedron* **2003**, *59*, 7–36.

(2) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

(3) Li, X.; Hewgley, B.; Mulrroney, C. A.; Yang, J.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 5500–5511.

(4) Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187–198.

(5) (a) Huang, K.-S.; Wang, E.-C. *Tetrahedron Lett.* **2001**, *42*, 6155–6157. (b) van Otterlo, W. A. L.; Ngidi, E. L.; Coyanis, M.; de Koning, C. B. *Tetrahedron Lett.* **2003**, *44*, 311–313.

(6) (a) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 7342–7349. (b) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *Org. Lett.* **2003**, *5*, 4121–4123. (c) Viswanathan, G. S.; Wang, M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2138–2141. (d) Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7280–7286. (e) Pena, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Am. Chem. Soc.* **1999**, *121*, 5827–8.

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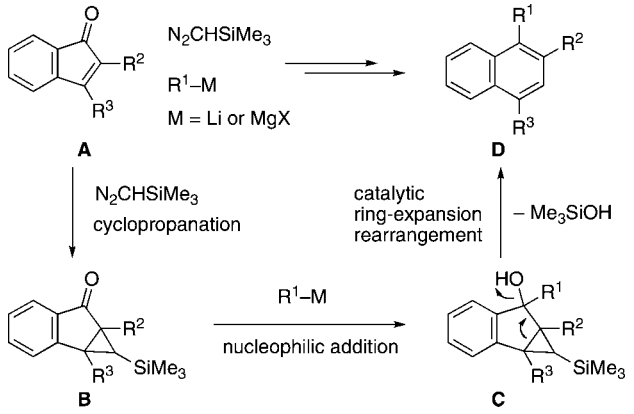
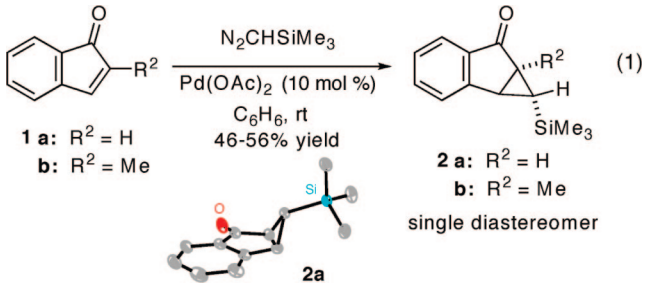
We envisioned that cyclopropyl carbinol[10] intermediate **C** (Scheme 2) could be poised to undergo a ring-expansion

**Scheme 2**



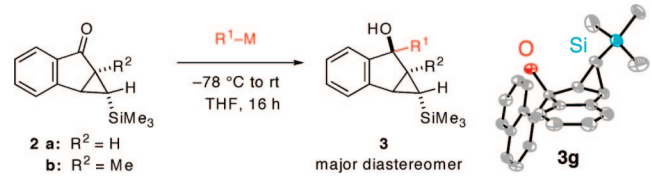

rearrangement to furnish naphthalenes **D** in a regioselective fashion. Intermediate **C** can be prepared from indenones **A** via a straightforward two-step process, i.e., cyclopropanation followed by nucleophilic addition. The salient feature of this methodology is that the pivotal C−C coupling between $R^1$ and the naphthalene core is accomplished through a simple addition of a nucleophile to a carbonyl.[11]




Treatment of indenones **1**[12] with commercially available trimethylsilyldiazomethane in the presence of a catalytic amount of $Pd(OAc)_2$ furnishes silylcyclopropanated adducts **2**.[13,14] The exo diastereomer has been isolated as the major product, the structure of which has been determined by single-crystal X-ray crystallography (eq 1).

Table 1 illustrates that addition of nucleophiles to ketones **2** can be readily accomplished with organolithiums (entry

**Table 1.** Nucleophilic Addition to **2**




| entry | $R^2$ | $R^1$–M | product | yield (%)[a] | dr[b] |
|---|---|---|---|---|---|
| 1 | H | Ph–Li | **3a** | 73 | >95:5 |
| 2 | H | 4-$MeO_2CC_6H_4$–MgX | **3b** | 50 | >95:5 |
| 3 | H | 4-$MeOC_6H_4$–MgBr | **3c** | 52 | >95:5 |
| 4 | H | 4-$ClC_6H_4$–MgBr | **3d** | 58 | >95:5 |
| 5 | H | 4-$FC_6H_4$–MgBr | **3e** | 56 | >95:5 |
| 6 | H | 2-$MeC_6H_4$–Li | **3f** | 67 | >95:5 |
| 7 | H | 1-napthyl–MgBr | **3g** | 62 | >95:5 |
| 8 | Me | Ph–Li | **3h** | 70 | 74:26 |
| 9 | Me | 2-$MeC_6H_4$–Li | **3i** | 81 | >95:5 |
| 10 | Me | 2-$MeOC_6H_4$–MgBr | **3j** | 44 | 76:24 |
| 11 | Me | 2,6-$(MeO)_2C_6H_3$–Li | **3k** | 53 | >95:5 |

[a] Isolated yield. [b] Determined by $^1H$ NMR.

1) as well as with functionalized Grignard reagents (entries 2−5). More hindered ortho-substituted nucleophiles also serve as suitable coupling partners (entries 6−7). Entries 8−11 of Table 1 show that the nucleophilic attack at the more sterically demanding electrophile **2b** is feasible as well, even with a 2,6-disubstituted aryl nucleophile (entry 11). With the exception of two examples (entries 8 and 10), only one diastereomer has been observed for the nucleophilic addition. We have structurally characterized the adduct between ketone **2a** and 1-naphthylmagnesium bromide, i.e., **3g**, via X-ray crystallography. The relative stereochemistry of the structure is consistent with an approach of the nucleophile opposite the blocking silylcyclopropane group.

We chose to optimize the synthesis of naphthalenes via the proposed ring expansion rearrangement using substrate **3a**. A survey of Lewis acids and solvents reveals that the optimal reaction conditions involve 10 mol % of $Eu(OTf)_3$ in 1,2-dichloroethane as solvent (see Supporting Information for details). The presence of the silicon group is crucial. A control experiment performed with a substrate bearing H in place of $SiMe_3$ under the optimized reaction conditions produced very little of the desired naphthalene product.

Cyclopropyl carbinols **3** from Table 1 were subjected to the optimized reaction conditions. Table 2 shows that our catalytic ring-expansion rearrangement is compatible with

(7) Shibata, T.; Ueno, Y.; Kanda, K. *Synlett* **2006**, 411–414.

(8) For leading references, see: (a) Shao, L.-X.; Zhang, Y.-P.; Qi, M.-H.; Shi, M. *Org. Lett.* **2007**, *9*, 117–120. (b) Hamura, T.; Suzuki, T.; Matsumoto, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 6294–6296. (c) Nishii, Y.; Yoshida, T.; Asano, H.; Wakasugi, K.; Morita, J.-i.; Aso, Y.; Yoshida, E.; Motoyashiya, J.; Aoyama, H.; Tanabe, Y. *J. Org. Chem.* **2005**, *70*, 2667–2678.

(9) For examples of biaryl synthesis that do not involve cross-couplings, see: (a) Perkins, J. R.; Carter, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 3290–3291. (b) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3951–3954. (c) Kotnis, A. S.; Zhu, K.; Lotz, B. L.; Natalie, K. J.; Simpson, J. H.; Kacusr, D.; Thurston, D.; Prasad, J. S.; Mathew, S.; Singh, A. K. *Chem. Ind.* **2005**, *104*, 217–226.

(10) For a review of cyclopropanes in organic synthesis, see: Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C. *Chem. Rev.* **1989**, *89*, 165–198.

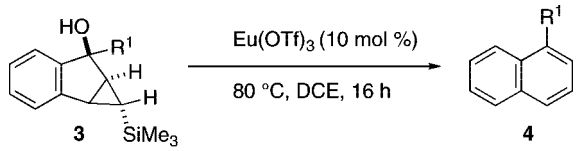
(11) Hatano, M.; Miyamoto, T.; Ishihara, K. *Curr. Org. Chem.* **2007**, *11*, 127–157.

(12) Indenones **1** were prepared from the corresponding bromoindanones. See Supporting Information for details.

(13) Aoyama, T.; Iwamoto, Y.; Nishigaki, S.; Shioiri, T. *Chem. Pharm. Bull.* **1989**, *37*, 253–256.

(14) For a review of silylcyclopropanes, see: Paquette, L. *Chem. Rev.* **1986**, *86*, 733–750.

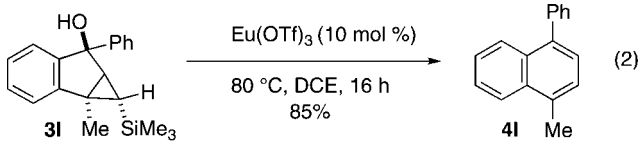
**Table 2.** Catalytic Ring Expansion Rearrangement of **3**




| entry | $R^1$ | product | yield (%)[a] |
|---|---|---|---|
| 1 | Ph | **4a** | 84 |
| 2 | 4-$MeO_2CC_6H_4$ | **4b** | 42 |
| 3 | 4-$MeOC_6H_4$ | **4c** | 46 |
| 4 | 4-$ClC_6H_4$ | **4d** | 56 |
| 5 | 4-$FC_6H_4$ | **4e** | 58 |
| 6 | 2-$MeC_6H_4$ | **4f** | 62 |
| 7 | 1-naphthyl | **4g** | 67 |

[a] Isolated yield.

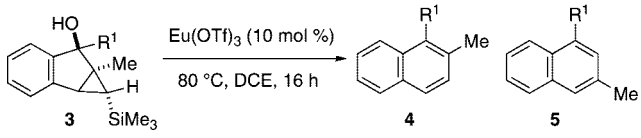
functionalized (entries 2−5) and hindered (entries 6 and 7) $R^1$ groups. We have also prepared a disubstituted naphthalene **4l** in a regioselective fashion from the corresponding precursor **3l** derived from a $\beta$-substituted indenone (eq 2).




(2)

Interestingly, we discovered that precursors **3h**−**3k**, which are derived from an α-substituted indenone, produce a mixture of naphthalene products **4** and **5** under our optimized conditions (Table 3). The desired 1,2-disubstituted regioisomer **4** is formed in high selectivity for substrates **3h** and **3i**, furnishing di- and triortho-substituted biaryl naphthalenes **4** in good yield (entries 1 and 2). A diminished regioselectivity is observed for substrate **3j**, which contains the *o*-methoxyphenyl substituent (entry 3). Noteworthy is the preparation of a tetraortho-substituted biaryl **4k** from precursor **3k**, although the regioselectivity of the rearrangement is only moderate (entry 4). We have determined the structure of the rearrangement byproduct **5k** via X-ray crystallography, thus unambiguously establishing the connectivity of the 1,3-disubstituted naphthalene regioisomer **5**.[15]

**Table 3.** Catalytic Ring Expansion of Hindered Precursors

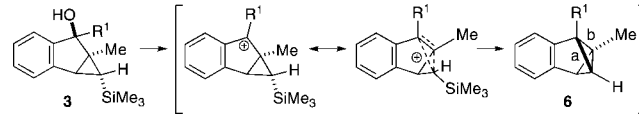



| entry | $R^1$ | product | yield (%)[a] | **4:5**[b] |
|---|---|---|---|---|
| 1 | Ph | **h** | 70 | 93:7 |
| 2 | 2-$MeC_6H_4$ | **i** | 70 | 93:7 |
| 3 | 2-$MeOC_6H_4$ | **j** | 85 | 83:17 |
| 4 | 2,6-$(MeO)_2C_6H_3$ | **k** | 77 | 64:36 |

[a] Isolated yield of a mixture of **4** and **5**. [b] Determined by $^1H$ NMR.

The presence of isomer **5** may provide some insight into the possible mechanism of the rearrangement process. The current mechanistic hypothesis for its formation involves a benzobenzvalene intermediate **6** (Scheme 3).[16] Breaking bond a in **6** produces the 1,2-disubstituted naphthalene **4**, whereas breaking bond b yields the 1,3-disubstituted isomer **5**.

**Scheme 3.** Possible Intermediate for the Rearrangement




In summary, we have developed a new method for the synthesis of substituted naphthalenes based on a catalytic ring-expansion rearrangement process. Starting from readily available indenones, biaryl naphthalenes, including hindered triortho-substituted ones, can be accessed in a few steps. Our method provides an alternative to cross-coupling procedures for the synthesis of biaryl naphthalenes, and it distinguishes itself from coupling protocols by achieving the crucial C−C bond-forming step through a simple nucleophilic addition to a carbonyl. Our experimental observations are consistent with a rearrangement mechanism involving a benzvalene-like intermediate. Current efforts are geared toward obtaining a better understanding of the reaction mechanism and improving the substrate scope and reaction efficiency.

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**Supporting Information Available:** Experimental procedures, compound characterization data, and CIF files for structures **2a** and **3g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) See Supporting Information for details.

(16) (a) Christl, M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 529–546. (b) Katz, T. J.; Roth, R. J.; Acton, N.; Carnahan, E. J. *J. Org. Chem.* **1999**, *64*, 7663–7664.