Advanced Synthesis & Catalysis

Accepted Article

Title: Synthesis of Unsymmetrical Bisindolylmethanes by Reaction of Indolylmagnesium Bromides with Sulfonyl Indoles

Authors: Marino Petrini, Alessandro Palmieri, and Lixia Yuan

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201901357

Link to VoR: http://dx.doi.org/10.1002/adsc.201901357

10.1002/adsc.201901357

FULL PAPER

DOI: 10.1002/adsc.200((will be filled in by the editorial staff))

Synthesis of Unsymmetrical Bisindolylmethanes by Reaction of Indolylmagnesium Bromides with Sulfonyl Indoles.

Lixia Yuan,[a,b] Alessandro Palmieri,[a,*] and Marino Petrini [a,*]

[a] School of Science and Technology, Chemistry Division, University of Camerino, Via S. Agostino 1, 62032 Camerino, Italy. E-mail: alessandro.palmieri@unicam.it; marino.petrini@unicam.it.

[b] School of Chemistry and Chemical Engineering, Liaocheng University, Hunan Road, Liaocheng 252000, P. R. China.

Received: ((will be filled in by the editorial staff))

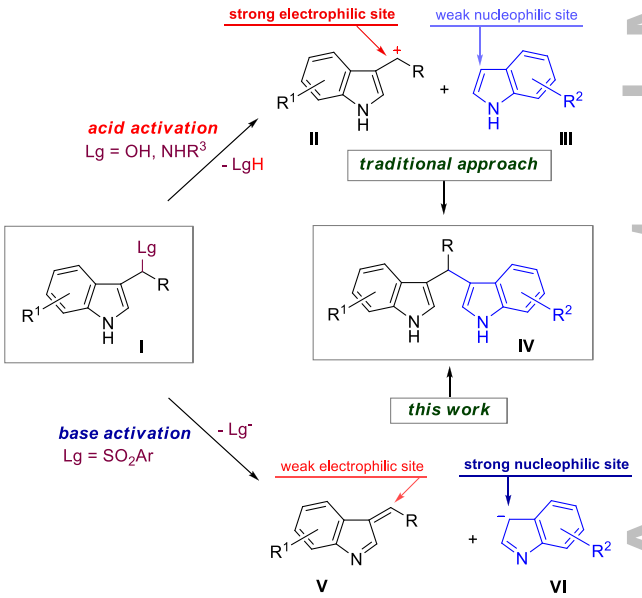
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200######.

Abstract. Sulfonyl indoles are widely recognized as alkylideneindolenine precursors amenable to provide functionalized indole derivatives upon reaction with nucleophiles. In this paper reaction of sulfonyl indoles with indolylmagnesium bromides is used to access unsymmetrical bisindolylmethanes. The target compounds are obtained in satisfactory yields starting from a wide range of substrate/reagent combinations. The utilization of pyrrolylmagnesium bromides for the same reaction also affords the expected adducts albeit in moderate yield.

Keywords: bisindolylmethanes; Grignard reagents; indolenines; indolyl anions; nucleophilic additions.

Introduction

Bisindolylmethanes are indole derivatives featured by two indole units connected through a simple or a substituted methylene bridge, widely known for their enhanced pharmacological profile.[1] Considering the reactive positions at the azole ring of indoles, it can be observed that 3,3'-bisindolylmethanes are the most commonly found derivatives although a number of regioisomeric 3,2'-bisindolylmethanes are also known for their biological activity. A further distinction can be made according to the nature of the indole frameworks embedded in these derivatives. Symmetrical bisindolylmethanes which contain a couple of identical units, can be easily obtained by an acid catalyzed reaction of a carbonyl derivative with an excess of the indole reactant.[2] Conversely, synthetic approaches to unsymmetrical bisindolylmethanes require more challenging operations involving coupling of different indole units with opposite electronic character.[3] In most of the existing procedures, a suitable indole substrate **I** bearing a good leaving group at benzylic position is activated under acidic conditions in order to generate a stabilized carbocation **II**.[4] Carbocation **II** is a strong electrophilic species able to react with weak nucleophiles represented by a neutral indole reagent **III** leading to the unsymmetrical bisindolylmethane **IV** (Scheme 1).[5] This process can be considered in every way as a Friedel–Crafts reaction and therefore can be catalyzed/promoted either by Lewis or Brønsted acids.[6]



Scheme 1. Synthetic approaches to unsymmetrical bisindolylmethanes.

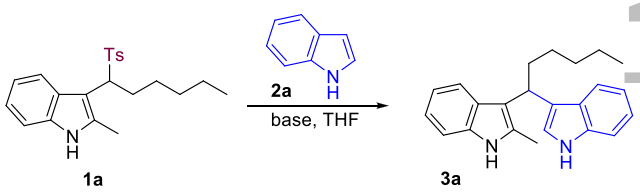
Our approach has been designed accounting for a reversal of the electronic strength of the reactants, envisaging the reaction of a weakly electrophilic alkylideneindolenine **V** obtained from a base

promoted elimination from substituted indole **I**, with a rather strong, although stabilized, nucleophilic indole reagent **VI**. In this context, the alkylideneindolenine intermediate acts as a vinylogous imine while the nucleophilic indole can be considered a stabilized azaenolate anion involved in a Michael-type process.[7] The nature of the leaving group Lg in substrate **I** plays a fundamental role in driving the formation of intermediates **II** and **V**. 3-Indolylmethanols (**I**, Lg = OH) can be activated only under acidic conditions and therefore can mainly be used for the generation of carbocationic systems **II**.[8] Gramines (**I**, Lg = NR_2) can eliminate dialkylamines under basic conditions but this operation usually require high temperatures or special activating procedures.[7b,9] Conversion of gramines into the corresponding ammonium salts (**I**, Lg = NR_3I) allows a ready elimination of a tertiary amine resulting in an efficient addition of several azole derivatives.[10] 3-(1-Arylsulfonylalkyl) indoles (sulfonyl indoles **I**, Lg = SO_2Ar) have been discovered by us more than a decade ago and since then have emerged as reliable precursors of both cationic intermediates **III** and alkylideneindolenines **V**.[11] Sulfonyl indoles can be readily prepared by an acid catalyzed three component coupling of aldehydes, indoles and arylsulfinic acids and this reaction has been previously used for the synthesis of unsymmetrical arylsulfonyl bisindolylmethanes starting from indole-3-carboxaldehydes.[12] The relatively high acidity level of the indole N-H bond (pKa = 16.2), makes the corresponding deprotonation quite easy to carry out using commonly available bases.[13] Thus, conversion of indoles into the corresponding anion **VI** could in principle be made using various basic systems including metal hydrides, organolithiums or Grignard reagents. The strongly ionic *N*-metal bond provided by alkali metal cations usually favors the reaction with electrophiles at the nitrogen atom. This process is largely used in several reactions aimed at the *N*-protection of indoles.[14] Conversely, an enhancement of the nucleophilic character of the indole ring in order to obtain C-3 substituted derivatives could be reached using less electropositive metals able to establish a more covalent bond with the nitrogen atom. As a matter of fact, the few available examples of indole 3-functionalizations refer to deprotonation reactions using Grignard reagents. The obtained 1-indolylmagnesium halides have been used in conjugate addition reaction to nitroalkenes,[15] ring opening of epoxides,[16] and acylation reactions.[17] In this paper we report a simple and effective synthesis of unsymmetrical bisindolylmethanes by reaction of 3-(1-arylsulfonylalkyl) indoles with 1-indolylmagnesium bromides under mild reaction conditions.

Results and discussion

The peculiar reactivity of alkylideneindolenines **V** which have never been involved in the reaction with metalated aromatic and heteroaromatic compounds prompted us to evaluate different basic systems in order to further evidence the reactivity trend already observed with other electrophiles. The results for the reaction of sulfonyl indole **1a** with indole **2a** confirm that the utilization of common basic systems having alkali metal countercations do not give significant results in this reaction (Table 1, entries 1,2).[18] Conversely, generation of indolylmagnesium bromide, by reaction of MeMgBr with **2a** at low temperature affords bisindolylmethane **3a** in satisfactory yield (Table 1, entry 3). Increasing the temperature of the reaction to 0 °C provides a significant raise in the efficiency of the process which can be carried out even at room temperature without any reduction in the chemical yield (Table 1, entries 4,5). For a correct development of this strategy, two equivalents of the indole nucleophile are required being the first one employed to generate the alkylideneindolenine **V**. As a matter of fact, a trial using 1.5 equivalents of indolylmagnesium bromide resulted in the formation of the target compound **3a** in reduced yield (Table 1, entry 6). Finally, transmetalation of the initially formed indolylmagnesium bromide using anhydrous zinc chloride was made in order to test the behavior of the corresponding indolyl nucleophile.[19] The resulting indolylzinc bromide was effective in the reaction with **1a** although the obtained yield of bisindolylmethane **3a** was comparable with that recorded for the use of methylmagnesium bromide (Table 1, entry 7).

Table 1. Optimization of the reaction conditions.[a]



Ts = SO_2p-Tolyl

Entry	Base	T ° C	Yield[b] (%)
1	NaH	20	5
2	*n*-BuLi	0	23
3	MeMgBr	-20	60
4	MeMgBr	0	75
5	MeMgBr	20	76
6[c]	MeMgBr	20	41
7[d]	MeMgBr, $ZnCl_2$	20	77

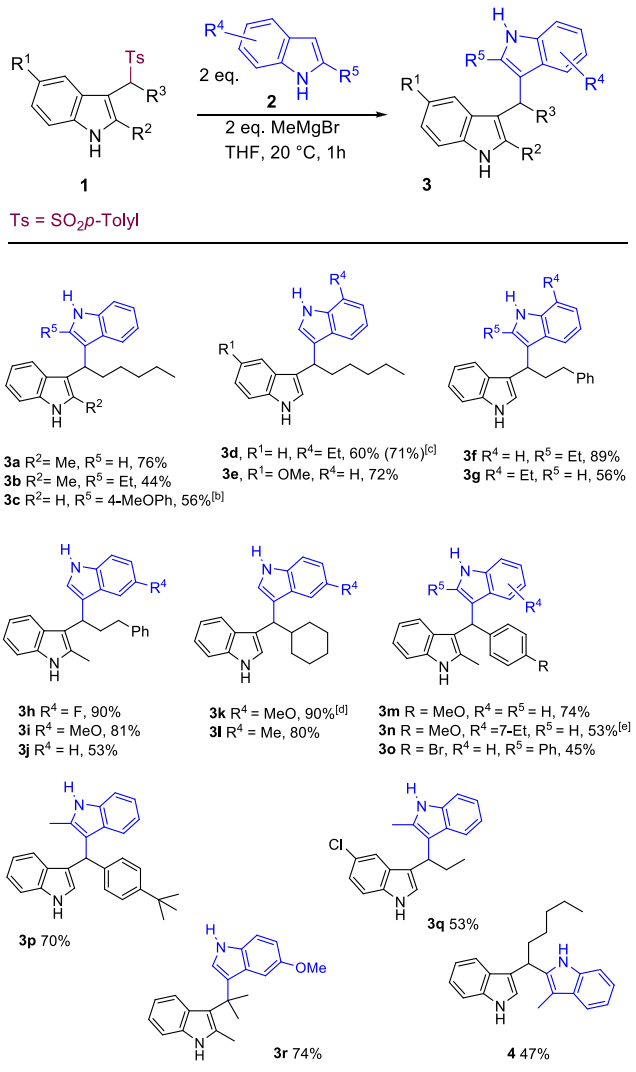
[a] Conditions: indole **2a** (0.6 mmol), base (0.6 mmol) then after 30 min sulfonyl indole **1a** (0.3 mmol), THF (2.0 mL), 1h. [b] Isolated yield after chromatography on silica gel. [c] 1.5 eq. of **1a** and 1.5 eq of MeMgBr were used. [d] 2 eq of dry $ZnCl_2$ were added after deprotonation of **2a** with 2 eq. of MeMgBr.

A notable improvement in the addition of Grignard reagents to aldimines has been observed using a catalytic amount of zinc(II) chloride.[20] However a trial using 10 mol% of this zinc salt led only to a slight improvement of the yield comparable to that

10.1002/adsc.201901357

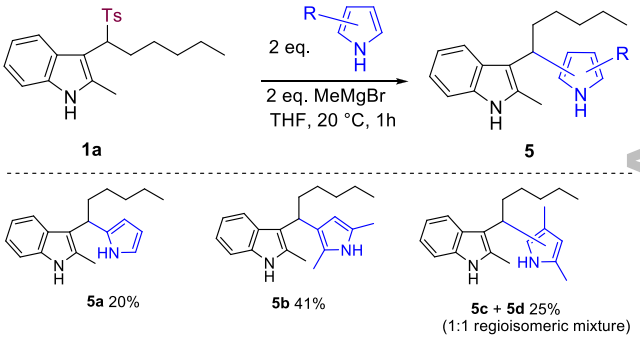
obtained with indolylmagnesium bromide. Considering that Lewis acids are known to promote the elimination of arylsulfinyl group from sulfonyl indoles, a direct assistance of magnesium salts in the generation of the alkylideneindolenine intemediate **V** could be envisaged.[21]

Table 2. Scope of the reaction between sulfonyl indoles **1** and indoles **2**.[a]



[a] Reaction conditions: Indole **2** (2 mmol), MeMgBr (2 mmol) at rt, after 30 min sulfonyl indole **1** (1 mmol). [b] Purified by crystallization (EtOAc/hexane). [c] Yield in parenthesis refers to the reaction of indole with 7-ethyl-3-(1-tosylhexyl)-1H-indole. [d] Reaction time 1.5 h. [e] Reaction time 3.5 h.

The optimized reaction conditions have been applied to a series of sulfonyl indoles **1** and indoles **2** leading to the results displayed in Table 2. Sulfonyl indoles **1** bearing aliphatic or aromatic side chains usually give satisfactory results with a wide range of indolylmagnesium bromide reagents **2**. The utilization of 2-substituted indoles **2** is also effective as evidenced in the formation of products **3f** and **3p**. However, when 2-methyl substituted sulfonyl indoles **1** are employed as substrates the utilization of 2-substituted indoles **2** may become troublesome. The effect of different substituents in the benzene portion of the indole reactants **2** is generally positive regardless the electronic aptitude of the corresponding group. The only notable exception is represented by the utilization of 5-chloro-3-(1-tosylethyl)-1*H*-indole which in the reaction with 2-methylindole affords compound **3q** in moderate yield (40%). Finally, this procedure has also been tested with 2-methyl-3-(2-tosylpropan-2-yl)-1*H*-indole having the sulfonyl moiety linked to a tertiary cabon atom. The reaction with 5-methoxyindolylmagnesium bromide gives compound **3r** in good yield (74%) evidencing a notable versatility of this procedure. The reactivity of 3-substituted indoles in this process has been evaluated using 3-methylindolylmagnesium bromide as reactant. Interestingly, the nucleophilicity of the reagent is high enough to provide the corresponding 3,2'-bisindolylmethane derivative **4** although in moderate yield (47%). The optimized procedure has been tested for the reaction of other azole derivatives such as indazole and 6-azaindole but unclean reaction mixtures have been observed with these heterocyclic reagents. In order to explore de boundaries of this synthetic approach we also applied this method to the reaction of *N*-metalated pyrroles with sulfonyl indoles. In principle, the same behavior would be expected for this reaction, considering that C-alkylation of pyrroles is known to proceed *via* the corresponding pyrrylmagnesium halide reagents.[22] In an unoptimized process, pyrrole and a couple of bismethylated pyrrole derivatives have been tested in this reaction giving only modest results in the formation of the corresponding adducts **5** (Scheme 2). Thus the prominent reactivity of pyrrole at 2 position is confirmed for the synthesis of derivative 5a while 2,5-dimethylpyrrole gives compound 5b since the two equivalent 3 and 4 positions are the only available for the addition. As expected, an equimolar mixture of regioisomers 5c,d are obtained using 2,4-dimethylpyrrole as reagent. In this case both the free positions in the pyrrole ring are activated by the electron-donating effect of the methyl groups.



Scheme 2. Reaction of pyrrolylmagnesium bromides with sulfonyl indoles.

Conclusion

The new synthetic approach to unsymmetrical bisindolylmethanes devised in this paper entails the reaction of sulfonyl indoles with an excess of indolylmagnesium bromides. The metalated indole reactant initially acts as a basic system providing the elimination of the arylsulfinate anion with formation of an alkylideneindolenine. This intermediate actually behaves as a vinylogous imino derivative capable of reacting with excess of the indolylmagnesium bromide with complete 1,4 regioselectivity. The resulting bisindolylmethane compounds are obtained under mild reaction conditions and in moderate to good yields. A similar unoptimized process using pyrrolylmagnesium bromides has been attempted but the yield of the obtained adducts is rather modest.

Experimental Section

General Procedure for the Preparation of Bisindolylmethanes 3.

To a stirred solution of indole **2** (2 mmol) in THF (15 mL), CH_3MgBr (0.67 mL, 3M solution in diethyl ether, 2 mmol) was added dropwise under nitrogen at 20 °C. After stirring for 30 minutes at 20 °C, the sulfonyl indole **1** dissolved in THF (10 mL) was added dropwise. The resulting reaction mixture was stirred for 1 h and then treated with a saturated aqueous solution of NH_4Cl (6 mL) and the aqueous layer extracted with CH_2Cl_2 (3 × 15 mL). The crude product **3** obtained after filtration and removal of the solvent at reduced pressure, was purified by column chromatography (hexane/ethyl acetate, 8:2).

Acknowledgements

We acknowledge financial support from University of Camerino (FAR program).

References

[1] a) M. Shiri, M. A. Zolfigol, H. G. Kruger, Z. Tanbakouchian, *Chem. Rev.* **2010**, *110*, 2250–229; b) S. Imrana, M. Tahaa, N. H. Ismail, *Curr. Med. Chem.* **2015**, *22*, 4412–443; c) L. Gupta, A. Talwar, P. M. S. Chauhan, *Curr. Med. Chem.* **2007**, *14*, 1789–1803.

[2] For some very recent examples see: a) S. Guo, Z. Fang, B. Zhou, J. Hua, Z. Dai, Z. Yang, C. Liu, W. He, K. Guo, *Org. Chem. Front.* **2019**, *6*, 627–631; b) F. Ling, L. Xiao, L. Fang, C. Feng, Z. Xie, Y. Lv, W. Zhong, *Org. Biomol. Chem.* **2018**, *16*, 9274–9278; c) N. Saehlim,† T. Kasemsuk, U. Sirion, R. Saeeng, *J. Org. Chem.* **2018**, *83*, 13233–13242; d) C. Qiao, X.-F. Liu, H.-C. Fu, H.-P. Yang, Z.-B. Zhang, L.-N. He, *Chem. Asian J.* **2018**, *13*, 2664–2670.

[3] Review: a) A. Palmieri, M. Petrini, *Synthesis* **2019**, *51*, 829–841. For other very recent papers see: b) T. Pillaiyar, M. Uzair, S. Ullah, G. Schnakenburg, C. E. Müller, *Adv. Synth. Catal.* **2019**, *361*, 4286–4293; c) X.-K. Guan, H. Zhang, J.-G. Gao, D.-Y. Sun, X.-S. Qin, G.-F. Jiang, G.-L. Zhang, S. Zhang, *J. Org. Chem.* **2019**, *84*, 12562–1257; d) Y. Kim, J. Lee, J. Jung, S.-G. Kim, *Tetrahedron Lett.* **2019**, *60*, 1625–163; e) R. Ali, M. Z. Ahamad, S. Singh, W. Haq, *Eur. J. Org. Chem.* **2019**, 1820–1824; f) P. Kamboj, S. Dutt, S. Chakroborty, V. Tyagi, *Tetrahedron Lett.* **2019**, *60*, 15116.

[4] a) E. Follet, P. Mayer, H. Mayr, *Eur. J. Org. Chem.* **2016**, 4050–4058; b) E. Follet, G. Berionni, P. Mayer, H. Mayr, *J. Org. Chem.* **2015**, *80*, 8643–8656.

[5] Other procedures involve the coupling of 3-indolecarboxyaldehydes with indoles: a) Y. Zhang, S.-X. Zhang, L.-N. Fu, Q.-X. Guo, *ChemCatChem* **2017**, *9*, 3107–3110; b) B. S. Chinta, B. Baire, *Tetrahedron Lett.* **2016**, *57*, 5381–5384; c) T. P. Pathak, J. G. Osiak, R. M. Vaden, B. E. Welm, M. S. Sigman, *Tetrahedron* **2012**, *68*, 5203–5208; d) M. Barbero, S. Cadamuro, F. Cauda, S. Dughera, G. Gervasio, P. Venturello, *J. Org. Chem.* **2012**, *77*, 4278–4287.

[6] a) I. P. Beletskaya, A. D. Averin, *Curr. Organocatal.* **2016, *3***, 60–83; b) R. Dalpozzo, *Chem. Soc. Rev.* **2015**, *4*, 742–778; c) M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644.

[7] a) L. Wang, Y. Chen, J. Xiao, *Asian J. Org. Chem.* **2014**, *3*, 1036–1052; b) A. Palmieri, M. Petrini, R. R. Shaikh, *Org. Biomol. Chem.* **2010**, *8*, 1259–1270.

[8] Synopsis: a) G.-J. Mei, F. Shi, *J. Org. Chem.* **2017**, *82*,7695–7707. For very recent papers on the synthesis of unsymmetrical bisindolylmethanes using indolylmethanols not included in ref. 3 see: b) Y. Ling, D. An, Y. Zhou, W. Rao, *Org. Lett.* **2019**, *21*, 3396–3401; c) A. Muthukumar, G. N. Rao, G. Sekar, *Org. Biomol. Chem.* **2019**, *17*, 3921–3933.

[9]a) B. B. Semenov, V. G. Granik, *Pharm. Chem. J.* **2004**, *38*, 287–310. For a very recent paper on activation of gramines see: b) H. Fujita, R. Nishikawa, O. Sasamoto, M. Kitamura, M. Kunishima, *J. Org. Chem.* **2019**, *84*, 8380–8391.

[10] T. Pillaiyar, E. Gorska, G. Schnakenburg, C. E. Müller, *J. Org. Chem.* **2018**, *83*, 9902–9913.

[11] Personal account: A. Palmieri, M. Petrini, *Chem. Rec.* **2016**, *16*, 1353–1379.

[12] S. Lancianesi, A. Palmieri, M. Petrini, *Adv. Synth. Catal.* **2012**, *354*, 3539–3544.

[13] J. A. Joule, K. Mills, *Heterocyclic Chemistry*, 5th Ed. Wiley, New York, **2010**.

[14] P. G. M. Wuts, *Greene's Protective Groups in Organic Synthesis*, 5th Ed., Wiley, New York, **2014**, p.1120.

[15] a) W. E. Noland, G. M. Christensen, G. L. Sauer, G. G. S. Dutton, *J. Am. Chem. Soc.* **1955**, *77*, 456–457; b) S. Mahboobi, W. Wiegrebe, A. J. Popp, *Nat. Prod.* **1999**, *62*, 577–579; c) R. S. Kusurkar, N. A. H. Alkobati, A. S. Gokule, P. M. Chaudhari, P. B. Waghchaure, *Synth. Commun.* **2006**, *36*, 1075–1081. Reaction of indoles with nitroalkenes is commonly

10.1002/adsc.201901357

catalyzed/promoted by Lewis acids exploiting a Friedel–Crafts process; for a recent report see: (c) S. Lancianesi, A. Palmieri, M. Petrini, *Chem. Rev.* **2014**, *114*, 7108–7149.

[16] A. Hasuoka, Y. Nakayama, M. Adachi, H. Kamiguchi, K. Kamiyama, *Chem. Pharm. Bull.* **2001**, *49*, 1604–1608.

[17] (a) Y. Deng, Q. Xie, M. G. LaPorte, A. T. A. Chasnoff, M. A. Mortensen, D. Patra, S. A. Putrelo, R. S. Antonovich, H. Cao, J. Yan, A. J. Cooper, S. R. Rippin, M. D. Alexander, P. T. Kumar, M. S. Hendi, Y.-H. Lee, T. Haimowitz, S. M. Condon, *Org. Process Res. Dev.* **2016**, *20*, 242–252; (b) A. C. Lindsay, J. Sperry, *Tetrahedron* **2017**, *73*, 4355–4362.

[18] a) S. Numomoto, Y. Kawakami, Y. Yamashita, H. Takeuci, S. Eguchi, *J. Chem. Soc. Perkin Trans. 1*, **1990**, 111-114; b) M. G. Reinecke, J. F. Sebastian, H. W. Johnson Jr., C. Pyun, *J. Org. Chem.* **1972**, *37*, 3066–3068. The poor yield recorded using the indole sodium salt is in sharp contrast with the good results obtained in the addition of sodium nitronates to sulfonyl indoles: c) A. Palmieri, M. Petrini, E. Torregiani, *Tetrahedron Lett.* **2007**, *48*, 5653–5656.

[19] J. Bergman, L. Venemalm, *Tetrahedron* **1990**, *46*, 6061–6066.

[20] M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc.* **2006**, *128*, 9998–9999.

[21] a) L. Marsili, A. Palmieri, M. Petrini, *Org. Biomol. Chem.* **2010**, *8*, 706–712. In related derivatives such as α-amido sulfones, Lewis acids, even under catalytic conditions, are able to promote the elimination of the arylsulfonyl group leading to the corresponding *N*-acylimine. For a review article see: b) E. Marcantoni, A. Palmieri, M. Petrini *Org. Chem. Front.* **2019**, *6*, 2142–2182.

[22] a) W. R. Scaggs, T. D. Scaggs, T. N. Snaddon, *Org. Biomol. Chem.* **2019**, *17*, 1787–1790; b) G. C. Schloemer, R. Greenhouse, J. M. Muchowski, *J. Org. Chem.* **1994**, *59*, 5230–5234.

10.1002/adsc.201901357

FULL PAPER

Synthesis of Unsymmetrical Bisindolylmethanes by Reaction of Indolylmagnesium Bromides with Sulfonyl Indoles.

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Lixia Yuan, Alessandro Palmieri,* and Marino Petrini*