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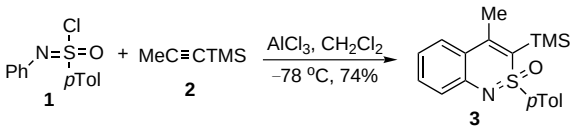
A One-Pot, One-Operation [3+3] Annulation Approach to Benzothiazines**

Michael Harmata* and Neville Pavri

Some time ago we introduced the Lewis acid mediated reaction of *N*-aryl sulfonimidoyl chlorides with alkynes as a means of accessing 2,1-benzothiazines.[1] For example, the reaction of **1** (pTol = p-$H_3CC_6H_4$) with 1-trimethylsilyl-1-propyne (**2**, TMS = Me_3Si) in the presence of $AlCl_3$ afforded benzothiazine **3** regioselectively and in good yield [Eq. (1)].



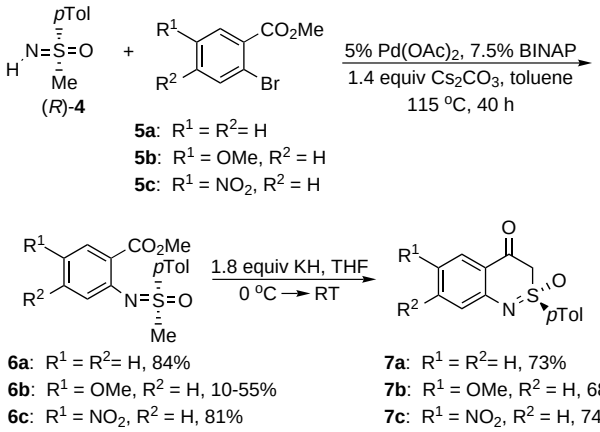
(1)

The reaction proceeded in a Markownikoff fashion and generally afforded good yields of adducts with a variety of alkynes. We extended this reaction to alkenes with equal success[2] and have subsequently demonstrated that the heterocycles produced by either sequence are useful in the preparation of other compounds, including 2-allyl-, 2-alkyl-, and 2-alkenylanilines.[3]

Although benzothiazines such as **3** are chiral the stereochemical lability of sulfonimidoyl chlorides[4] suggested that it would be difficult to prepare enantiomerically pure benzothiazines with the reaction we had introduced, thus limiting the possiblities of exploiting such compounds in asymmetric synthesis as chiral templates, for example.

Advances in the amination of aryl halides, however, indicated that a solution to this problem might be found.[5] In particular, Bolm and Hildebrand reported[6] that NH sulfoximines could be coupled to aryl halides, which suggested to us that it would be possible to devise a one-pot, one-operation synthesis of enantiomerically pure benzothiazines using enantiomerically pure sulfoximines and appropriately substituted aryl halides such as *ortho*-bromobenzaldehydes or benzoate esters.

Our initial studies were conducted with a small number of *ortho*-bromobenzoate esters. The results are summarized in Scheme 1. Formation of a nitrogen – carbon bond was at-



Scheme 1. Two-pot procedure for benzothiazine synthesis. BINAP = 1,1′-binaphthalene-2,2′-diylbis(diphenylphophane).

tempted using (*R*)-**4**[7] and the bromoarene in the presence of 5 mol% of $Pd(OAc)_2$, 7.5 mol% of racemic BINAP, and 1.4 equivalents of cesium carbonate, as described by Bolm and Hildebrand.[6] Although more studies are needed to define substituent effects in this series it is clear that a π donor *para* to the bromine substituent, as in **5b**, is detrimental to the coupling process; adduct **6b** is obtained in only 10% yield. A similar result was obtained by Bolm and Hildebrand with 4-*tert*-butyl bromobenzene.[6] However, the yield of **6b** could be improved to 55% if the catalyst and ligand loading were doubled.

Despite the fact that the coupling occurred under basic conditions, only formation of a nitrogen – carbon bond was observed. Attempts to convert **6a** into **7a** by using sodium methoxide in methanol were unsuccessful. However, stronger bases such as NaH and KH worked well, and we used excess KH in THF to effect this transformation. The benzothiazines **7a** – **c** were prepared in good yield with this procedure (Scheme 1).

We were also able to prepare the cinnamate derivative **8** in 59% yield by using the coupling methodology. Cyclization to the benzothiazine **9** occurred in 70% yield upon treatment with lithium diisopropylamide (LDA) [Eq. (2)]. A single stereoisomer was obtained, and its structure was assigned on the basis of X-ray data.[8]

[*] Prof. M. Harmata, N. Pavri
Department of Chemistry
University of Missouri-Columbia
Columbia, MO 65211 (USA)
Fax: (+1) 573-882-2754
E-mail: harmatam@missouri.edu

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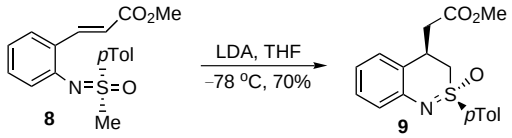
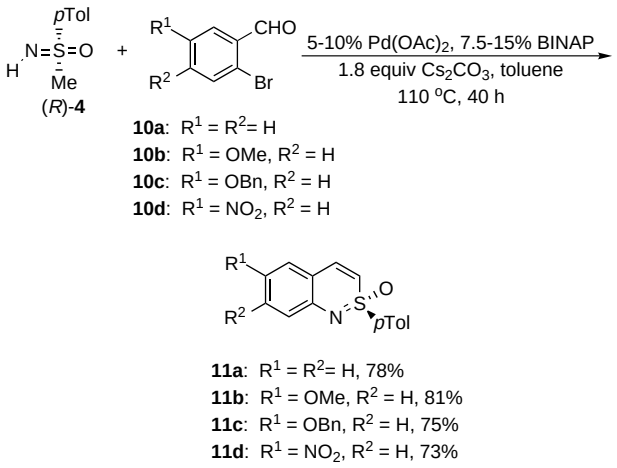


(2)

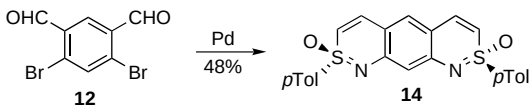
The weakly basic conditions of the coupling reaction suggested to us that a more electrophilic group *ortho* to the bromine atom might make ring formation possible in one pot and one operation. Indeed, treatment of a small selection of *ortho*-bromobenzaldehydes with (*R*)-**4** under slightly modified coupling conditions afforded benzothiazines **11a–d** in good yields (Scheme 2). Interestingly, in this case an alkoxy



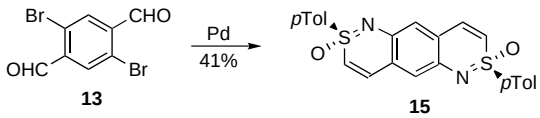
Scheme 2. One-pot, one-operation benzothiazine synthesis.

substitutent *para* to the bromine substituent was not detrimental to the reaction. We are not yet certain of the exact sequence of events leading to the formation of **11a–d**, but we assume that formation of the nitrogen–carbon bond precedes the condensation.[9]

Dibromides **12**[10] and **13**[11] led to the bisbenzothiazines **14** and **15** in 48 and 41% yields, respectively [Eq. (3) and (4)]. The reasons for the rather low yields in these cases remain to

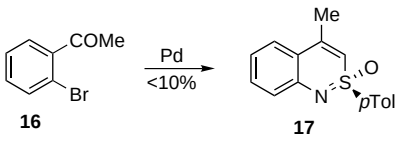


(3)



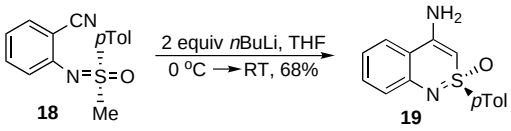
(4)

be elucidated. However, it should be noted that once formation of the first nitrogen–carbon bond is complete the arene possesses a π-electron-donating substituent which may interfere with subsequent coupling. Unfortunately, *ortho*-bromoacetophenone **16** gave the benzothiazine **17** in less than 10% yield under reaction conditions that were successful for the aldehydes [Eq. (5)].



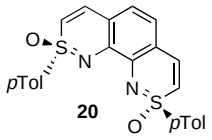
(5)

Finally, Bolm reported and we confirmed that *ortho*-bromobenzonitrile undergoes the coupling reaction extremely well, to afford **18** in 94% yield. Initial efforts to cyclize this adduct with NaH or KH failed. However, we found that treatment of **18** with two equivalents of *n*BuLi resulted in the formation of **19** in 68% yield [Eq. (6)].



(6)

In summary, we have developed a one-pot, one-operation and a two-pot procedure for the synthesis of various enantiomerically pure 1,3-benzothiazines. Efforts to expand the scope and generality of both reaction types and explore the chemistry of the benzothiazines are underway. The synthesis of **20**, a potentially useful ligand for asymmetric catalysis, is also being explored.[12]



Experimental Section

One-pot, one-operation synthesis of **11a**: A flame-dried Schlenk flask that was maintained under an N_2 atmosphere was equipped with a stirrer bar and condenser and charged with 10 mol% (based on bromobenzaldehyde) $Pd(OAc)_2$, 15 mol% of racemic BINAP, 1.8 equivalents of Cs_2CO_3, and 1.2 equivalents of (*R*)-**4**. One equivalent of *ortho*-bromobenzaldehyde (85 mg) and 5 mL of freshly distilled toluene were added and the mixture was heated in an oil bath at 115 °C for 38–44 hours. The flask was removed from the bath, silica gel was added, and the toluene was removed in vacuo. Purification of the product by column chromatography afforded **11a** in 78% yield, m.p. 141–143 °C. ^{1}H NMR: (250 MHz, $CDCl_3$): $\delta = 7.77$ (d, $J =$ 8.3 Hz, 2H), 7.64 (d, $J = 9.8$ Hz, 1H), 7.45 (dt, $J = 1.6$, 8.5 Hz, 1H), 7.34 (m, 4H), 7.03 (dt, $J = 1.2$, 7.2 Hz, 1H), 7.37 (d, $J = 9.8$, 1H), 2.45 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 145.1$, 144.3, 138.7, 138.3, 131.9, 129.6, 129.5, 128.8, 124.1, 120.0, 116.1, 110.1, 21.5; elemental analysis calcd for $C_{15}H_{13}NOS$: C 70.56, H 5.13; found: C 70.38, H 5.26.

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Asymmetric Synthesis of Novel Ferrocenyl Ligands with Planar and Central Chirality**

Dieter Enders,* René Peters, René Lochtman, and Gerhard Raabe

The application of ferrocenyl ligands possessing planar chirality to asymmetric catalysis has recently received considerable interest, especially in their use as P,P- and P,N-chelating systems.[1] Planar-chiral ferrocenes of the Kumada – Hayashi type **A**, which additionally possess a stereocenter in the α-position, have shown efficiency as catalysts for asymmetric synthesis both in research and industrial processes.[1, 2] We report here a straightforward asymmetric synthesis of planar-chiral ferrocenyl ligands of type **B** bearing a

A **B**

stereogenic center in the β-position of the side chain. The field of such planar-chiral ferrocenes has been little studied until now, since it was previously not possible to synthesize these compounds stereoselectively. In 1981 Kumada et al. described the only synthesis of ligand **B** ($E^1 = NMe_2$, $E^2 = PPh_2$), a homologue of diphenylphosphanylferrocenylethylamine (PPFA), which required separation of racemates and diastereoisomers.[3]

Our SAMP/RAMP-hydrazone method (SAMP and RAMP = (*S*)- and (*R*)-1-amino-2-(methoxymethyl)pyrrolidine) seemed to be appropriate for the asymmetric synthesis of planar-chiral ligands bearing a stereogenic center at the β-position of the ferrocene backbone. Not only would the highly diastereoselective alkylation α to the hydrazone functional group be possible,[4] but also various heteroatom functionalities could be introduced with similar highly asymmetric inductions. In the context of ligand synthesis this would necessarily require the use of phosphorus,[5] sulfur,[6] and nitrogen electrophiles.[7] Since we have recently demonstrated that benzoylferrocene – SAMP-hydrazones may be easily functionalized at the *ortho* position with high diastereoselectivity,[8] it was decided to combine both synthetic strategies. Ferrocenyl ketones **1** with α-positioned acidic protons, which may be accessed simply by Friedel – Crafts acylation,[9] served as starting material. Because the ketones were only weakly electrophilic, owing to the electron-donating character of the ferrocenyl system, quantitative conversion into the *E*/*Z*-SAMP-hydrazone mixtures **2** ($E:Z \approx 3:1$) was achieved through activation with $AlMe_3$ (Scheme 1).[8, 10]

The regioselective metalation of the side chain was possible by the use of lithium diisopropylamide (LDA). After trapping the azaenolate with electrophiles, we first obtained *E*/*Z*-hydrazone mixtures **3** ($E:Z = 3:1$ to 1:3), in which the new stereogenic center in the *E* and *Z* isomers unexpectedly show the opposite configuration. It was therefore necessary to find conditions that would yield only one geometric hydrazone isomer. Accordingly, we examined the influence of base, solvent, cosolvent, additives, reaction time, reaction temperature, transition metal salts for transmetalation of the lithio azaenolates, and SAMP auxiliary derivatives on the $E:Z$ ratio. We discovered that for metalation in diethyl ether at room temperature, the addition of $LiClO_4$ resulted in the desired high $E:Z$ ratios. Without $LiClO_4$ the azaenolate formed a yellow-orange percipitate; however, with $LiClO_4$ orange-brown homogeneous solutions were obtained. It is well known that $LiClO_4$ leads to deaggregation of organolithium species, and this explains the differing solubilities and selectivities.[11] Through trapping of the metalated species at $-100\,^{\circ}C$ with the requisite electrophile, the desired α-functionalized hydrazones **3** were available in good yields and with $E:Z$ ratios varying from 9:1 to 50:1. The *E* isomers were diastereomerically pure (Table 1).

[*] Prof. Dr. D. Enders, Dipl.-Chem. R. Peters, Dr. R. Lochtman, Priv.-Doz. Dr. G. Raabe
Institut für Organische Chemie der RWTH Aachen
Professor-Pirlet-Strasse 1, D-52074 Aachen (Germany)
Fax: (+49) 241-8888-127
E-mail: enders@rwth-aachen.de

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