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Highly Diastereoselective Zinc-Catalyzed Propargylation of *tert*-Butanesulfinyl Imines

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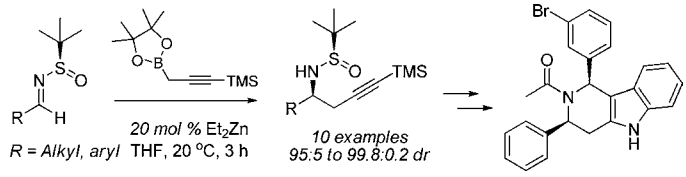
ABSTRACT



A zinc-catalyzed diastereoselective propargylation of *t*-butanesulfinyl imines is presented. The methodology provided both aliphatic and aryl homopropargylic amines in up to 98:2 and 99.8:0.2 dr, respectively. The utility of the homopropargylic amines was demonstrated by the application to the synthesis of a *cis*-substituted pyrido-indole through a diastereoselective Pictet−Spengler cyclization.

The prevalence of chiral α-branched amines in natural products, active biological molecules, and ligands underscores the importance for general asymmetric methods for their efficient construction.[1] Nucleophilic additions to enantiomerically pure sulfinyl imines have quickly emerged as a practical and highly diastereoselective approach for the synthesis of this functional group.[2] The alkynyl functionality within homopropargylic amines derived from a propargylation of imines provides a synthetic handle for couplings or further derivation.[3] The diastereoselective propargylation of chiral *t*-butanesulfinyl imines has been reported by the addition with a stoichiometrically pregenerated Grignard[4] or allenylzinc[3,5] reagent. Recently, we reported the zinc-catalyzed propargylation of aldehydes with propargyl borolanes wherein a catalytic cycle was achieved through a B/Zn exchange between an alkoxide−zinc intermediate and the borolane reagent.[6] A complementary catalytic cycle can also be achieved if the sulfinyl imido zinc product **4** from the propargylation of a sulfinyl imine with an allenylzinc species can also participate in a B/Zn exchange with the borolane reagent **1** (Scheme 1). Herein, we report this diastereose-

(1) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kesseler, M.; Stuermer, R.; Zelinski, T. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 788–824.

(2) For recent reviews, see: (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995. (b) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003–8030. (c) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Han, Z.; Gallou, I. *Aldrichimica Acta* **2005**, *38*, 93–104. (d) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869–8905. (e) Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162–1186.

(3) For selected examples of synthetic application of chiral amines derived from the propargylation of sulfinyl imines, see: (a) Voituriez, A.; Ferreira, F.; Perez-Luna, A.; Chemla, F. *Org. Lett.* **2007**, *9*, 4705–4708. (b) Voituriez, A.; Ferreira, F.; Chemla, F. *J. Org. Chem.* **2007**, *72*, 5358–5361. (c) Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *J. Org. Chem.* **2009**, *74*, 2238–2241.

(4) Hashmi, A. S. K.; Schafer, S.; Bats, J. W.; Frey, W.; Rominger, F. *Eur. J. Org. Chem.* **2008**, *489*, 1–4899.

(5) (a) Chemla, F.; Ferreira, F. *J. Org. Chem.* **2004**, *69*, 8244–8250. (b) Ferreira, F.; Audouin, M.; Chemla, F. *Chem.—Eur. J.* **2005**, *11*, 5269–5278. (c) Chemla, F.; Ferreira, F. *Synlett* **2006**, 2613–2616. (d) Chemla, F.; Ferreira, F.; Gaucher, X.; Palasi, L. *Synthesis* **2007**, 1235–1241. (e) Seguin, C.; Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *J. Org. Chem.* **2009**, *74*, 6986–6992. (f) Voilturiez, A.; Perez-Luna, A.; Ferreira, F.; Botuha, C.; Chemla, F. *Org. Lett.* **2009**, *11*, 931–934.

(6) Fandrick, D. R.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Johnson, C. S.; Lee, H.; Song, J. J.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 88–91.

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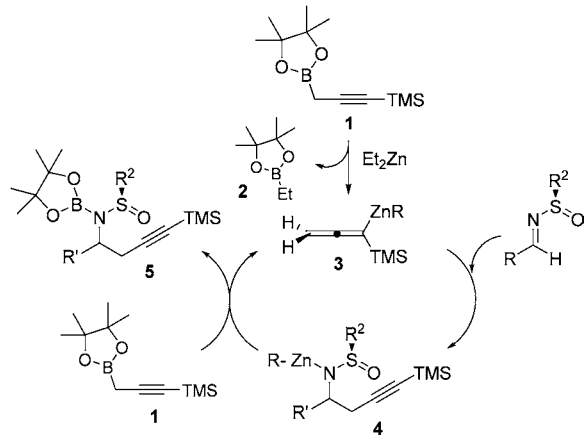
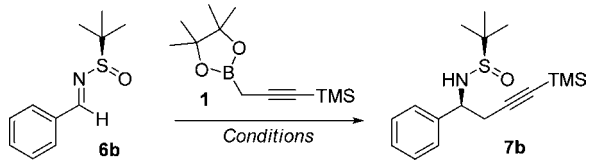
Scheme 1. Proposed Catalytic Cycle for the Zinc-Catalyzed Propargylation of Sulfinyl Imines



lective zinc-catalyzed propargylation of *t*-butanesulfinyl imines with propargyl borolanes.

No reaction was observed between the propargyl borolane **1** and *t*-butanesulfinyl imine **6b** at ambient temperature (Table 1). The addition of catalytic diethyl zinc (10 mol %)

Table 1. Optimization of the Zinc-Catalyzed Propargylation of *tert*-Butanesulfinyl Imines[a]



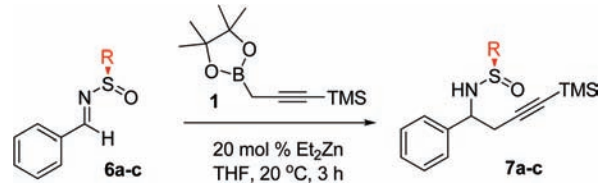
entry	Et_2Zn	temp	solvent	time[b]	yield[c]	dr[d]
1	none	20 °C	THF	30 h[e]	0%	–
2	10%	20 °C	THF	18 h	90%	99.3:0.7
3	20%	20 °C	THF	3 h	91%[f]	99.4:0.6
4	40%	20 °C	THF	1 h	80%	99.6:0.4
5	80%	20 °C	THF	1 h	77%	99.6:0.4
6	20%	40 °C	THF	1 h	86%	99.5:0.5
7	20%	0 °C	THF	21 h	88%	99.5:0.5
8	20%	−20 °C	THF	72 h	86%	99.4:0.6
9	20%	20 °C	CH_2Cl_2	16 h	91%	99.5:0.5
10	20%	20 °C	EtOAc	16 h	91%	99.7:0.3
11	20%	20 °C	MTBE	16 h	92%	99.7:0.3
12	20%	20 °C	DMF	1 h	89%	92:8

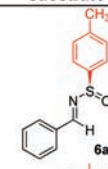
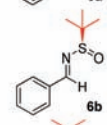
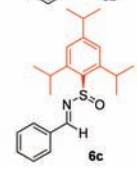
[a] Reactions performed with 1.5 equiv of borolane **1**. [b] Time until complete conversion. [c] HPLC assay yield. [d] dr determined by HPLC.[7] [e] At 30 h, < 5% conversion. [f] 83% Isolated yield.

promoted the propargylation reaction to afford the homopropargylic amine **7b** in 90% yield with high diastereoselectivity (>99:1) (entry 2). Increasing the catalyst loading to 20 mol % enabled complete conversion within 3 h while maintaining the high yield. Interestingly, the diastereoselectivity (>99:1 dr) was generally insensitive to temperature, solvent, and catalyst loading. However, the use of a highly coordinating solvent such as DMF reduced the selectivity.

The structure of the chiral auxiliary showed a more pronounced effect on the diastereoselectivity (Table 2).

Table 2. Effect of Sulfinyl Substituent on Diastereoselectivity[a]



entry	substrate	yield[b]	dr[c]
1	 6a	94%	85:15
2	 6b	83%[d]	99.4:0.6
3[e]	 6c	59%	97:3

[a] Reaction performed with 1.5 equiv of borolane **1**. [b] Isolated yield. [c] dr determined by ^1H NMR or HPLC.[7] [d] 91% HPLC assay yield. [e] 18 h reaction.

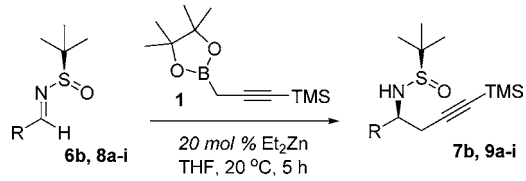
Utilizing the *p*-toluene sulfinyl auxiliary afforded an 85:15 diastereomeric ratio. The more sterically demanding 2,4,6-triisopropylphenyl substituent[8] also lowered the diastereoselectivity compared to the parent *t*-butyl group. This reaction with the more hindered substituent was also significantly slower than the parent system and furnished a lower yield.

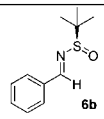
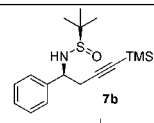
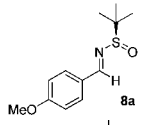
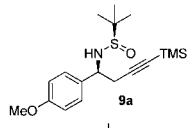
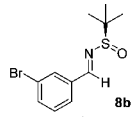
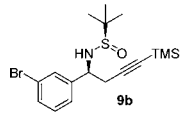
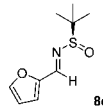
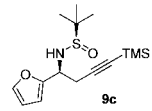
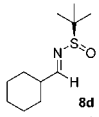
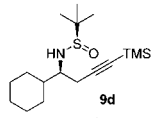
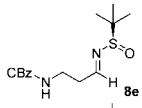
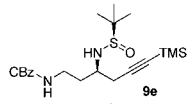
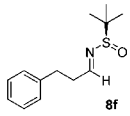
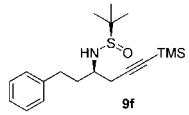
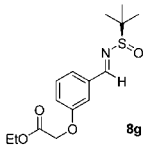
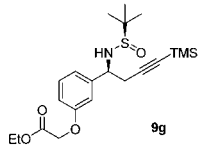
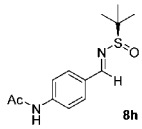
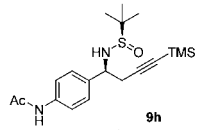
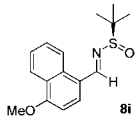
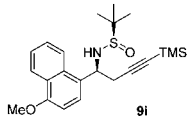
After establishing the optimal conditions with the parent *t*-butanesulfinyl auxiliary, the substrate scope was examined (Table 3). High diastereoselectivities were achieved for both aryl (>98:2) and alkyl substrates (>94:6). A positive correlation between the diastereoselectivity and the steric influence at the α-position of the substrate was apparent. For example, a 99.4:0.6 dr (entry 1) was obtained with the phenyl substrate, and a 99.8:0.2 dr (entry 10) was observed with the α-naphthyl imine. A similar increase was exhibited between the primary and secondary aliphatic imines (entries

(7) Diastereoselectivity determined by HPLC analysis compared to diastereomer mixture standards prepared acoording to: Brak, K.; Barrett, K. T.; Ellman, J. A. *J. Org. Chem.* **2009**, *74*, 3606–3608.

(8) (a) Han, Z.; Krishnamurthy, D.; Grover, P.; Fang, Q. K.; Pflum, D. A.; Senanayake, C. H. *Tetrahedron Lett.* **2003**, *44*, 4195–4197. (b) Schenkel, L. B.; Ellman, J. A. *J. Org. Chem.* **2004**, *69*, 1800–1802. (c) Savile, C. K.; Magloire, V. P.; Kazlauskas, R. J. *J. Am. Chem. Soc.* **2005**, *127*, 2104–2113. (d) Davis, F. A.; Song, M. *Org. Lett.* **2007**, *9*, 2413–2416. (e) Davis, F. A.; Chai, J. *ARKIVOC* **2008**, 190–203.

Table 3. Substrate Scope for the Zinc-Catalyzed Propargylation of Sulfinyl Imines[a]



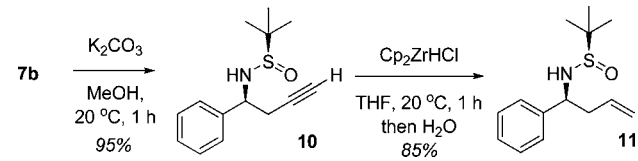
entry	substrate	product	yield[b] dr[c]
1	 6b	 7b	83% 99.4:0.6
2	 8a	 9a	85% 99.5:0.5
3	 8b	 9b	90% 98.5:1.5
4	 8c	 9c	86% 99.7:0.3
5	 8d	 9d	84% >98:2[d]
6	 8e	 9e	86% 95:5
7	 8f	 9f	81% 96:4
8	 8g	 9g	77% 99.8:0.2
9	 8h	 9h	43% 98.5:1.5
10	 8i	 9i	81% 99.8:0.2

[a] Reaction performed with 1.5 equiv of borolane **1**. [b] Isolated yield. [c] Diastereoselectivity determined by HPLC.[7] [d] Diastereoselectivity determined by ^{1}H NMR, and the minor diastereomer was not detected.

5−7). The methodology tolerated numerous functional groups including halides, esters, primary amides, and carbamates.

The stereochemical outcome of the zinc-catalyzed propargylation of sulfinyl imines was determined by conversion

Scheme 2. Conversion to Homoallylic Sulfinylamine and Determination of Configuration

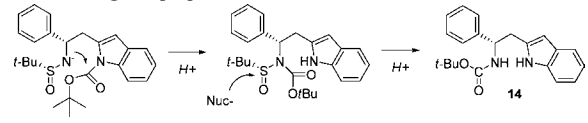


to the known homoallylic amine **11** (Scheme 2). Standard trimethylsilyl deprotection and hydrozirconation provided olefin **11** in good yield. The relative configuration of homoallylic amine **11** derived from the propargylation reaction was readily established by spectral comparison to both previously characterized diastereomers of amine **11**.[9] The relative stereochemical assignments of the propargylation products **9a**−**i** were assigned by analogy.

The utility of the homopropargylic amines was demonstrated by the application to the synthesis of the pyrido-indole **17** through a diastereoselective Pictet−Spengler cyclization[10] (Scheme 3). Sonogashira coupling of the homopropargylic amine **10** to the *o*-iodoaniline **12** furnished the indole precursor **13** in good yield. The subsequent TBAF-promoted cyclization[11] also proceeded with BOC migration and sulfinyl deprotection to provide the BOC-protected aminoindole **14** in high yield. To probe whether TBAF can directly deprotect sulfinyl auxiliaries, the *t*-butanesulfinyl homopropargylic amine **10** was subjected to the TBAF cyclization conditions and showed minimal deprotection after 15 h. Accordingly, the sulfinyl deprotection observed during the TBAF-promoted cyclization of alkyne **13** reasonably occurred after acyl migration.[12] The aminoindole **14** showed some instability to strong acids. Therefore, BOC deprotection was performed with TBSOTf[13] to cleanly provide amine **15**. The Pictet−Spengler reaction between amine **15** and 3-bromobenzaldehyde readily proceeded at ambient temperature with good diastereoselectivity (>10:1 dr) by simple treatment with $MgSO_4$ to afford the *cis*-substituted pyrido-indole **17** in reasonable yield after acylation.

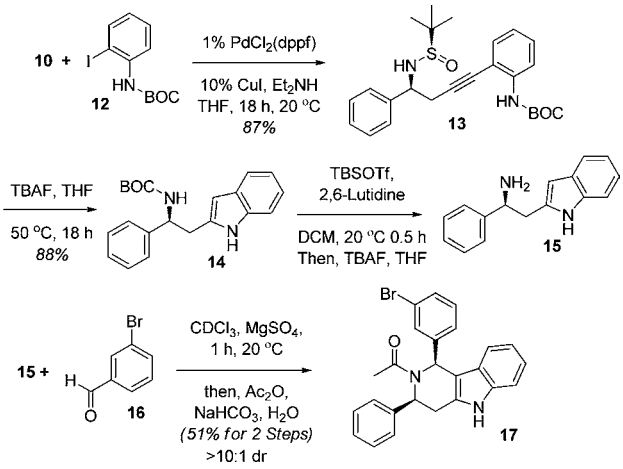
The catalytic activity observed with zinc for the propargylation of sulfinyl imines can be reasonably rationalized by a zinc-mediated propargylation and a subsequent B/Zn exchange between the imidozinc adduct **4** and the propargyl borolane reagent **1** (Scheme 1). Previously, the rapid conversion of propargyl borolane **1** to ethyl borolane **2** with diethyl

(9) Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979–4982.
(10) For related Pictet−Splenger reactions, see: (a) Molina, P.; Alcantara, J.; Lopez-Leonardo, C. *Tetrahedron Lett.* **1996**, *36*, 953–956. (b) Bailey, P. D.; Morgan, K. M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3578–3583.
(11) Xiong, X.; Pirrung, M. C. *Org. Lett.* **2008**, *10*, 1151–1154.
(12) Proposed mechanism for the acyl migration and sulfinyl deprotection observed during the preparation of indole **14**:



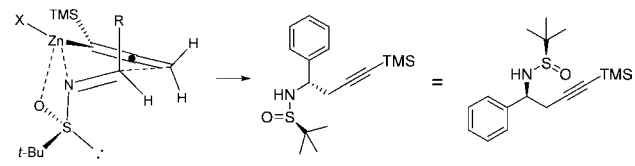
(13) Trost, B. M.; Fandrick, D. R. *Org. Lett.* **2005**, *7*, 823–826.

Scheme 3. Application toward Indole Synthesis and a Diastereoselective Intramolecular Pictet−Spengler Reaction



zinc was demonstrated.[6] The selective formation of the propargyl product over the allenyl adduct is consistent with a zinc-mediated propargylation.[5,14] Alternatively, the direct reaction of the propargyl borolane with the electrophile commonly proceeds through an inversion mechanism to favor the allenyl isomer.[15] Employing the chelated six-membered

Scheme 4. Mechanism Proposal for Stereocontrol



transition state previously proposed for the zinc-mediated allylation[9] of chiral sulfinyl imines also predicts the stereochemical outcome observed for the zinc-catalyzed propargylation (Scheme 4). By analogy to the B/Zn exchange described between an alkoxyzinc species and an allyl[16] or propargyl borolane,[6] a similar exchange can be proffered between the imidozinc adduct **4** and the propargyl borolane reagent **1**. Accordingly, this exchange readily regenerates the allenyl zinc reagent and establishes a catalytic cycle to require substoichiometric amounts of zinc to effect a propargylation of sulfinyl imines.

In conclusion, we demonstrated the highly diastereoselective zinc-catalyzed propargylation of *t*-butanesulfinyl imines. This process wherein the propargylation of sulfinyl imines is achieved by charging catalytic diethyl zinc to a solution of propargyl borolane and substrate at ambient temperature provides an operationally simple method for the synthesis of synthetically useful chiral homopropargylic amines.

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C for all products and unknown substrates. This material is available free of charge via the Internet at http://pubs.acs.org.

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