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Stereoselective addition to chiral *p*-toluene sulfinimines

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Abstract

Diastereoselective addition of a number of Grignard reagents to chiral *p*-toluene sulfinimines **2b–2d** under the mediation of copper salts afforded various protected α-branched amines. © 2000 Elsevier Science Ltd. All rights reserved.

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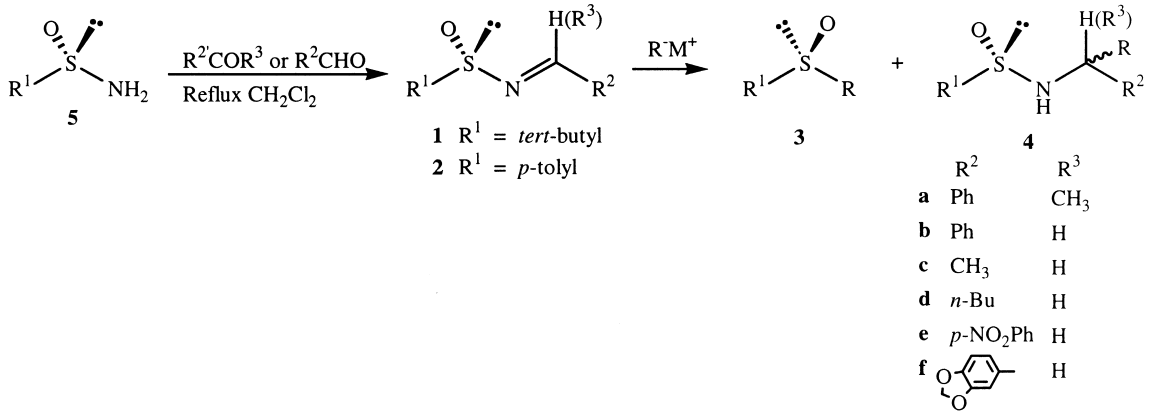
Enantiopure sulfinimines have been demonstrated to be versatile synthetic intermediates for the synthesis of a variety of chiral materials.[1,2] As a great number of drugs and drug candidates possess an amine functionality, the asymmetric synthesis of enantiopure amines has become the focus of considerable attention.[3–7] The reactions between chiral sulfinimines and an organometallic reagent, in principle, could give two types of nucleophilic attack, resulting in the formation of the substitution and addition products, respectively (Scheme 1). For Ellman's *tert*-butylsulfinimines (**1**), the steric bulk of the *tert*-butyl group completely excludes direct



Scheme 1.

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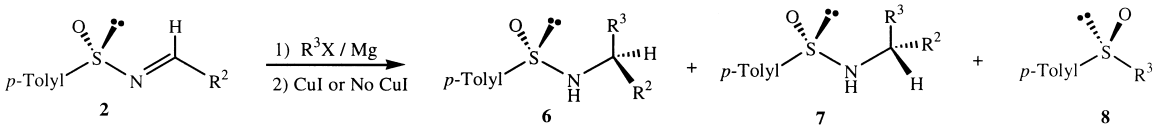
substitution at the stereogenic sulfur atom, thus affording only the protected α-branched amines in a highly regio- and diastereoselective manner.[4] In contrast, *p*-toluene sulfinimines (**2**) are readily accessible materials but are sterically less demanding and do not undergo clean addition reactions with Grignard reagents. Only activated benzylmagnesium chloride and allylmagnesium bromide react with **2** in an addition mode while direct substitution of **2** occurs in the reaction with methylmagnesium bromide.[5,7] Herein, we report the effect of cuprous iodide in mediating the regio- and diastereoselectivity of the Grignard reaction of *p*-toluenesulfinimines (**2**).

The enantiopure *p*-toluenesulfinimines were synthesized according to Davis' protocol.[8] With the chiral sulfinimines in hand, we first explored the reaction between (*S*)-**2b** and 3-butenylmagnesium bromide under a number of reaction conditions. In the absence of cuprous iodide, a 1:1 diastereomeric mixture of sulfinamides **6a** and **7a** was formed as only the minor products irrespective of the solvent and the reaction temperature (Table 1, entries 1–3). Similarly when *n*-butylmagnesium bromide was used, a 68% yield of sulfoxide **8d** was obtained together with only 7% of a 1:1 diastereomeric mixture of addition products (Table 1, entry 16). The composition and assignment of the reaction products was assessed by ^{1}H NMR spectroscopy.[4] Most of the products can be separated in pure form by combined column chromatography and preparative TLC. Remarkably, under the mediation of cuprous iodide, (*S*)-**2b** underwent regioselective and diastereoselective reaction with 3-butenylmagnesium chloride in THF at –15°C for 3 h affording sulfinamides in 80% total yield with a 14:86 ratio of (S_S,*S*)-**6a** to (S_S,*R*)-**7a** (Table 1, entry 7). Impressively, no appreciable amount of the corresponding substitution product **8** was formed. Apparently, catalytic amounts of CuI are insufficient to promote the conjugated addition (Table 1, entries 4–6). On the other hand, as expected, increasing the reaction temperature deteriorates the diastereoselectivity of the reaction (Table 1, entry 8). Attempts to further improve the selectivity of the reaction by lowering the reaction temperature were unsuccessful. When *n*-butylmagnesium bromide, after mixing with cuprous iodide, was allowed to react with (*S*)-**2b**, a comparably high level of selectivity was achieved giving the corresponding sulfinamides in 70% yield with a diastereomeric ratio (dr) of 18:82 (Table 1, entry 17). For the more sluggish and bulky *i*-propylmagnesium bromide, the regio-directing effect of a cuprous salt became less important. Almost identical results in terms of the chemical yield, regio- and diastereo-selectivity were observed irrespective of the presence or absence of cuprous iodide (Table 1, entries 20 and 21). In both cases, over a 30% yield of *N*-benzyl *p*-tolylsulfinamide was formed via a reaction in which the Grignard reagent functioned as a hydride donor. Presumably, due to the bulkiness of the *i*-propyl group, the addition to the sulfinimine was facilitated even in the absence of cuprous iodide. On the other hand, the generality of the cuprous salt mediated reaction was evaluated by performing the addition reaction of 3-butenylmagnesium bromide to (*S*)-**2c**, (*S*)-**2d**, (*S*)-**2e** and (*S*)-**2f**. Except for (*S*)-**2e**, all of the substrates reacted with 3-butenylmagnesium bromide in the presence of 0.5 equivalent of CuI to give a high yield of adducts with excellent regioselectivity (> 98/2) (Table 1, entries 9–11). The nitro substituent in (*S*)-**2e** which is susceptible to reducing agents caused complications in the reaction.[5] On the other hand, the diastereoselectivity of the addition reaction appeared to be strongly related to the structure of the sulfinimine. By comparing the dr observed in entries 7, 9, 10 and 11 in Table 1, it becomes evident that the larger substituent appended at the imino carbon the higher degree of asymmetric induction. The relative stereochemistry of the major diastereoisomer **6e** was established by X-ray crystallographic analysis (Fig. 1). This result is consistent with structure assignments by ^{1}H NMR (vide supra).

Reminiscent of the chemistry of conjugate addition of organocuprates to α,β-unsaturated ketones, the Grignard reagents, after modification with CuI as demonstrated in the present work,

Table 1
Regio- and stereoselective additions of chiral *p*-toluenesulfinimines



Entry	R^2	R^3	CuI:RX (mole ratio)	Temp. (°C)	Solvent	Time (h)	Sulfinamides [a] **6**:**7** (dr)	total yield (%)	Sulfoxides **8** cpd	yield (%)	**6**+**7** / **8** ratio
1	Ph	*n*-Bu-3-enyl	–	0	Et_2O	3	**6a**:**7a** (1:1)	10	**8a**	40	20:80
2	Ph	*n*-Bu-3-enyl	–	-30-r.t.	THF-Toluene (*ca* 1:1)	4-overnight	**6a**:**7a** (1:1)	14	**8a**	43	25:75
3	Ph	*n*-Bu-3-enyl	–	-15-r.t.	THF	6-overnight	**6a**:**7a** (1:1)	4	**8a**	58	6:94
4	Ph	*n*-Bu-3-enyl	0.2 : 3	-15	Et_2O-THF (*ca* 1:1)	4	**6a**:**7a** (4:1)	27	**8a**	16	63:37
5	Ph	*n*-Bu-3-enyl	0.5 : 3	-15-r.t.	THF	4-overnight	**6a**:**7a** (1:2.8)	48	**8a**	27	64:36
6	Ph	*n*-Bu-3-enyl	1 : 1.5	-15	THF	4	**6a**:**7a** (1:6)	78		–	98:2
7	Ph	*n*-Bu-3-enyl	1 : 2	-15	THF	4	**6a**:**7a** (1:6)	81		–	98:2
8	Ph	*n*-Bu-3-enyl	1 : 2	-6	THF	2.5	**6a**:**7a** (1:2.6)	80		–	98:2
9		*n*-Bu-3-enyl	1 : 2	-15	THF	4	**6b**:**7b** (1:3.6)	79		–	>98:2
10	Me	*n*-Bu-3-enyl	1 : 2	-15	THF	2.5	**6c**:**7c** (1:1.9)	82		–	>98:2
11	*n*- Bu	*n*-Bu-3-enyl	1 : 2	-15	THF	2.5	**6d**:**7d** (1:1)	80		–	>98:2
12	Ph	CH_3	1 : 2	-15	Et_2O-THF (*ca* 1:1)	4	**6e**:**7e** (1:2) [b]	27	**8b**	61	31:69
13	Me	Ph	1 : 2	-15	Et_2O-THF (*ca* 1:1)	4	**6e**:**7e** (1:1)	39	**8c**	23	63:37
14	Me	Ph	–	-15	THF	7	**6e**:**7e** (5:1)	38	**8c**	26	59:41
15	Me	Ph	1 : 2	-15	THF	4	**6e**:**7e** (1.5:1)	49	**8c**	21	70:30
16	Ph	*n*-Bu	–	-15	THF	7	**6f**:**7f** (1:1) [c]	7	**8d**	68	9:91
17	Ph	*n*-Bu	1 : 2	-15	THF	5.5	**6f**:**7f** (1:4.5)	70	**8d**	8	89:11
18	*n*- Bu	Ph	–	-15-r.t.	THF	6-overnight	**6f**:**7f** (1.2:1)		**8c**	55	25:75
19	*n*- Bu	Ph	1 : 2	-15	THF	4	**6f**:**7f** (2.8:1)	57	**8c**	24	70:30
20	Ph	*i*-Pr	–	-15	Et_2O-THF (*ca* 1:4)	4	**6g**:**7g** (1:3.5) [b]	21	**8d**	22	50:50
21	Ph	*i*-Pr	1 : 2	-15	Et_2O-THF (*ca* 1:4)	4	**6g**:**7g** (1:4)	22	**8d**	20	54:46
22		Ph	1 : 2	-15-r.t.	THF	4-overnight	**6h**:**7h** (1:2)	20		–	–

[a] Diastereomeric ratios were determined by the 270 MHz ^1H NMR method, and all new compounds were characterized by ^1H, ^{13}C NMR, MS and elemental analysis.

[b] Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Chem. Soc. Perkin 1,* **1982**, 339.

[c] Reference 7.

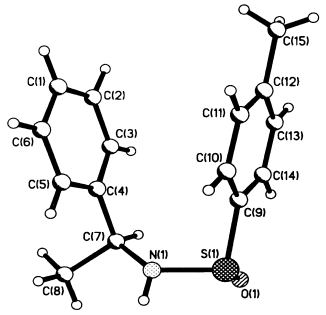


Figure 1.

exhibited a higher propensity to undergo addition to sulfinimines. A six-membered ring transition state for this addition is proposed (Fig. 2). The copper center of the organometallic agents chelates with the oxygen atom of sulfinimines **2**, hence, approach of the carbanions takes place from the *re*-face of the sulfinimines.

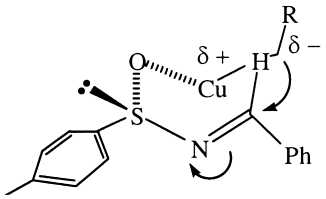


Figure 2.

In conclusion, the methodology described in this communication offers an efficient and enantioselective route to various protected α-branched amines.

Acknowledgements

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