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Palladium-Catalyzed N-Vinylation of Sulfoximines

Juan R. Dehli and Carsten Bolm*

Institut für Organische Chemie der RWTH Aachen, Professor-Pirlet-Str. 1, D-52056 Aachen, Germany

carsten.bolm@oc.rwth-aachen.de

Received August 18, 2004

Abstract: New previously unavailable *N*-vinyl sulfoximines have been synthesized by intermolecular palladium-catalyzed coupling between sulfoximines and vinyl bromides in excellent yield. Hydrogenation of the vinyl moiety opens a novel way to α-branched *N*-alkyl sulfoximines.

During the past decade, various sulfoximines have been shown to be applicable as chiral ligands in metal-catalyzed asymmetric reactions.[1,2] However, although the results of these pioneering studies were very promising in terms of catalytic activity and stereoselectivity, they still fell short when compared to other well-established ligand structures.[3] It was not until a general methodology for the N-arylation of sulfoximines (via palladium-catalyzed cross-coupling with aryl halides[4] and sulfonates[5]) had been developed that a new generation of these compounds (exemplified by **1**, **2**, or **3**, Figure 1) reached the required level to compete with the above-mentioned ligands in metal-catalyzed asymmetric Diels–Alder,[6] hetero-Diels–Alder,[7] allylic alkylation,[8] and Mukaiyama-type aldol reactions.[9]

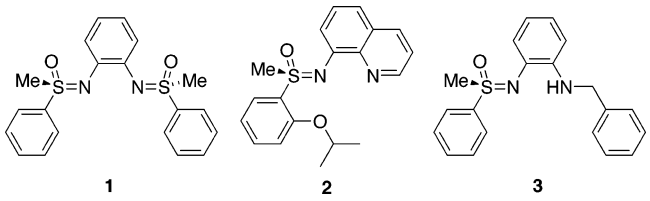
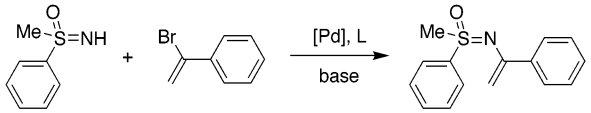


FIGURE 1. Successfully applied N-arylated sulfoximines in copper-catalyzed C–C bond-forming reactions.

SCHEME 1. Palladium-Catalyzed Coupling of *S*-Methyl-*S*-phenylsulfoximine (4a) and α-Bromostyrene (5a) To Give 6



On the other hand, during the last years, several groups reported on palladium-catalyzed coupling reactions of vinyl bromides with amines,[10] amides,[11] azoles,[12] and trialkylsilylimines,[13] based on the methodology introduced by Buchwald and Hartwig for the arylation of amines.[14] In the frame of our ongoing studies concerning the synthesis of new sulfoximines with novel structural motives and taking into account the excellent results obtained with sulfoximine ligands in which the nitrogen was directly bound to an sp^2 carbon, we regarded the development of a method for the introduction of a vinyl moiety at the sulfoximine nitrogen of utmost importance. *S*-Methyl-*S*-phenylsulfoximine (**4a**) and α-bromostyrene (**5a**) were chosen as model substrates for the synthesis of **5**, and this educt combination was tested for coupling under various reaction conditions (Scheme 1).

We were pleased to find that under the optimized conditions for the N-arylation of sulfoximines [using Pd_2dba_3 (5 mol % in Pd), *rac*-BINAP (7.5 mol %), NaO-*t*-Bu (1.5 equiv) in refluxing toluene],[4] the coupling proceeded with complete conversion within 24 h. Furthermore, no byproducts were detected by NMR and GC if dry and nonacidic conditions were maintained throughout the workup.

A series of experiments was then performed in order to investigate the reagent flexibility of the coupling process (Table 1). A control reaction under the same conditions in the absence of palladium confirmed that the

* To whom correspondence should be addressed. Fax: +49 241 809 2391. Phone: +49 241 809 4675.

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10.1021/jo0485583 CCC: $27.50
Published on Web 11/04/2004

TABLE 1. Synthesis of Vinylsulfoximine 6 Starting from 4a and 5a under Various Reaction Conditions[a]

entry	Pd source	Pd amt (mol %)	phosphine[b]	base[c]	*T* (°C)	conv[d] (%)
1	Pd_2dba_3	5	BINAP	NaO-*t*-Bu	110	>98
2			BINAP	NaO-*t*-Bu	110	0
3	$Pd(OAc)_2$	5	BINAP	NaO-*t*-Bu	110	>98
4	$Pd(OAc)_2$	5	P(*o*-tolyl)$_3$	NaO-*t*-Bu	110	0
5	$Pd(OAc)_2$	5	BINAP	Cs_2CO_3	110	>98
6	$Pd(OAc)_2$	5	BINAP	NaO-*t*-Bu	80	>98
7	$Pd(OAc)_2$	5	BINAP	NaO-*t*-Bu	50	<5
8	$Pd(OAc)_2$	1	BINAP	NaO-*t*-Bu	110	>98
9	$Pd(OAc)_2$	0.5	BINAP	NaO-*t*-Bu	110	>98
10	$Pd(OAc)_2$	0.1	BINAP	NaO-*t*-Bu	110	~25

[a] The reaction mixture was stirred under argon in toluene for 24 h. [b] A Pd-to-ligand molar ratio of 1:1.5 was used. [c] The substrate-to-base ratio was 1:1.5. [d] Determined by GC and ^{1}H NMR of the reaction crude.

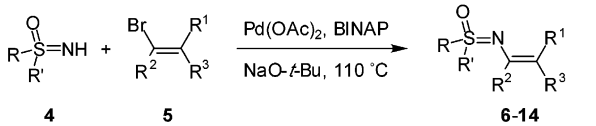
reaction was indeed palladium-catalyzed (entry 2). Instead of Pd_2dba_3, the more stable $Pd(OAc)_2$ could also be applied as the palladium source. The substitution of BINAP by P(*o*-tolyl)$_3$, however, resulted in a nonefficient catalytic system (entry 4), as it had also been observed in the N-arylation process.[4] Use of the weaker base Cs_2CO_3 (instead of NaO-*t*-Bu) or decreasing the temperature (from 110 °C) to 80 °C (entry 6) did not lead to any detectable change. At 50 °C, however, only traces of the expected product were detected. Very satisfyingly, and in contrast to the analogous N-arylation reaction, the catalyst concentration could be reduced to 0.5 mol % (entry 9).

To explore the generality of this C−N coupling reaction, the use of other sulfoximines was then examined in reactions with vinyl bromides. Unless otherwise stated, a standard catalytic system consisting of 1 mol % of $Pd(OAc)_2$, 1.5 mol % of BINAP, and 1.5 equiv of NaO-*t*-Bu was used, and the reaction was performed in refluxing toluene. The results summarized in Table 2 show that the reaction is rather general, as far as the sulfoximine moiety is concerned. In fact, both alkyl aryl and dialkyl sulfoximines, as well as cyclic and acyclic derivatives, give excellent results when coupled with α-bromostyrene (**5a**) affording the corresponding *N*-vinyl sulfoximines in essentially quantitative yield.

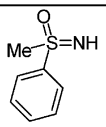
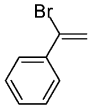
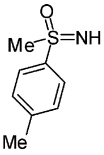
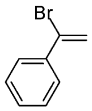
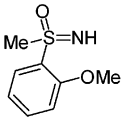
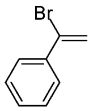
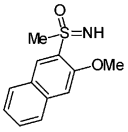
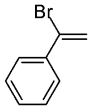
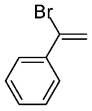
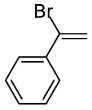
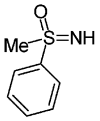
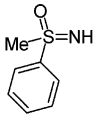
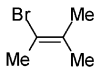
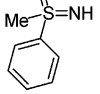
Furthermore, simple vinyl bromides could be coupled with sulfoximines (Table 2, entries 7 and 8), and even 2-bromo-3-methylbut-2-ene (**5c**), a sterically highly demanding vinyl bromide, was a suitable substrate. β-Bromostyrene (**5d**) was also tested as coupling partner for **4a**, but in contrast to other reports on *N*-vinyl coupling reactions, no product could be isolated here. The fact that neither **4a** nor **5d** was recovered after the workup suggests that the instability of the coupled product rather than a low reactivity of the substrate is the reason for the failure of the experiment.

Recently, vinyl triflates[15] were shown to be suitable partners in palladium-catalyzed couplings with amines[16] and amides.[17] With the goal to extend the scope of the N-vinylation reaction of sulfoximines, couplings with such

TABLE 2. Synthesis of *N*-Vinyl Sulfoximines[a]



4 **5** **6-14**

Entry	Sulfoximine		Vinyl bromide		Product	Yield (%)[b]
1		**4a**		**5a**	**6**	>98
2		**4b**		**5a**	**7**	>98
3		**4c**		**5a**	**8**	>98
4		**4d**		**5a**	**9**	>98
5		**4e**		**5a**	**10**	>98
6		**4f**		**5a**	**11**	>98
7		**4a**		**5b**	**12**	>98[c]
8		**4a**		**5c**	**13**	>98[c]
9		**4a**		**5d**	**14**	0

[a] Conditions: sulfoximine (1 mmol), vinyl bromide (1 mmol), $Pd(OAc)_2$ (0.01 mmol), BINAP (0.015 mmol), and NaO-*t*-Bu (1.5 mmol) in toluene (5 mL) under Ar at 110 °C. [b] Based on the amount of essentially pure product. [c] Use of 0.05 mmol of $Pd(OAc)_2$, 0.075 mmol of BINAP, and 1.5 mmol of vinyl bromide. **5d** was used as a *cis*/*trans* mixture.

compounds were studied here as well.[15] Gratifyingly, when 3,4-dihydronaphth-1-yl triflate (**15**) was used as substrate under the optimized conditions described above [$Pd(OAc)_2$/BINAP/NaO-*t*-Bu], the coupling proceeded smoothly, and after 24 h reaction time, full conversion of **15** was achieved. Unfortunately, however, a significant

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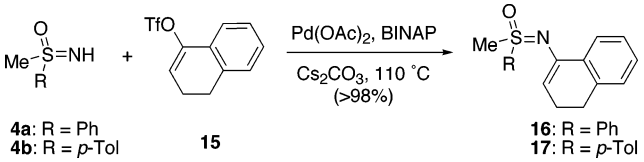
SCHEME 2. Palladium-Catalyzed Coupling of Sulfoximines with Vinyl Triflate 15

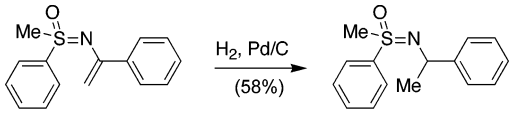


4a: R = Ph
4b: R = *p*-Tol

15

16: R = Ph
17: R = *p*-Tol

SCHEME 3. Hydrogenation of *N*-Vinyl Sulfoximine 6 To Give *N*-Alkyl Sulfoximine 18



6 **18**

amount of α-tetralone (ca. 35%, as determined from the ^{1}H NMR of the crude reaction mixture) was detected, most likely formed by hydrolysis of the substrate. The use of the softer base Cs_2CO_3 solved the problem, and starting from **4a** and **4b** essentially pure vinyl sulfoximines **16** and **17**, respectively, were obtained in quantitative yield (Scheme 2).

Finally, initial studies were undertaken to investigate the reactivity of the *N*-vinyl sulfoximines. For that purpose, the reduction of **6** was studied. Attempts to use of $NaBH_4$ as reducing agent, even at high temperature, remained unsuccessful, and no expected product was obtained. Hydrogenation of **6** with palladium over charcoal, however, yielded *N*-*sec*-alkyl sulfoximine **18** as a mixture of diastereomers (dr = 4:1) in 58% yield (Scheme 3).

Although the stereoselectivity in the formation of **18** is only moderate and the chemical yield still needs to be improved, the hydrogenation approach is a rather unique and simple method for the preparation of *N*-alkyl sulfoximines. Due to the low nucleophilicity of the sulfoximine nitrogen, such compounds are usually difficult to obtain, and only a few methods are known for their efficient synthesis.[2,18,19]

In summary, a simple method for the synthesis of previously unknown *N*-vinyl sulfoximines has been described. By palladium-catalyzed coupling of N-unsubstituted sulfoximines with vinyl bromides or vinyl triflates the desired products can be obtained in high yields. The reduction of the vinyl moiety by hydrogenation represents a new approach to *N*-alkyl sulfoximines, which are otherwise difficult to prepare.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or C_6D_6 using TMS as internal standard. Chemical shifts, δ, are given in ppm, and spin−spin coupling constants, J, in Hz. Toluene and THF were distilled over Na and stored under Ar. N-Unsubstituted sulfoximines were prepared according to a method recently reported in the literature.[20]

Representative Procedure for the Coupling of Sulfoximines with Vinyl Bromides. A dry Schlenk tube equipped with a magnetic stirbar was charged with $Pd(OAc)_2$ (2.2 mg, 1 mol %), BINAP (9.4 mg, 1.5 mol %), NaO-*t*-Bu (144 mg, 1.5 mmol), and toluene (5 mL) under Ar. Then, *S*-methyl-*S*-phenylsulfoximine (**4a**, 155 mg, 1.0 mmol) and α-bromostyrene (**5a**, 183 mg, 1.0 mmol) were added. The tube was sealed and the mixture stirred at 110 °C for 24 h. After being cooled to room temperature, the reaction mixture was diluted with Et_2O (10 mL) and filtered through a thin plug of Celite, which was rinsed with additional Et_2O. The solvents were removed in vacuo, yielding essentially pure sulfoximine **6**.

***S*-Methyl-*S*-phenyl-*N*-(1-phenylvinyl)sulfoximine (6).** ^{1}H NMR ($CDCl_3$): 3.09 (s, 3H), 4.52 (s, 1H), 4.77 (s, 1H), 7.15−7.25 (m, 3H), 7.35−7.45 (m, 3H), 7.60−7.65 (m, 2H), 7.80−7.85 (m, 2H). ^{13}C NMR ($CDCl_3$): 45.3 (CH_3), 96.6 (CH_2), 125.9 (CH), 128.0 (CH), 128.2 (CH), 128.4 (CH), 129.6 (CH), 133.3 (CH), 138.7 (C), 140.2 (C), 147.7 (C). IR: ν 3317, 2969, 1682, 1630, 1224, 748. MS (EI): *m/z* 257 (M^+, 9), 242 (12), 194 (100), 91 (63). HRMS for $C_{15}H_{15}NOS$: calcd 257.0874, found 257.0874.

Hydrogenation of 6 To Give *N*-Alkyl Sulfoximine 18. A dry Schlenk flask equipped with a magnetic stirbar was charged with Pd over charcoal (100 mg, 10%), sulfoximine **6** (257 mg, 1.0 mmol), and THF (5 mL). The flask was then purged with H_2 (1 atm) and the mixture stirred for 2 h. Then, the reaction mixture was filtered through a thin plug of Celite and rinsed with additional Et_2O, and the solvents were removed in vacuo. NMR analysis of the crude product indicated a ca. 4:1 ratio of diastereomers, which could finally be separated after flash chromatography (SiO_2, pentane/EtOAc, 3:1) to give the two stereoisomers of **18** with $R_f = 0.2$ and $R_f = 0.3$ in 46% and 12% yield, respectively.

***S*-Methyl-*S*-phenyl-*N*-(1-phenylethyl)sulfoximine (18, Major Diastereomer).** ^{1}H NMR ($CDCl_3$): 1.33 (d, J = 6.6 Hz, 3H), 2.94 (s, 3H), 4.26 (q, J = 6.6 Hz, 1H), 7.08−7.13 (m, 1H), 7.20−7.24 (m, 2H), 7.32−7.35 (m, 2H), 7.46−7.56 (m, 3H), 7.89−7.91 (m, 2H). ^{13}C NMR ($CDCl_3$): 27.3 (CH_3), 45.2 (CH_3), 53.9 (CH), 126.2 (CH), 126.5 (CH), 128.2 (CH), 128.4 (CH), 129.3 (CH), 132.8 (CH), 140.6 (C), 147.5 (C). IR: ν 3063, 3019, 2971, 1447, 1236, 1136, 748. MS (EI): *m/z* 259 (M^+, <1), 244 [$(M - 15)^+$, 100], 141 (32). HRMS (for $C_{15}H_{17}NOS-CH_3$): calcd 244.0796, found 244.0796.

Acknowledgment. We gratefully acknowledge the Deutsche Forschungsgemeinschaft (SFB 380) and the Fonds der Chemischen Industrie for financial support. J.R.D. thanks the European Commission for a Marie Curie postdoctoral fellowship (contract HPMF-CT-2002-01855). We also thank Marc Speer for experimental contributions.

Supporting Information Available: Characterization data for compounds **7**−**13**, **16**, and **17** and NMR spectra for sulfoximines **6**−**13** and **16**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0485583

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