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Asymmetric Alkylation of *N*-Toluenesulfonylimines with Dialkylzinc Reagents Catalyzed by Copper−Chiral Amidophosphine

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Received August 23, 2003

The synthetic procedure of a chiral amidophosphine ligand **5** bearing two bulky substituents, 2,4,6-trimethylphenylmethyl or 2,4,6-triisopropylphenylmethyl groups, on the pyrrolidine ring was improved by employing the borane−THF reduction of the lactam−alcohol intermediate **8**. The resulting amino alcohol was selectively acylated to give an amide−alcohol **11**, which was then converted to the chloride **12** in 55−73% yields by the treatment with methanesulfonyl chloride in collidine. The reaction of the chloride **12** with $NaPPh_2$ in dioxane−THF gave an amidophosphine **5** in an acceptably high 82−83% yields. Addition of a hexane solution of dialkylzinc reagent to a mixture of catalytic amount of an amidophosphine **5**, copper species, and *N*-toluenesulfonylimine **1a** of benzaldehyde in toluene provided a solution which gave the alkylated amide **3** in high yield and enantioselectivity up to 96%. A survey of copper sources and solvents concluded that copper(II) ditriflate and copper(I) triflate−benzene complex as good copper sources and toluene as a choice of solvent. *N*-Toluenesulfonylimines **1a**−**e** of arylaldehydes, furfural, and alkanals were successfully ethylated with diethylzinc to give the corresponding *N*-toluenesulfonylamides **3aE**−**eE** in satisfactorily good 69−97% yields and high 86−96% enantioselectivities.

Introduction

The catalytic asymmetric reactions that lead to C−C bond formation by the addition of organometallic reagents to C=N of imines are of fundamental importance in the continuing development of efficient chemical synthetic processes.[1] Even the reactive organolithium reagents have been applied into a catalytic asymmetric addition to C=N of imines by activation with a chiral amino ether ligand.[2−4] Among considerably energetic approaches toward the catalytic asymmetric addition of organometallic reagents to C=N of imines,[5,6] zinc triflate−chiral amino alcohol-catalyzed acetylide addition,[7] chiral amino alcohol-controlled addition of organozinc,[8] chiral π-allylpalladium-catalyzed allylation with allylstannane or allylsilane,[9] and rhodium−MOP-based-phosphine-catalyzed arylation with arylstannanes[10] showed

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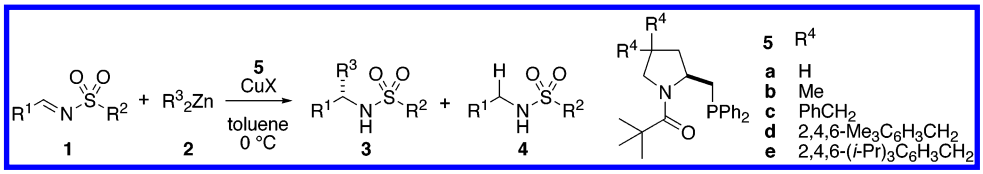
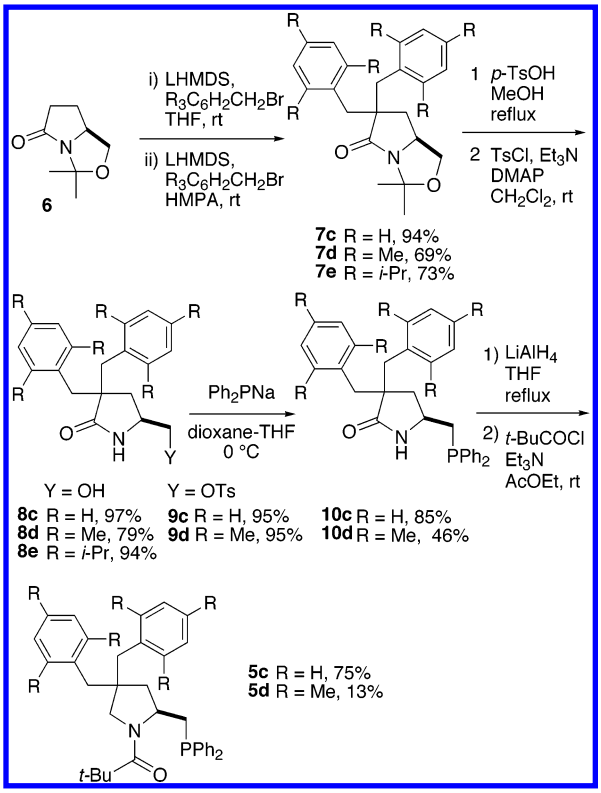
10.1021/jo035234q CCC: $25.00
Published on Web 11/15/2003

SCHEME 1. Asymmetric Alkylation of *N*-Sulfonylimine 1 with Dialkylzinc 2 under 5-Copper Catalysis



impressive success.[11] However, undeveloped situation of the catalytic and efficient asymmetric reaction of simple alkylmetals[12] was in contrast to the chiral amino alcohol-catalyzed asymmetric alkylation of aldehydes with organozinc reagents.[13] We have previously documented our observations involving the addition of diethylzinc to C=N of *N*-sulfonylimines **1** of arylaldehydes in the presence of a catalytic amount of copper(II) triflate and a chiral amidophosphine **5** in a toluene solvent under mild conditions (0 °C) yielding an ethylation product **3** in high enantioselectivity (Scheme 1).[14] The enantioselectivity reached to 94% by using the most suitable *N*-methanesulfonylimine **1** (R^2 = Me) and dibenzylamidophosphine **5c** (R^4 = Bn). A series of impressive approaches has followed using catalysts derived from zirconium−peptide,[15] copper−oxazoline,[16] amino alcohol,[17] and copper−binaphthylthiophosphoramide[18] to provide the addition product with high enantioselectivity.[19] In these approaches, attention has been paid to the removal of the activating group of the imine functionality. In our approach, *N*-methanesulfonylimine **1** (R^2 = Me) was alkylated to the *N*-methanesulfonylamide **3** (R^2 = Me) in higher enantioselectivity than *N*-toluenesulfonylimine **1** (R^2 = Tol); however, the removal of a methanesulfonyl group of **3** by a DIBAL reduction proceeded with a concomitant partial racemization.[14] Since the removal of a toluenesulfonyl group of **3** was conveniently carried out without racemization by a samarium iodide treatment

SCHEME 2. Synthetic Scheme for 5 from 6



to give the corresponding chiral amine, a chiral ligand **5** was modified to give satisfactorily high enantioselectivity in the ethylation of *N*-toluenesulfonylimine **1** (R^2 = Tol).[20] We describe herein that further studies including steric modification of an amidophosphine structure provided a better catalyst by which alkylation of *N*-toluenesulfonylimine **1** (R^2 = Tol) with dimethyl- and diisopropylzinc reagents gave **3** in high enantioselectivity. Furthermore, enolizable *N*-toluenesulfonylimines **1d**,**e** bearing alkyl substituents (R^1) were successfully alkylated to the corresponding *N*-toluenesulfonylamides **3** in high enantioselectivity.

Synthesis of Chiral Amidophosphine 5. The synthesis of amidophosphines **5d**,**e** bearing bulky substituents on the pyrrolidine ring was followed the previously reported scheme for **5b**,**c** that started from dialkylation of **6** (Scheme 2).[14,21] However, the synthesis of **5d** bearing two mesitylenemethyl groups were needed to be improved because of the poor 13% yield at the final lactam reduction and subsequent acylation steps of the phosphine **10d**.[20] The poor efficiency in the final step was ascribable to the slow reduction of the sterically hindered lactam carbonyl group of **10d** and concomitant oxidation

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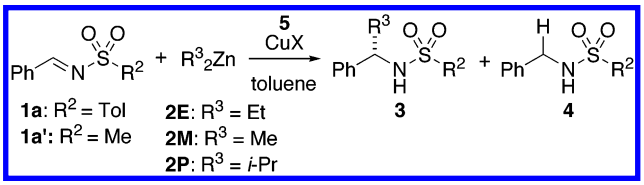
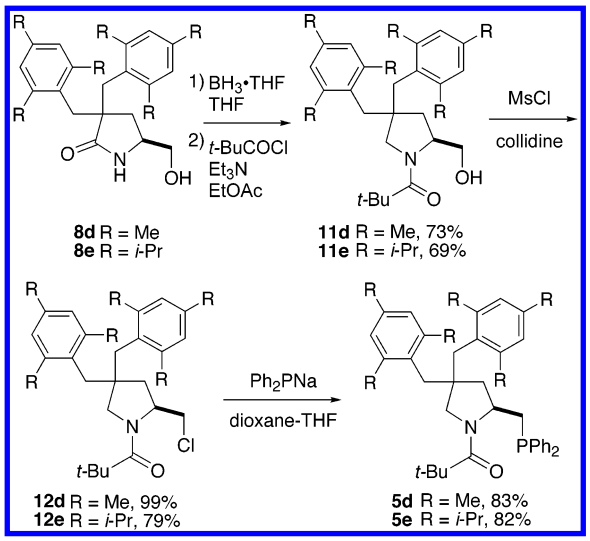
TABLE 1. Alkylation of *N*-sulfonylaldimines 1A,A′ of Benzaldehyde with Dialkylzinc Reagents 2 Catalyzed by Cu-amidophosphines[a]



	1a,a′	2		5		CuX				3			4
entry	R^2	R^3	equiv	**a**−**e**	mol %		mol %	*T*/°C	time/h		yield/%	ee/%	yield/%
1	Tol	Et	3	**a**	1.3	$Cu(OTf)_2$	1	0	4	**3aE**	79	63	20
2	Tol	Et	3	**b**	1.3	$Cu(OTf)_2$	1	0	5	**3aE**	79	79	15
3	Tol	Et	2	**c**	1.3	$Cu(OTf)_2$	1	0	5	**3aE**	94	90	<1
4	Tol	Et	2	**d**	1.3	$Cu(OTf)_2$	1	0	3	**3aE**	93	95	<1
5	Tol	Et	2	**d**	6.5	$Cu(OTf)_2$	5	0	5	**3aE**	97	96	<1
6	Tol	Et	2	**e**	6.5	$Cu(OTf)_2$	5	0	4	**3aE**	96	88	<1
7	Tol	Et	2	**e**	19.5	$Cu(OTf)_2$	15	0	2	**3aE**	99	93	<1
8	Tol	Me	2	**d**	6.5	$(CuOTf)_2$−PhH	2.5	rt	23	**3aM**	5[b]	12	nd
9	Tol	Me	15	**d**	19.5	$Cu(OTf)_2$	15	rt	20	**3aM**	39	82	nd
10	Me	Me	30	**d**	6.5	$(CuOTf)_2$−PhH	2.5	rt	19	**3a′M**	62	81	nd
11	Me	Me	15	**d**	22.5	$(CuOTf)_2$−PhH	7.5	rt	19	**3a′M**	95	85	nd
12	Me	Me	8	**e**	22.5	$(CuOTf)_2$−PhH	7.5	rt	20	**3a′M**	96	86	nd
13	Tol	Me	8	**e**	19.5	$Cu(OTf)_2$	15	rt	20	**3aM**	97	87	<1
14	Tol	Me	8	**e**	19.5	$Cu(OTf)_2$	7.5	rt	17	**3aM**	96	86	<1
15	Tol	*i*-Pr	2	**d**	19.5	$(CuOTf)_2$−PhH	7.5	0	1	**3aP**	79	71	10
16	Tol	*i*-Pr	2	**e**	19.5	$Cu(OTf)_2$	15	0	2	**3aP**	92	78	5

[a] The results of entries 1−3 were referenced from ref 14. nd: not determined. [b] The imine **1a** was recovered as a major product.

SCHEME 3. Improved Synthetic Scheme for 5d,e from 8



of the phosphorus moiety to its oxide. Fortunately, the borane reduction of the lactam−alcohol **8d** followed by acylation successfully provided **11d** in 73% yield (Scheme 3).[22] The amidophosphine **5d** was obtained in 82% yield via chloride **12d**. This synthetic scheme was beneficial in the preparation of **5e** bearing a more bulky triisopropylphenylmethyl group, giving **5e** in 45% from **8e**.

Reaction Procedure and Applicability of Dialkylzinc Reagents. Addition of a toluene solution of a chiral amidophosphine ligand **5** to a suspension of copper(II) ditriflate in toluene afforded a solution, indicating formation of a **5**−copper(II) complex that is soluble in toluene. Upon further addition of a hexane solution of diethylzinc into a solution of 1 mol % of copper(II) triflate and 1.3 mol % (1.3 equiv to copper) of **5d** in a toluene solvent, a small amount of a brown gum precipitated. Further addition of a toluene solution of **1a** (R^1 = Ph, R^2 = Tol) and stirring at 0 °C for 2 h afforded (*S*)-**3aE**[23,24] (R^1 = Ph, R^2 = Tol, R^3 = Et) in 93% ee and 96% yield. Ultrasonication of the reaction did not affect the gummy precipitate, giving the same level of yield and enantioselectivity. Finally, we found that addition of diethylzinc solution to a mixture of copper(II) triflate, **5d**, and **1a** in toluene formed an almost clear solution without gummy precipitate, and stirring of the mixture at 0 °C for 3 h gave **3aE** in an improved 95% ee and 93% yield (Table 1, entry 4). The 5 mol % catalyst loading gave **3aE** in 96% ee and 97% yield, comparable to the 1 mol % catalyst (entry 5).

The catalytic efficiency of **5a**−**d**−copper(II) complex is highly dependent on the bulkiness of the substituents on the pyrrolidine ring of **5**; that is, the more bulky is, the more efficient (entries 1−4). The poorer catalytic performance yielded a greater amount of the reduction product **4**, arising from direct reduction with diethylzinc. The efficiency of **5e** bearing the bulkiest triisopropylphenylmethyl group unfortunately did not exceed **5d**, giving **3aE** in 88% ee at the 5 mol % catalyst loading (entry 6). The selectivity was improved upon loading 15 mol % catalyst, giving **3aE** quantitatively in 93% ee (entry 7). The bulkiness of **5e** should interfere the formation of the reactive complex of copper−ligand−diethylzinc reagent with imine **1a**. The reaction of the less reactive dimethylzinc provided a good chance to bring **5e**'s ability into full play.

The methylation of **1a** with dimethylzinc **2M** (R^3 = Me) was slow at room temperature to give **3aM** (R^3 = Me) in

(22) The borane reduction of **10d** was not successful.

(23) The first **a** and second **M** of **3aM** refer to **1a** and **2M**, respectively. For example, **3aM** comes from **1a** and **2M**.

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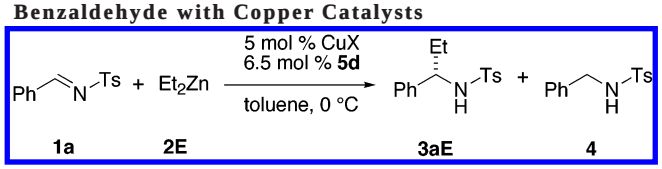
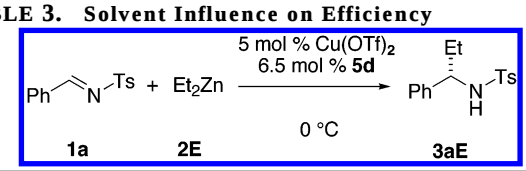
TABLE 2. Ethylation of *N*-Tosylimine 1a of Benzaldehyde with Copper Catalysts



			3aE		4
entry	CuX	time/h	yield/%	ee/%	yield/%
1	$Cu(OTf)_2$	5	97	96	<1
2	$(CuOTf)_2$−PhH	0.5	95	90	<1
3	$Cu(naphthenate)_2$	22	82	19	10
4	$Cu(OAc)_2$−H_2O	12	86	17	8
5	CuTC[a]	24	80	18	9
6	$Cu(O_2CCPh_3)_2$	24	19	0	25
7	CuCN	24	40	1	12
8	Cu_2O	21	30	0	11
9	CuCl	20	81	35	4
10	CuI	16	16	2	15
11	CuCl−SMe_2	20	85	48	5
12	CuBr−SMe_2	24	47	45	6
13	CuI−SMe_2	20	65	20	8

[a] CuTC = copper(I) thiophene-2-carboxylate.

TABLE 3. Solvent Influence on Efficiency



entry	solvent	time/h	yield/%	ee/%
1	toluene	5	97	96
2	*c*-C_5H_9OMe	2	83	84
3	Et_2O	18	53	40
4	THF	18	39	17
5	CH_2Cl_2	20	68	19
6	MeCN	17	48	0

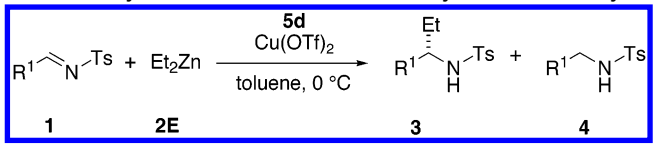
5% yield and 12% ee (entry 8). The attempted reaction of **1a** in a THF solvent gave the corresponding THF adduct of **1a** in high yield, which arises from the addition of a THF radical.[25] The improvement was observed by using 15 equiv of dimethylzinc under 15 mol % of the catalyst, giving **3aM** in 39% yield and 82% ee (entry 9). The more reactive methanesulfonylimine **1a′** (R^2 = Me) was converted to **3a′M**[26] in 62% and 81% ee (entry 10). The conversion was improved by using 15 mol % loading of the catalyst to afford **3a′M** in 95% yield and 85% ee (entry 11). The use of **5e** was beneficial in methylation giving (*S*)-(−)-**3aM**[27] with 87% ee in nearly quantitative yield irrespective to methanesulfonyl or toluenesulfonylimine **1a** (entries 12−14). An isopropylation of **1a** (R^2 = Tol) with 2 equiv of diisopropylzinc was catalyzed by **5e** giving (*S*)-**3aP** (R^2 = *i*-Pr)[27] in 92% yield and 78% ee (entries 15 and 16).

Since the copper source and solvent influence the efficiency of the reaction,[28] we examined the reaction for formation of **3aE** using different copper salts and solvents. Although copper(II) ditriflate gave the best efficiency (Table 2, entry 1), copper(I) triflate−benzene complex was the most active catalyst that brought the reaction to completion within 0.5 h, giving **3aE** with 90% ee (entry 2). Other copper carboxylates, oxide, cyanide, and halides were the not choice of copper source (entries 3−10), while dimethyl sulfide complexes of copper chloride and bromide were better copper sources, giving **3aE** in relatively high yields and moderate enantioselectivities (entries 11−13). It is important to note that copper(II) triflate was purified through dissolution in acetonitrile and then precipitation upon addition of ether.[29] Direct use of commercial copper salt without purification afforded **3aE** in 21% ee and 97% yield.

Toluene was the first choice of solvent followed by cyclopentyl methyl ether[30] in which **3** was obtained in 83% yield and 84% ee (Table 3, entries 1 and 2). Other solvents were not the choice, especially acetonitrile in which **3aE** was obtained as a racemate, probably due to the activation of diethylzinc by the high polarity of acetonitrile (entry 6). Poor efficiency in ether and THF solvents is attributable to coordination of etheral oxygen to zinc, which interferes with coordination of zinc to the amide carbonyl oxygen of **5** (entries 3 and 4).[31,32]

The reaction of diethylzinc under the catalysis of copper(II) ditriflate **5d** in toluene was successfully applied to the ethylation of a variety type of *N*-toluenesulfonylimines **1b**−**e**[33] (R^2 = Tol) of 4-methoxybenzaldehyde, 2-furfural, cyclohexanecarbaldehyde, and also 3-phenylpropanal, giving the corresponding products in high yield and enantioselectivity (Table 4). It is noteworthy that enolizable imines **1d**,**e** (R^1 = *c*-hex, $Ph(CH_2)_2$, entries 4 and 5) were successfully ethylated without enolization, giving the corresponding products **3dE**−**eE** in reasonably high enantioselectivities and yields.

TABLE 4. Ethylation of *N*-Toluenesulfonylaldimines 1a−e with Diethylzinc 2E Catalyzed by $Cu(OTf)_2$−5d



	1		5d			3			4
entry		R^1	mol %	$Cu(OTf)_2$/mol %	time/h		yield/%	ee/%	yield/%
1	**a**	Ph	6.5	5	5	**3aE**	97	96	**4a** <1
2	**b**	4-$MeOC_6H_4$	1.3	1	12	**3bE**	78	86	**4b** 18
3	**c**	2-furyl	1.3	1	1	**3cE**	96	91	**4c** 2
4	**d**	*c*-C_6H_{11}	6.5	5	1	**3dE**	84	96	**4d** nd[a]
5	**e**	$Ph(CH_2)_2$	6.5	5	3	**3eE**	69	93	**4e** nd[a]

[a] nd: not determined.

Conclusion

Steric tuning of a chiral amidophosphine ligand **5** and optimization of the reaction procedure led to the copper-catalyzed asymmetric alkylation of *N*-toluenesulfonylimines **1** with dialkylzincs in a satisfactorily high level. Since the toluenesulfonyl activating group of imines is easily removable from the product amide **3** by a samarium iodide treatment, the procedure is applicable to the synthesis of chiral amines. Furthermore, the reaction was shown to be applicable to the enolizable imines of alkanals, which provide an advantage over the previous alkylation methodology with organolithium reagents.

Acknowledgment. This research was partially supported by the 21st Century COE (Center of excellence) Program "Knowledge Information Infrastructure for Genome Science" and a Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" from the Ministry of Education, Culture, Sports, Science and Technology, Japan. M.K. was supported by a fellowship from the JSPS.

Supporting Information Available: General experimental procedure and spectroscopic data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035234Q

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