Tetrahedron Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Asymmetric synthesis of *N*-aryl sulfinamides: copper(I)-catalyzed coupling of sulfinamides with aryl iodides via kinetic resolution

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ARTICLE INFO

Article history:
Received 1 March 2016
Revised 12 April 2016
Accepted 14 April 2016
Available online xxxx

Keywords:
N-Aryl sulfinamide
Copper
Asymmetric catalysis
Cross-coupling
Kinetic resolution

ABSTRACT

An asymmetric synthesis of *N*-aryl sulfinamides was achieved through copper-catalyzed coupling reactions of aryl iodides with sulfinamides. Such a kinetic resolution process provided the desired coupling products in moderate to good yields and with moderate enantioselectivities.

Sulfinamides have found extensive applications as easily-removed protection groups or functional groups in synthetic chemistry.[1] Among them, chiral sulfinamides such as chiral *t*-butanesulfinamide and analogues are especially important, which have been widely used as chiral auxiliaries or chiral ligands in asymmetric reactions.[2]

Many methods have been developed for the synthesis of racemic sulfinamides.[3] However, the enantioselective synthesis of chiral sulfinamides is relatively rare, especially for the synthesis of *N*-aryl sulfinamides.[4]

Transition-metals such as Pd[5] or Cu-[6]catalyzed C–N coupling reactions have been extensively studied in the last few decades for the formation of aryl carbon–nitrogen and carbon–heteroatom bonds. The coupling reaction of aryl halides with sulfinamides is an important method for the formation of *N*-aryl sulfinamides. In 2010, Touré[7] reported a copper-catalyzed coupling reaction of *tert*-butanesulfinamide with 2-bromopyridine with >90% conversion. However, the substrate scope was great limited in this work. In a later study, Zeng and co-workers[8] found that only low yields (<30%) were obtained for most aryl halide substrates under the copper catalytic system. Thus they resorted to Pd catalytic system, which could afford the coupling products *N*-aryl sulfinamides in high yields. Other groups also developed similar Pd catalysts for the coupling reactions of aryl halides and sulfonamides. For example, Du and coworkers[9] used a Pd catalytic system for the coupling reactions of chiral 2-(2′-bromophenyl)oxazolines and (*s*)-*tert*-butanesulfinamides, while Selvakumar and coworkers[10] developed a Pd-catalyzed C–N coupling reaction of racemic *tert*-butanesulfinamide and aryl bromides and chlorides. In these cases, chiral sulfinamide substrates were used for the formation of chiral products. No asymmetric coupling reactions were reported with racemic sulfinamide substrates to date.

As part of our continuous studies[11,12] on transition-metal catalyzed asymmetric C–N couplings, we have developed some copper catalytic system for asymmetric aryl C–N coupling reactions[12] through kinetic resolution strategy.[13] This promoted us to envision that the asymmetric synthesis of *N*-aryl sulfinamides may be achieved through coupling reactions of racemic sulfinamides and aryl halides under the catalysis of copper salts and chiral ligands through kinetic resolution (Fig. 1). Herein we'd like to disclose the details.

Our investigation was initiated with the CuI-catalyzed coupling reaction of 4-chloro-iodobenzene (**1a**) and recemic *tert*-butanesulfinamide (**2a**) as a model case. A variety of chiral ligands such as binol (L1),[14] amino acid (L2),[15] box (L3), were first screened and only a trace amount of desired coupling product was obtained (Table 1, entries 1–3). However, when a diamine-derived ligand L4 was used,[16] good yield was obtained albeit in only 30% ee (Table 1, entry 4). Further exploration of diamine-type ligands (Table 1, entries 5–9, L5–L9) revealed that L6 was relatively better, which afforded the product in 82% yield and 56% ee (Table 1, entry

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http://dx.doi.org/10.1016/j.tetlet.2016.04.049
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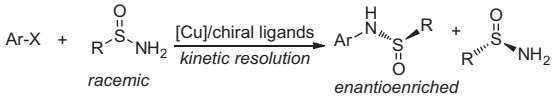


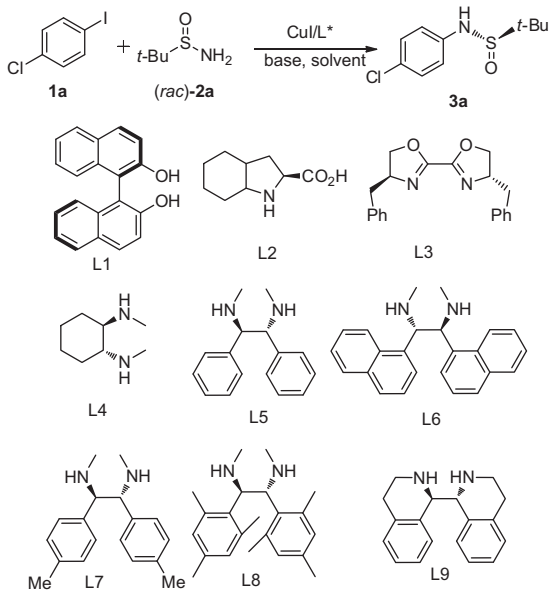
Figure 1. Design of asymmetric C–N coupling reactions for the synthesis of *N*-aryl sulfonamides via kinetic resolution strategy.

6). Similar results were achieved by switching the base from K_3PO_4 to K_2CO_3 or Cs_2CO_3 (Table 1, entries 10 and 11). Further screening of other solvents revealed that a higher yield and better enantioselectivity were obtained in toluene (Table 1, entry 12, 86% yield and 60% ee). It is noticeable that in this study, 3 equiv of racemic **2a** was used, and when only 2 equiv of **2a** was used, an inferior yield and enantioselectivity were observed (Table 1, entry 16), while little influence was observed for the yield and enantioselectivity when more than 3 equiv of racemic **2a** was used.

With the optimized conditions in hand, we further explored the substrate scope for the reactions. As shown in Table 2, a variety of aryl iodides were explored and all delivered the corresponding coupling products in moderate to good yields and moderate ee values. Both electron-donating and withdrawing substituents on the aryl rings were well tolerated. However, the substituents at the *ortho*-position were disfavored for conversion and only low yields were obtained (Table 2, entries 5 and 6). Several other sulfinamides such as i-Pr, *n*-Bu-, and 2-butylphenyl sulfinamides, were also explored and all delivered the corresponding products in moderate yields and moderate enantioselectivities. While the reaction of phenylsulfinamide and 4-chloro-iodo-benzene afforded the desired product **3r** in only 5% ee (Table 2, entry 19). Aryl bromides were also tested in these reactions, however, they were not suitable substrates for this reaction since a much higher reaction temperature was needed for the conversion and only a small amount of the desired products (<10%) were obtained (data not shown). In all these cases, the selective factors are relatively low.[17] For example, in the case of **3l**, the selective factor is only about 4 by calculation, which indicated that more efforts should be put to improve the enantioselectivity for practical use. A simple recrystallization worked well for the improvement of the enantiopurity in this case. The product **3l** was obtained in 50% yield and 92% ee after recrystallization. The absolute configuration of coupling product **3a** was determined as *S* by comparing with the literature reported data.[8b] The absolute configurations of other products were designed by analogue to that of **3a**.

In summary, a copper-catalyzed coupling reaction for the asymmetric synthesis of chiral *N*-aryl sulfinamides was developed through kinetic resolution. The desired coupling products were obtained in high yields and with moderate enantioselectivity. Further endeavors were needed in this field.

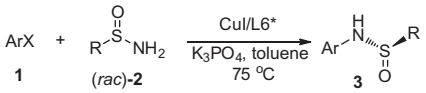
Table 1
Screening of the ligands and reaction conditions[a]



Entry	L*	Base/solvent	Yield (%)[b]	ee (%)[c]
1	L1	K_3PO_4/1,4-dioxane	<10	10
2	L2	K_3PO_4/1,4-dioxane	<10	rac
3	L3	K_3PO_4/1,4-dioxane	<10	16
4	L4	K_3PO_4/1,4-dioxane	79	30
5	L5	K_3PO_4/1,4-dioxane	70	24
6	L6	K_3PO_4/1,4-dioxane	82	56
7	L7	K_3PO_4/1,4-dioxane	72	25
8	L8	K_3PO_4/1,4-dioxane	<10	9
9	L9	K_3PO_4/1,4-dioxane	15	13
10	L6	K_2CO_3/1,4-dioxane	43	50
11	L6	Cs_2CO_3/1,4-dioxane	82	52
12	L6	K_3PO_4/acetone	76	40
13	L6	K_3PO_4/MeCN	82	34
14	L6	K_3PO_4/THF	80	48
15	L6	K_3PO_4/toluene	86	60
16	L6	K_3PO_4/toluene	60	45[d]

[a] *Reagents and reaction conditions:* **1a** (0.2 mmol), **2a** (0.6 mmol, 3.0 equiv), CuI (0.02 mmol, 10 mol %), ligand (0.03 mmol, 15 mol%), base (0.4 mmol), 75 °C, 24 h.
[b] Isolated yields.
[c] Determined by HPLC analysis.
[d] **2a** (0.4 mmol, 2.0 equiv) was used.

Table 2
Substrate scope[a]



Entry	ArI	R	Product	Yield (%)[b]	ee (%)[c]
1	4-ClC_6H_4I	*t*-Butyl	**3a**	86	60
2	PhI	*t*-Butyl	**3b**	86	55
3	4-FC_6H_4I	*t*-Butyl	**3c**	87	52
4	4-MeC_6H_4I	*t*-Butyl	**3d**	85	53
5	2-MeC_6H_4I	*t*-Butyl	**3e**	54	36
6	2-$^{i}PrC_6H_4I$	*t*-Butyl	**3f**	34	31
7	3,5-dimethyl C_6H_3I	*t*-Butyl	**3g**	74	57
8	3-$MeOC_6H_4I$	*t*-Butyl	**3h**	93	53
9	3,5-difluoro C_6H_3I	*t*-Butyl	**3i**	90	49
10	3-CNC_6H_4I	*t*-Butyl	**3j**	95	48
11	3-$CF_3C_6H_4I$	*t*-Butyl	**3k**	92	51
12	4-$CF_3C_6H_4I$	*t*-Butyl	**3l**	95	49
13	4-$CO_2MeC_6H_4I$	*t*-Butyl	**3m**	85	55
14	1-iodonaphthalene	*t*-Butyl	**3n**	57	26
15	2-iodopyridine	*t*-Butyl	**3o**	72	45
16	4-ClC_6H_4I	*i*-Pr	**3p**	60	51
17	4-ClC_6H_4I	*n*-Butyl	**3q**	45	45
18	4-ClC_6H_4I	*ph*	**3r**	40	5
19	4-ClC_6H_4I	*2-t*-Butyl-phenyl	**3s**	37	40

[a] *Reagents and reaction conditions:* **1** (0.2 mmol), 2 (0.6 mmol, 3.0 equiv), CuI (0.02 mmol, 10 mol %), ligand (0.03 mmol, 15 mol %), K_3PO_4 (0.4 mmol), 75 °C, 24 h.
[b] Isolated yields.
[c] Determined by HPLC analysis.

Acknowledgments

The authors are grateful to the National Natural Science Foundation (Grant 21272234, & 21572229) for their financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.04.049.

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