ORGANIC LETTERS

2010
Vol. 12, No. 6
1336−1339

Simple and Versatile Catalytic System for N-Alkylation of Sulfonamides with Various Alcohols

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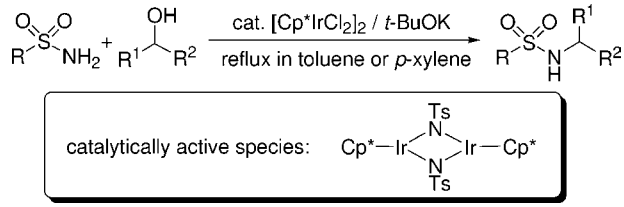
Received January 30, 2010

ABSTRACT



A simple and versatile catalytic system for N-alkylation of sulfonamides with various alcohols based on a catalytic hydrogen transfer reaction has been developed under a low catalyst loading of $[Cp^*IrCl_2]_2$ (0.050−1.5 mol %) in the presence of *t*-BuOK. A variety of N-alkylated sulfonamides were prepared in good to excellent yields. Mechanistic investigations revealed that the key catalytic species in the present system is a sulfonylimido-bridged unsaturated diiridium complex $[(Cp^*Ir)_2(\mu\text{-NTs})_2]$.

Sulfonamides are a highly important class of compounds because of their biological activities such as antibacterial agents, anticancer agents, antiviral drugs, and antiviral HIV protease inhibitors.[1] The synthesis of sulfonamides having a substituent on nitrogen usually has been carried out by the reaction of primary or secondary amines with sulfonyl halides[2] or catalytic cross coupling of sulfonamides with organic halides.[3] Aminosulfonation of hydrocarbons has also been reported very recently.[4] However, these reactions have drawbacks from environmental and atom economical points of view, because they generate equimolar amounts of wasteful byproducts such as hydrogen halides, metal halogen salts, or organic halides.[5]

Meanwhile, much attention has been focused on the catalytic N-alkylation reactions with alcohols as alkylating agents based on hydrogen transfer, using iridium,[6] ruthenium,[7] and other transition metal catalysts.[8] Such methodologies with alcohols are apparently attractive because they do not produce wasteful coproducts (only water is produced as coproduct) and highly atom economical synthesis can be

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(1) (a) Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Med. Chem.* **2003**, *10*, 925, and references cited therein. (b) Drew, J. *Science* **2000**, *287*, 1960. (c) Scozzafava, A.; Supuran, C. T. *J. Med. Chem.* **2000**, *43*, 3677.

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(5) Catalytic hydroamination of alkenes with sulfonamides also affords N-alkylated sulfonamides with high atom economy. However, these reactions give Markovnikov products selectively, and terminally alkylated sulfonamide cannot be obtained. (a) Karshtedt, D.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 12640. (b) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798.

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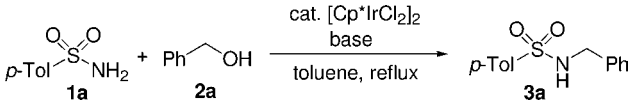
10.1021/ol1002434
Published on Web 02/25/2010

Table 1. Cp*Ir-Catalyzed N-Alkylation of *p*-Toluenesulfonamide (**1a**) with Benzyl Alcohol (**2a**) under Various Conditions[a]



entry	cat. (mol %)	base (mol %)	time (h)	yield (%)[b]
1	0.050	none	17	trace
2	0.050	Li_2CO_3 (1.0)	17	17
3	0.050	Na_2CO_3 (1.0)	17	80
4	0.050	K_2CO_3 (1.0)	17	92
5	0.050	Cs_2CO_3 (1.0)	17	97
6	0.050	MeOK (1.0)	17	99
7	0.050	*t*-BuOK (1.0)	17	100 (95)
8	0.025	*t*-BuOK (1.0)	17	82
9	0.050	*t*-BuOK (1.0)	7	89
10	none	*t*-BuOK (1.0)	17	0

[a] The reaction was carried out with **1a** (2.0 mmol), **2a** (2.2 mmol), $[Cp^*IrCl_2]_2$ (0.050 mol %), and base (1.0 mol %) in toluene (1 mL) under reflux. [b] Determined by ^1H NMR. The value in parentheses is isolated yield.

achieved. To date, several catalytic systems for the N-alkylation of amines, ammonium salts, and carboxamides with alcohols have been reported. In contrast, only a few publications on the catalytic N-alkylation of sulfonamides with alcohols have appeared,[7d,9−11] in spite of the importance of N-alkylated sulfonamides as mentioned above.[12] Moreover, alcohols used in these catalytic systems are almost limited to benzylic and allylic ones. We report here a simple and versatile catalytic system for the N-alkylation of sulfonamides with various alcohols catalyzed by $[Cp^*IrCl_2]_2$/*t*-BuOK, which requires very small amounts of the iridium catalyst (0.050−1.5 mol %). Mechanistic studies of this catalytic system are also demonstrated.

(7) (a) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599, and references cited therein. (b) Hollmann, D.; Tillack, A.; Michalik, D.; Jackstell, R.; Beller, M. *Chem. Asian J.* **2007**, *2*, 403. (c) Tillack, A.; Hollmann, D.; Mevius, K.; Michalik, D.; Bähn, S.; Beller, M. *Eur. J. Org. Chem.* **2008**, 4745. (d) Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766.

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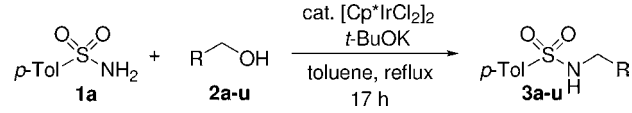
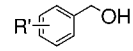
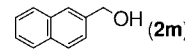
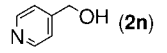
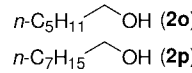
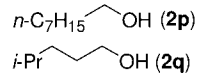
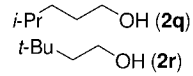
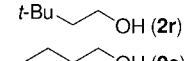
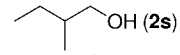
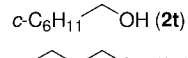
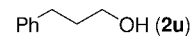
(10) Eisenstein and Crabtree have reported the N-alkylation of *p*-toluenesulfonamide with benzyl alcohol catalyzed by the $[Cp^*IrCl_2]_2/K_2CO_3$ system in their mechanistic study on Cp*Ir-catalyzed N-alkylation of amines (ref 6e). However, only one example was presented for the N-alkylation of sulfonamide, and the yield of the product was moderate (53%) although a relatively large amount of the catalyst (2.5 mol %) was employed.

(11) Some publications on Lewis acid-catalyzed amidation of alcohols with sulfonamides via stabilized carbocation intermediates have also appeared. (a) Terrasson, V.; Marque, S.; Georgy, M.; Campagne, J.-M.; Prim, D. *Adv. Synth. Catal.* **2006**, *348*, 2063. (b) Reddy, C. R.; Madhavi, P. P.; Reddy, A. S. *Tetrahedron Lett.* **2007**, *48*, 7169. (c) Sreedhar, B.; Reddy, P. S.; Reddy, M. A.; Neelima, B.; Arundhathi, R. *Tetrahedron Lett.* **2007**, *48*, 8174. (d) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409.

(12) N-Alkylation of sulfonamides is also important as an alternative to the direct alkylation of ammonia, since N-alkylated sulfonamides can be easily converted to primary amines by deprotection.

Table 2. Cp*Ir-Catalyzed N-Alkylation of *p*-Toluenesulfonamide (**1a**) with Various Primary Alcohols[a]

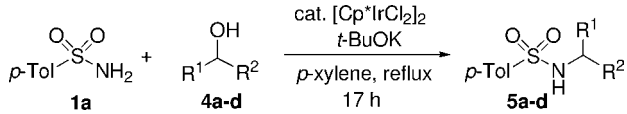


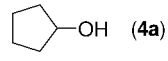
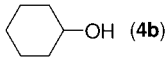
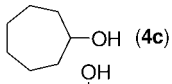
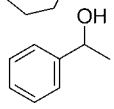
entry	primary alcohol	$[Cp^*IrCl_2]_2$ (mol %)	*t*-BuOK (mol %)	yield (%)[b]
				
1	R' = H (**2a**)	0.050	1.0	95
2	R' = 4-Me (**2b**)	0.050	1.0	95
3	R' = 4-OMe (**2c**)	0.050	1.0	85
4	R' = 4-Ph (**2d**)	0.050	1.0	80
5	R' = 2-Cl (**2e**)	0.050	1.0	82
6	R' = 3-Cl (**2f**)	0.050	1.0	94
7	R' = 4-Cl (**2g**)	0.050	1.0	89
8	R' = 2-Br (**2h**)	0.050	1.0	81
9	R' = 3-Br (**2i**)	0.050	1.0	98
10	R' = 4-Br (**2j**)	0.050	1.0	86
11	R' = 4-CF_3 (**2k**)	0.050	1.0	91
12	R' = 4-CO_2Me (**2l**)	0.25	5.0	91
13	 (**2m**)	0.050	1.0	87
14	 (**2n**)	1.5	30	71
15	 (**2o**)	0.25	5.0	82
16	 (**2p**)	0.25	5.0	92
17	 (**2q**)	0.25	5.0	86
18	 (**2r**)	0.25	5.0	70
19	 (**2s**)	1.0	20	92
20	 (**2t**)	1.0	20	97
21	 (**2u**)	1.0	20	93

[a] The reaction was carried out with **1a** (2.0 mmol), primary alcohol (2.2 mmol), $[Cp^*IrCl_2]_2$ (0.050−1.5 mol %), and *t*-BuOK (1.0 − 30 mol %) in toluene (1 mL) under reflux for 17 h. [b] Isolated yield.

At first, we examined the reaction of *p*-toluenesulfonamide (**1a**) with benzyl alcohol (**2a**) under various conditions. The results are summarized in Table 1. When the reaction of **1a** with **2a** was carried out in the presence of $[Cp^*IrCl_2]_2$ (0.050 mol %) under reflux in toluene for 17 h, only a trace amount of *N*-benzyl-*p*-toluenesulfonamide **3a** was formed (entry 1). The reaction was considerably accelerated by the addition of a base (entries 2−5). When the reactions were carried out in the presence of Na_2CO_3, K_2CO_3, and Cs_2CO_3 (1.0 mol %, respectively), the yields of **3a** were improved up to 80%, 92%, and 97%, respectively (entries 3−5). Stronger base (MeOK and *t*-BuOK) was more effective, giving a quantitative yield of **3a** (entries 6 and 7). With a lower amount of the iridium catalyst (0.025 mol % Ir), **3a** was formed in a lower yield (entry 8). The optimum reaction time was 17 h, since the reaction for 7 h resulted in a slightly lower yield (entry 9). The reaction with *t*-BuOK as a base in the absence of iridium catalyst gave no product (entry 10), indicating that a combination of the iridium catalyst and base is indispensable to afford **3a**.

Table 3. Cp*Ir-Catalyzed N-Alkylation of *p*-Toluenesulfonamide (**1a**) with Secondary Alcohols[a]



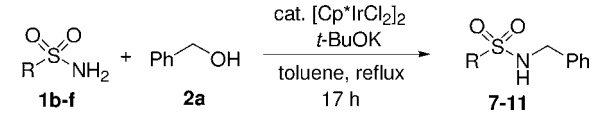
entry	secondary alcohol		$[Cp^*IrCl_2]_2$ (mol %)	*t*-BuOK (mol %)	yield (%)[b]
1		(**4a**)	0.50	10	70
2		(**4b**)	0.50	10	93
3		(**4c**)	0.50	10	72
4		(**4d**)	0.50	10	46

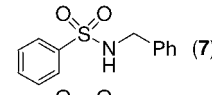
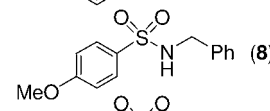
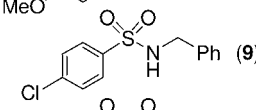
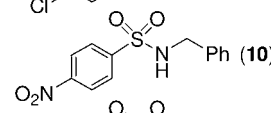
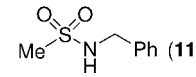
[a] The reaction was carried out with **1a** (1.0 mmol), secondary alcohol (1.5 mmol), $[Cp^*IrCl_2]_2$ (0.50 mol %), and *t*-BuOK (10 mol %) in *p*-xylene (1 mL) under reflux for 17 h. [b] Isolated yield.

The N-alkylation reactions of **1a** with various primary alcohols were conducted under the optimized reaction conditions. The results are summarized in Table 2. The reactions with benzylic alcohols bearing electron-donating (methyl and methoxy groups) and electron-withdrawing substituents (chloro, bromo, trifluoromethyl, and methoxycarbonyl groups) at the aromatic ring proceeded to give the corresponding N-alkylated products in good to excellent yields (entries 2−12). Chloro and bromo substituents were tolerant in this catalytic system, indicating that the N-alkylated *p*-toluenesulfonamides thus produced can be subjected to further transformation such as transition metal-catalyzed coupling reactions (entries 5−10). The reactions of sterically demanding 2-chloro- and 2-bromobenzyl alcohols proceeded smoothly to give the corresponding products in high yields (entries 5 and 8). The N-alkylation with 2-naphthalenemethanol took place in high yield (entry 13). However, the reaction with 4-pyridylmethanol required relatively higher catalyst loading (1.5 mol %) in order to obtain good yield (entry 14), probably due to the coordinating ability of the pyridine ring. The reactions of **1a** with a variety of aliphatic primary alcohols also proceeded to give the corresponding N-alkylated *p*-toluenesulfonamides in good to excellent yields by using $[Cp^*IrCl_2]_2$ (0.25 to 1.0 mol % Ir) and *t*-BuOK (5.0 to 20 mol %) (entries 15−21), demonstrating the versatility of the present catalytic system. In any of the reactions in Table 2, no formation of dialkylated product was observed.

We next investigated the N-alkylation of **1a** with secondary alcohols. The reactions with secondary alcohols were conducted under reflux in *p*-xylene. The results are summarized in Table 3. The reactions with cyclic secondary alcohols using 0.50 mol % of the iridium catalyst and 10 mol % of base gave N-alkylated products in good to high yields (entries 1−3). However, the reaction with 1-phenylethanol resulted in moderate yield of the product (entry 4).

Table 4. Cp*Ir-Catalyzed N-Alkylation of Various Sulfonamides (**1b−f**) with Benzyl Alcohol (**2a**)[a]

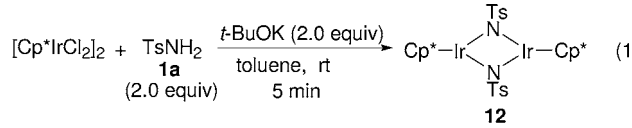


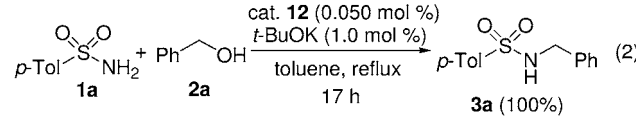
entry	$[Cp^*IrCl_2]_2$ (mol %)	*t*-BuOK (mol %)	product	yield (%)[b]
1	0.050	1.0	 (**7**)	92
2	1.0	20	 (**8**)	83
3	0.050	1.0	 (**9**)	98
4	0.10	2.0	 (**10**)	75
5	1.0	20	 (**11**)	90

[a] The reaction was carried out with **1b−f** (2.0 mmol), **2a** (2.2 mmol), $[Cp^*IrCl_2]_2$ (0.050−1.0 mol %), and *t*-BuOK (1.0−20 mol %) in toluene (1 mL) under reflux for 17 h. [b] Isolated yield.

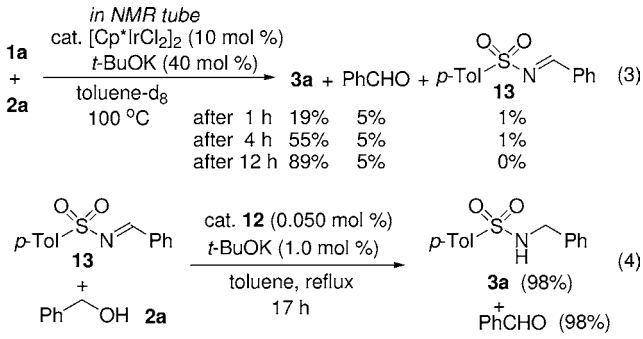
We also examined the reactions of sulfonamides bearing various functional groups on the aromatic ring (Table 4). The reactions of electron-deficient sulfonamides proceeded to give good to excellent yields with a smaller amount of the iridium catalyst (0.050 to 0.10 mol %) (entries 1, 3, and 4), while a higher catalyst loading (1.0 mol %) was necessary in the case of an electron-rich sulfonamide (entry 2). Methanesulfonamide could be also used as a good substrate (entry 5).

To isolate and characterize the catalytically active species, a stoichiometric reaction of the catalyst precursor, $[Cp^*IrCl_2]_2$, with *p*-toluenesulfonamide under basic condition was carried out. When the suspension of $[Cp^*IrCl_2]_2$ (0.5 mmol), **1a** (1.0 mmol), and *t*-BuOK (1.0 mmol) in toluene was stirred at room temperature for 5 min, a dinuclear complex, $[(Cp^*Ir)_2(\mu\text{-}NTs)_2]$ (**12**), having bridging imido ligands was formed quantitatively (eq 1).[13] The complex **12** exhibited high catalytic activity comparable to that of the $[Cp^*IrCl_2]_2$ catalyst for the reaction of **1a** with **2a** (eq 2), suggesting its importance as a catalytically active species.



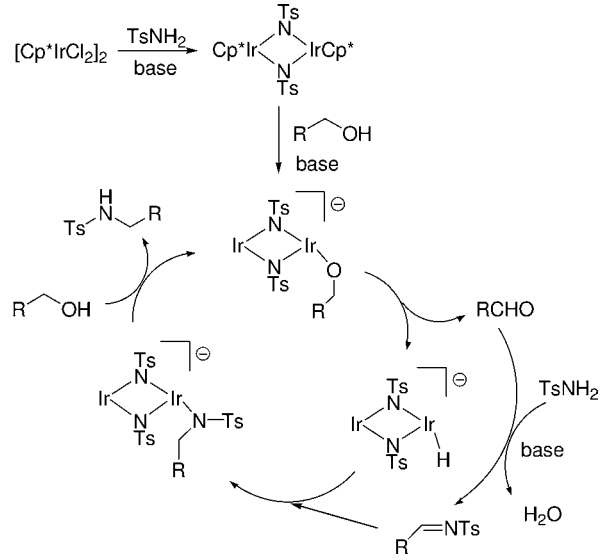


According to our previous studies on the N-alkylation of amines, carbamates, and carboxamides catalyzed by Cp*Ir complexes,[6a−d,g] the mechanism for the present N-alkylation of sulfonamides would be based on a "hydrogen-transfer mechanism", i.e., (1) hydrogen transfer oxidation of an alcohol to an aldehyde, (2) formation of an iminic intermediate by condensation, and (3) transfer hydrogenation of the iminic intermediate with the transient iridium hydride species generated in step 1 to give the product. To confirm the proposed mechanism, the catalytic reaction was monitored by ^{1}H NMR. The reaction of **1a** with **2a** in the presence of $[Cp^*IrCl_2]_2$ (10 mol %) and *t*-BuOK (40 mol %) in toluene-d_8 was conducted in an NMR tube. After the reaction at 100 °C for 1 h, the formation of benzaldehyde (5%) and the iminic intermediate **13** (1%), in addition to the product **3a** (19%), was observed (eq 3), supporting the hydrogen-transfer mechanism. Additionally, the reaction of separately prepared **13** with benzyl alcohol **2a** in the presence of catalytic amounts of **12** and *t*-BuOK gave **3a** (98%) and benzaldehyde (98%) via transfer hydrogenation of the iminic C═N bond, also supporting the hydrogen-transfer mechanism.



On the basis of these experimental results, a possible mechanism for the Cp*Ir-catalyzed N-alkylation of sulfonamides with alcohols is illustrated in Scheme 1. The first step of the reaction would involve the formation of the catalytic species **12**. Then, the hydrogen transfer oxidation of a primary alcohol to an aldehyde would occur through an alkoxo species accompanied by the formation of an iridium hydride species.[14] Next, the condensation of the aldehyde with a sulfonamide would proceed to afford an iminic intermediate.[15] Addition of the iridium hydride to the iminic intermediate followed by the reaction with the alcohol would occur to give the product and regenerate the catalytically active species.

Scheme 1. Plausible Mechanism for the Cp*Ir-Catalyzed N-Alkylation of Sulfonamides with Alcohols



In summary, a simple and versatile catalytic system for N-alkylation of sulfonamides with various alcohols based on hydrogen transfer methodology has been developed. With a low catalyst loading of Cp*Ir complex (0.050−1.5 mol %), a variety of N-alkylated sulfonamides were synthesized in good to high yields. Mechanistic investigations revealed that the key catalytic species in the present system is a sulfonylimido-bridged unsaturated diiridium complex $[(Cp^*Ir)_2(\mu\text{-NTs})_2]$.

Acknowledgment. We thank Johnson Matthey, Inc., for a generous loan of iridium trichloride.

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

OL1002434

(13) Preparation of the complex **12** by the reaction of $[Cp^*IrCl_2]_2$ with **1a** in the presence of base (KOH) has been previously reported by Kuwata and Ikariya. However, catalytic activity of **12** has never been investigated. Ishiwata, K.; Kuwata, S.; Ikariya, T. *Organometallics* **2006**, *25*, 5847.

(14) We have also monitored the stoichiometric reaction of **12** with **2a** in the presence of *t*-BuOK at 100 °C in NMR tube (toluene-d_8), which indicated the formation of benzaldehyde, although the iridium species formed in the reaction has not been characterized yet.

(15) The condensation of an aldehyde and a sulfonamide affording an iminic intermediate was accelerated under basic conditions: The reaction of **1a** with benzaldehyde under toluene reflux for 1 h in the presence of *t*-BuOK (1 mol %) gave the imine **13** in 56% yield, while the reaction in the absence of base resulted in 13% yield.