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Transition-Metal-Free Intermolecular Amination of sp^3 C−H Bonds with Sulfonamides

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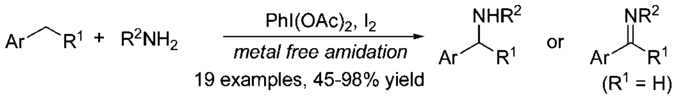
ABSTRACT



R^1 = alkyl, Ph, CH_2Cl, $CH_2CH_2OCOCH_3$, CH_2COOCH_3, $COOCH_3$
R^2 = *p*-$CH_3C_6H_4SO_2$, *p*-$ClC_6H_4SO_2$, $C_6H_5SO_2$, CH_3SO_2, *tert*-BuSO$_2$

An efficient transition-metal-free intermolecular benzylic amidation with sulfonamides is described. Various valuable nitrogen-containing compounds, including amines, *β*-chloro amine, amino alcohol, α-, *β*-amino ester, and *N*-sulfonyl imine, are generated from the preferential N-functionalization of saturated benzylic C−H bonds. The potential of this reaction system also lies in the fact it can be developed into an environmentally friendly intermolecular amidation process.

The selectively direct N-functionalization of saturated hydrocarbons, which provides an appealing way for the synthesis of valuable nitrogen-containing compounds, represents one of the formidable challenges in chemistry.[1,2] Since the seminal work by Breslow and co-workers,[3] transition-metal-catalyzed nitrene insertion into C−H bonds has been well-developed and widely used in organic synthesis.[1,2] In these elegant processes, ligand-bounded transition-metal complexes of rhodium,[4] ruthenium,[5] manganese,[5a,b,6] silver,[7] copper,[8] palladium,[9] cobalt,[10] and iron[11] as catalysts are essential to the C−H amination reactions. The wide distribution of amines in natural products along with their critical industrial application, however, causes intermolecular amination to remain a challenge for organic chemists. On the other hand, soaring environmental awareness demands "green" chemical procedures since the

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Table 1. Conditions Screening for Benzylic Amidation of Ethylbenzene with 4-Methylbenzenesulfonamide

entry	oxidant	additive	condition	**2a** (%)
1[a]		NBS (1 equiv)	$ClCH_2CH_2Cl$	–
2		NIS (1 equiv)	$ClCH_2CH_2Cl$	–
3	$PhI(OCOCF_3)_2$ (1 equiv)	I_2 (1 equiv)	$ClCH_2CH_2Cl$	–
4	PhIO (1 equiv)	I_2 (1 equiv)	$ClCH_2CH_2Cl$	2
5	*t*-BuOOH (1 equiv)	I_2 (1 equiv)	$ClCH_2CH_2Cl$	–
6	*t*-BuOI (1 equiv)		$ClCH_2CH_2Cl$	–
7	$PhI(OAc)_2$ (1 equiv)	I_2 (1 equiv)	*t*-BuOH	3
8	$PhI(OAc)_2$ (1 equiv)	I_2 (1 equiv)	benzene	–
9	$PhI(OAc)_2$ (1 equiv)	I_2 (1 equiv)	EtOAc	8[b]
10	$PhI(OAc)_2$ (1 equiv)	I_2 (1 equiv)	hexane	5
11[c]	$PhI(OAc)_2$ (1 equiv)	I_2 (1 equiv)	neat	14[d]
12	$PhI(OAc)_2$ (2 equiv)	I_2 (1 equiv)	neat	61
13	$PhI(OAc)_2$ (3 equiv)	I_2 (1 equiv)	neat	84
14	$PhI(OAc)_2$ (4 equiv)	I_2 (1 equiv)	neat	83
15	$PhI(OAc)_2$ (3 equiv)	I_2 (0.5 equiv)	neat	95
16	$PhI(OAc)_2$ (3 equiv)	I_2 (0.2 equiv)	neat	75
17	$PhI(OAc)_2$ (3 equiv)	I_2 (0.1 equiv)	neat	71
18	$PhI(OAc)_2$ (3 equiv)	I_2 (0.05 equiv)	neat	63
19	$PhI(OAc)_2$ (3 equiv)	I_2 (1 equiv)	neat, 25 °C	8
20	$PhI(OAc)_2$ (3 equiv)	I_2 (1 equiv)	neat, 75 °C, 24 h	72
21	$PhI(OAc)_2$ (3 equiv)	I_2 (1 equiv)	neat, 16 h ultrasonic,	74
22	$PhI(OAc)_2$ (3 equiv)	I_2 (1 equiv)	neat, *hν*, 14 h	75

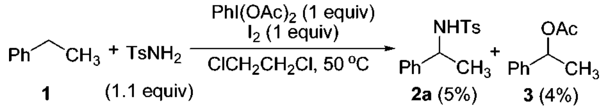
[a] Entries 1–10, ethylbenzene (0.3 mmol), $TsNH_2$ (0.33 mmol), oxidant and additive, solvent (1 mL), 50 °C, 48 h. [b] Entries 1–10, isolated yield based on ethylbenzene. [c] Entries 11–22, ethylbenzene (3 mmol), $TsNH_2$ (0.3 mmol), oxidant and additive, 50 °C, 48 h, unless noted. [d] Entries 11–22, isolated yield based on $TsNH_2$.

transition metals involved in these procedures are generally not environmentally friendly. Hence, the development of a broadly applicable *transition-metal-free* intermolecular amination method for saturated C–H bonds is desirable.

In this communication, we present a direct *transition-metal-free* amination of sp^3 C–H bonds with sulfonamides activated by the combination of iodobenzene diacetate[12] and iodine. Benzylic hydrocarbons are preferentially N-functionalized to afford amines, amino alcohol, α-, and *β*-amino esters. Moreover, *N*-sulfonyl imines are formed when toluene derivatives are used as substrates.

Compared to $ArI{=}NSO_2R$,[4] chloramine-T,[8a,d,13] bromamine-T,[10b,14] tosyloxycarbamates,[15] and azides,[16] unmodified sulfonamides are particularly attractive amidation reagents due to their availability and stability. The combination of $RSO_2NH_2/PhI(OCOR')_2$ has been used to generate $PhI{=}NSO_2R$ in situ for metal-catalyzed nitrene insertion.[4d,f,5,8b,11] Interestingly, in our experiments to develop the synthetic application of sulfonamides in the presence of hypervalent iodine compounds,[17] we observed the formation of an amidation product of ethylbenzene with $TsNH_2/PhI(OAc)_2$ in the presence of I_2 under metal-free conditions, albeit in a low yield (Scheme 1). In the control experiment of ethylbenzene/PhI=NTs with the aid of I_2 under the same conditions, no amidation product was detected.

Scheme 1. Amidation of Ethylbenzene with 4-Methylbenzenesulfonamide



Motivated by the synthetic potential of the possible method, efforts have been made to establish optimized

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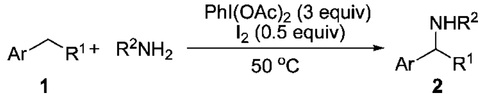
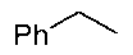
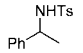
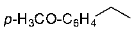
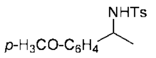
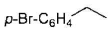
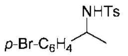
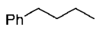
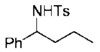
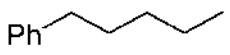
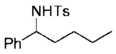
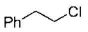
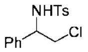
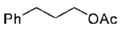
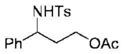
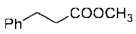
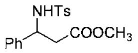
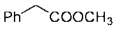
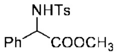
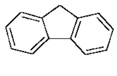
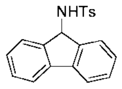
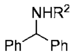
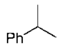
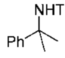
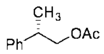
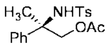
reaction conditions. To inhibit the deleterious acetoxylation, NIS, NBS, $PhI(OCOCF_3)_2$, PhIO, *t*-BuOOH, and *t*-BuOI were used as the replacement; however, inferior results were displayed (Table 1, entries 1−6). Further investigation revealed that the amidation proceeded better under the solvent-free conditions (Table 1, entries 7−11). Increasing the amount of $PhI(OAc)_2$ resulted in higher isolated yields (Table 1, entries 12−14). A catalytic amount of iodine could efficiently promote the amidation reaction: a satisfactory isolated yield (95% yield) was achieved when 0.5 equiv of iodine was utilized (Table 1, entry 15). For the basis of a mechanistic proposal, the role of $PhI(OAc)_2/I_2$ as a radical precursor is widely accepted.[12,18] Amidation reactions proceeded sluggishly at room temperature. Moreover, at higher temperature, photochemical or ultrasonic treatment accelerated the reaction but resulted in complicated reactions and lower isolated yields (Table 1, entries 19−22). In all cases, acetoxylation product **3** was isolated as the major byproduct in yields ranging from 2% to 98%.

The scope and selectivity of the amidation reaction were further investigated with a range of benzylic substrates (Table 2).[19] It was noteworthy that the reactions were highly regioselective with only the benzylic sulfonamides being detected. For most cases, the yields of the resulted nitrogen-containing compounds were comparable to those in transition-metal-catalyzed amidation reactions (Table 2, entries 1−16). Additionally, this iodine-induced amidation reaction could be applied to prepare some valuable functionalized amines. For example, β-chloro amine, amino alcohol, α-, and β-amino esters were generated from the corresponding amidation reactions in moderate yields under varied conditions (Table 2, entries 7−10). In the case of fluorene, a solvent was required to dissolve the reaction mixture. It resulted in a moderate yield of the corresponding product, though fluorene contains more activated benzylic C−H bonds (Table 2, entry 11). Attempts were made to extend the reaction system to other commercially available amides (Table 2, entries 12−16). Nearly quantitative yields were generated for the reactions of diphenylmethane with $TsNH_2$, $p\text{-}ClC_6H_4SO_2NH_2$, $C_6H_5SO_2NH_2$, and $CH_3SO_2NH_2$, while the reaction with *tert*-$BuSO_2NH_2$ gave rise to the corresponding N-substituted amide in 75% yield. When $PhCONH_2$ and $BocNH_2$ were employed, no amidation products were detected from their reactions. Substrates with tertiary benzylic positions

Table 2. Amidation Reaction of Benzylic Substrates with Sulfonamides[a]



entry	substrate	product	yield (%)[b]
1		 **2a**	95
2		 **2b**	88
3		 **2c**	92
4		 **2d**	85
5		 **2e**	78
6	$PhCH_3$	$PhCH_2NHTs$ **2f**	45
7[c]		 **2g**	50
8[d]		 **2h**	48
9[e]		 **2i**	53
10[f]		 **2j**	48
11[g]		 **2k**	56
12		 **2l** $R^2 = Ts$	98
13		**2m** $R^2 = p\text{-}ClC_6H_4SO_2$	97
14		**2n** $R^2 = C_6H_5SO_2$	96
15		**2o** $R^2 = CH_3SO_2$	98
16		**2p** $R^2 =$ *tert*-$BuSO_2$	75
17		 **2q**	0
18		 **2r**	0

[a] Reaction conditions: benzylic substrate (3.0 mmol), $TsNH_2$ (0.3 mmol), $PhI(OAc)_2$ (0.9 mmol), I_2 (0.15 mmol), 50 °C, 48−56 h, unless otherwise noted. [b] Isolated yield based on sulfonamide. [c] $PhI(OAc)_2$ was added in three portions over 3 h. [d] After 48 h, another 3 equiv of $PhI(OAc)_2$ was added. [e] 1 equiv of I_2 was used. [f] 4 equiv of I_2 was used. [g] EtOAc (0.5 mL) was added.

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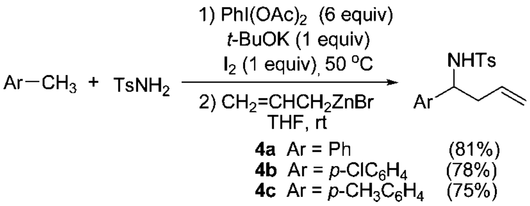
(19) Representative experimental procedure: A test tube with stir bar was charged with $PhI(OAc)_2$ (290 mg, 0.9mmol) and sulfonamide (0.3 mmol). The tube was evacuated and back-filled with argon. Benzylic substrate (3 mmol) and I_2 (38 mg, 0.15 mmol) were successively added. The reaction mixture was allowed to stir at 50 °C until the sulfonamide disappeared as monitored by TLC. The mixture was quenched with saturated $Na_2S_2O_3$ and extracted by ethyl acetate (25 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel to provide the desired product.

could not be functionalized under the same conditions (Table 2, entries 17 and 18). While hexene and cyclohexane were employed, the reactions were complicated, and no desired amidation products were obtained.

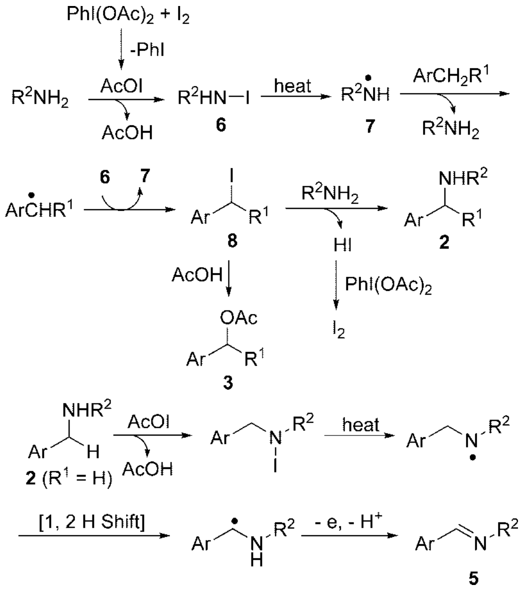
An interesting feature of this iodine-induced activation of sp[3] C−H bonds was observed when toluene derivatives were employed. Besides the formation of the expected benzylic sulfonamides (Table 2, entry 6), aryl sulfonyl imines **5**, presumably generated from the secondary oxidation of the corresponding benzylic sulfonamides,[17a,20] were detected from the reactions. Further investigation revealed that, by increasing the amount of $PhI(OAc)_2$ and I_2, and with the aid of *tert*-BuOK, reactions could afford imines as the major products. To confirm the yields of imines, the resulted crude products were treated with allylzinc bromide to afford the corresponding homoallylamines **4** (Scheme 2).

Scheme 2. Amidation Reactions of Toluene Derivatives with 4-Methylbenzenesulfonamide and the Subsequent Additions with Allylzinc Bromide



A tentative mechanism for the $PhI(OAc)_2/I_2$-mediated amidation reactions is shown in Scheme 3. Sulfonamidyl radicals, which are generated from the reactions of sulfonamides with acetyl hypoiodite, are proposed as the reactive intermediates.[17a,18]

Scheme 3. Tentative Mechanism for the $PhI(OAc)_2/I_2$-Mediated Amidation Reactions



In conclusion, our preliminary results of *transition-metal-free* amidation of benzylic C−H bonds with sulfonamides demonstrate that it is an efficient method to produce various amines with moderate to excellent yields. Besides optimization for a “greener” procedure, currently dedication has also been made to extend its scope and to explore its reaction mechanism and possible synthetic applications.

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Supporting Information Available: Experimental details and spectral data for the major products. This material is available free of charge via the Internet at http://pubs.acs.org.

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