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Selective Benzylic and Allylic Alkylation of Protic Nucleophiles with Sulfonamides through Double Lewis Acid Catalyzed Cleavage of sp^3 Carbon–Nitrogen Bonds

Cong-Rong Liu, Man-Bo Li, Cui-Feng Yang, and Shi-Kai Tian*[a]

Abstract: The acid-catalyzed benzylic and allylic alkylation of protic nucleophiles is fundamentally important for the formation of carbon–carbon and carbon–heteroatom bonds, and it is a formidable challenge for benzylic and allylic amine derivatives to be used as the alkylating agents. Herein we report a highly efficient benzylic and allylic alkylation of protic carbon and sulfur nucleophiles with sulfonamides through double Lewis acid catalyzed cleavage of sp^3 carbon–nitrogen bonds at room temperature. In the presence of a catalytic amount of inexpensive $ZnCl_2$-TMSCl (TMSCl: chlorotrimethylsilane), 1,3-diketones, β-keto esters, β-keto amides, malononitrile, aromatic compounds, thiols, and thioacetic acid can couple with a broad range of tosyl-activated benzylic and allylic amines to give diversely functionalized products in good to excellent yields and with high regioselectivity. Furthermore, the cross-coupling reaction of 1,3-dicarbonyl compounds with benzylic propargylic amine derivatives has been successfully applied to the one-step synthesis of polysubstituted furans and benzofurans.

Keywords: allylic compounds · benzylic compounds · carbon nucleophiles · oxygen heterocycles · sulfur

Introduction

The benzylic and allylic alkylation of protic nucleophiles is fundamentally important for the formation of carbon–carbon and carbon–heteroatom bonds, and benzylic and allylic halides and the corresponding sulfonates are frequently employed as the alkylating agents. In general, at least stoichiometric amounts of bases are needed to activate protic nucleophiles, such as active methylene compounds, alcohols and thiols, to facilitate the corresponding alkylating reactions. Alternatively, the alkylation of protic nucleophiles can be catalyzed by Lewis or Brønsted acids, owing to the ready cleavage of benzylic and allylic sp^3 carbon-halogen and sp^3 carbon-oxygen bonds under acidic conditions,[1] and the scope of protic nucleophiles for the acid-catalyzed alkylation has been successfully extended to aromatic compounds. Nevertheless, the use of benzylic and allylic halides and the corresponding sulfonates as alkylating agents in the reaction results in the formation of hydrogen halides and sulfonic acids, the strong acidity of which may lead to undesired side reactions. One of the promising approaches to avoid this problem is to explore benzylic and allylic amines or their derivatives as alkylating agents, which can completely shut down the formation of acidic by-products. However, it remains a formidable challenge for benzylic and allylic amines and their derivatives to be coupled with protic nucleophiles through catalytic cleavage of sp^3 carbon–nitrogen bonds under acidic conditions.[2]

Although benzylic amine derivatives have been reported to undergo Friedel–Crafts alkylation of aromatic compounds, such an alkylation is restricted by the use of highly activated substrates, a large excess of acids and/or elevated temperature, and at times the formation of a multitude of products.[3] Furthermore, the reaction conditions have not been extended to the benzylic and allylic alkylation of other important protic nucleophiles, such as active methylene compounds, thiols, and thioacids. To explore benzylic and allylic amines as useful alkylating agents, we planned to activate the amino groups with appropriate electron-withdrawing groups (EWG) and Lewis acids (LA) to facilitate the cleavage of benzylic and allylic sp^3 carbon–nitrogen bonds (Scheme 1). The cross-coupling reaction of benzylic and allylic amine derivatives with protic nucleophiles (Nu–H) results in the formation of ammonia derivatives, $H_2N(EWG)$,

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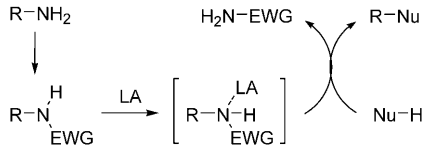


Scheme 1. Double activation of amino groups with EWG and LA.

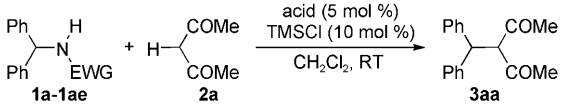
which do not exhibit strong acidity and therefore avoid considerable side reactions. Herein we report a highly efficient benzylic and allylic alkylation of various protic nucleophiles with sulfonamides through double Lewis acid catalyzed cleavage of sp^3 carbon–nitrogen bonds at room temperature and its application to the one-step synthesis of polysubstituted furans and benzofurans.

Results and Discussion

As a strong electron-withdrawing group that can be introduced easily from *p*-tosyl chloride, the tosyl group was first selected to activate the amino group. In the model reaction of *N*-tosyl benzhydrylamine (**1a**) with acetyl acetone (**2a**) a number of inexpensive Lewis and Brønsted acids (5 mol%), shown in Table 1, were examined at room temperature, but none of them showed significant catalytic activity. Gratifyingly, the catalytic activity of some of the Lewis and Brønsted acids were dramatically enhanced by the incorporation of chlorotrimethylsilane (TMSCl),[4,5] which when used alone failed to catalyze the reaction. $ZnCl_2$-TMSCl was identified as the catalyst system of choice judging by the yield and reaction time. In the presence of 5 mol% of $ZnCl_2$ and 10 mol% of TMSCl the reaction proceeded cleanly to give substituted 1,3-diketone **3aa** in 99% yield, and no intermediate was observed by ^{1}H NMR analysis of the reaction mixture (Table 1, entry 14). It should be noted that the replacement of the tosyl group in substrate **1a** with less electron-withdrawing groups such as SOPh, $PO(OPh)_2$, COPh and Cbz could not activate the amino group efficiently and therefore resulted in formation of product **3aa** in much lower yields (Table 1, entries 15–18).

A broad range of tosyl-activated benzylic and allylic amines were examined in the $ZnCl_2$-TMSCl-catalyzed alkylation of acetyl acetone (**2a**) at room temperature (Table 2). The cross-coupling reaction of tosyl-activated benzylic amines, bearing either electron-donating groups or electron-withdrawing groups on their aromatic rings, with acetyl acetone (**2a**) proceeded smoothly to give the corresponding substituted 1,3-diketones in good to excellent yields (Table 2, entries 1–8). With regard to the allylic alkylation of acetyl acetone (**2a**), tosyl-activated acyclic and cyclic allylic amines were found to serve as suitable substrates (Table 2, entries 9–13). As demonstrated by the lack of any isomeric products generated from the reaction with unsymmetric allylic amine derivatives **1j**–**1l** (Table 2, entries 10–12),[6] the attack of acetyl acetone (**2a**) to these amine derivatives took place only at the allylic positions in order to maintain a

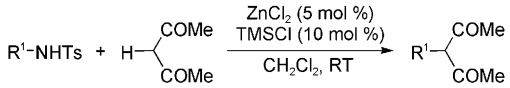
Table 1. Survey of catalysts and activating groups.[a]

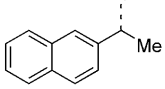
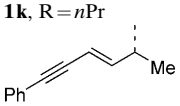
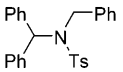


	1a–**1ae** EWG	Acid	*t* [h]	Yield [%][b]
1	**1a**, Ts	H_2SO_4	24	56
2	**1a**, Ts	TsOH	24	<5
3	**1a**, Ts	CF_3SO_3H	24	<5
4	**1a**, Ts	$AlCl_3$	24	<5
5	**1a**, Ts	$FeCl_3$	24	18
6	**1a**, Ts	$Fe_2(SO_4)_3{\cdot}5H_2O$	24	63
7	**1a**, Ts	$Fe(NO_3)_3{\cdot}9H_2O$	24	59
8	**1a**, Ts	$BiCl_3$	24	80
9	**1a**, Ts	$Bi_2(SO_4)_3$	24	60
10	**1a**, Ts	$SnCl_4{\cdot}5H_2O$	24	88
11	**1a**, Ts	$CuCl_2{\cdot}2H_2O$	24	<5
12	**1a**, Ts	$FeSO_4{\cdot}7H_2O$	24	9
13	**1a**, Ts	$FeCl_2{\cdot}4H_2O$	24	7
14	**1a**, Ts	$ZnCl_2$	4.5	99
15	**1ab**, SOPh	$ZnCl_2$	48	69
16	**1ac**, $PO(OPh)_2$	$ZnCl_2$	48	42
17	**1ad**, COPh	$ZnCl_2$	24	70
18	**1ae**, Cbz	$ZnCl_2$	24	<5

[a] Reaction conditions: **1a**–**1ae** (0.50 mmol), **2a** (1.2 equiv), acid (5 mol%), TMSCl (10 mol%), CH_2Cl_2 (0.50 mL), RT. [b] Isolated yield. Ts = *p*-toluenesulfonyl. Cbz = benzyloxycarbonyl.

Table 2. Catalytic alkylation of acetyl acetone with sulfonamides.[a]



	1, R^1	Product	*t* [h]	Yield [%][b]
1	**1a**, R = Ph	**3aa**	4.5	99
2	**1b**, R = PMP	**3ba**	1	98
3	**1c**, R = 4-ClC_6H_4	**3ca**	6	89
4	**1d**, R = Ph	**3da**	9	95
5	**1e**, R = PMP	**3ea**	8	96
6[c]	**1f**, R = 4-ClC_6H_4	**3fa**	30	85
7	**1g**, 	**3ga**	7	90
8	**1h**, 	**3ha**	24	73
9	**1i**, R = Ph	**3ia**	5	90
10	**1j**, R = Me	**3ja**	4	86
11	**1k**, R = *n*Pr	**3ka**	4	70
12	**1l**, 	**3la**	25	77
13	**1m**, 	**3ma**	7	91
14	**1af** = 	**3aa**	3	98

[a] Reaction conditions: **1** (0.50 mmol), **2a** (1.2 equiv), $ZnCl_2$ (5 mol%), TMSCl (10 mol%), CH_2Cl_2 (0.50 mL), RT. [b] Isolated yield. [c] 10 mol% of $ZnCl_2$ and 100 mol% of TMSCl were used. PMP = 4-methoxyphenyl.

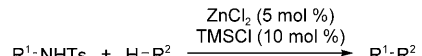
maximum degree of conjugation. Furthermore, excellent selectivity was observed in the application of tosyl-activated secondary amines as benzylic and allylic alkylating agents. For example, secondary amine derivative **1af** could donate its benzhydryl group exclusively to acetyl acetone (**2a**) in the presence of the $ZnCl_2$-TMSCl catalyst system (Table 2, entry 14).

The cross-coupling reaction of optically active sulfonamide (*R*)-**1e** (95% *ee*) with acetyl acetone (**2a**) was carried out to afford product **3ea** in nearly racemic form (Table 2, entry 5). This result suggests that a carbocation intermediate is generated from the sulfonamide and then couples with the nucleophile. Nevertheless, the observed racemization can also be ascribed, in part, to the reversible cleavage of sp^3 carbon–nitrogen bonds under the reaction conditions. When treated with 5 mol% of $ZnCl_2$ and 10 mol% of TMSCl, sulfonamide (*R*)-**1e** underwent racemization smoothly at room temperature and its optical purity decreased from 95% to 11% in 24 h.

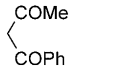
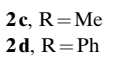
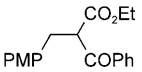
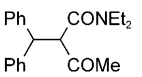
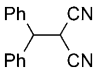
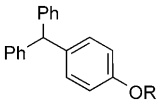
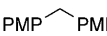
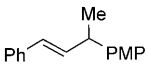
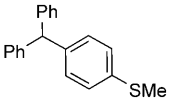
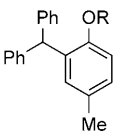
The scope of protic carbon nucleophiles is very general in the cross-coupling reaction with tosyl-activated benzylic and allylic amines (Table 3). As indicated by reaction time, yield and the amount of catalyst, 1,3-diketones and β-keto esters showed better reactivity than β-keto amides and malononitrile in the benzylic alkylation of active methylene compounds with tosyl-activated amines (Table 3, entries 1–6). Appropriately activated arenes could undergo Friedel–Crafts alkylation with tosyl-activated benzylic and allylic amines to give the corresponding products in very good to excellent yields[7] and with greater than 20:1 regioselectivity (Table 3, entries 7–14).[6] Owing to their electron-donating nature, hydroxy, methoxy, and methylmercapto not only activate arenes in the Friedel–Crafts reaction, but also dominate the regioselectivity thereof. As expected, the *para*-position of aromatic ring in the nucleophile, if available, was alkylated predominantly by a tosyl-activated amine. Alternatively, the *ortho*-position was the choice if the *para*-position was occupied previously by another group.

The cross-coupling reaction of 1,3-dicarbonyl compounds with benzylic propargylic amine derivatives was successfully applied to the synthesis of tetrasubstituted furans,[8] which are key moieties in many natural products and pharmaceuticals.[9] The $ZnCl_2$-TMSCl-catalyzed cross-coupling reaction of acetyl acetone (**2a**) with sulfonamide **1n** proceeded smoothly at room temperature to give β-alkynyl diketone **3na**, which was subsequently converted to tetrasubstituted furan **4na** through cycloisomerization in the presence of 10 mol% of $ZnCl_2$ and 50 mol% of TMSCl at 70°C (Scheme 2).[10] Tentatively, the intramolecular nucleophilic attack of the enolic form of 1,3-dicarbonyl group to carbon–carbon triple bond (5-exo-dig cyclization), which is activated by a Lewis acid (LA, $ZnCl_2$-TMSCl) through π-coordination (**A**), followed by the loss of proton to generate cyclic intermediate **B**. Protonolysis of intermediate **B** regenerates the Lewis acid catalyst and at the same time releases intermediate **C**, which subsequently undergoes the acid-catalyzed aromatization to give the final product **4na**.

Table 3. Catalytic alkylation of protic carbon nucleophiles with sulfonamides.[a]



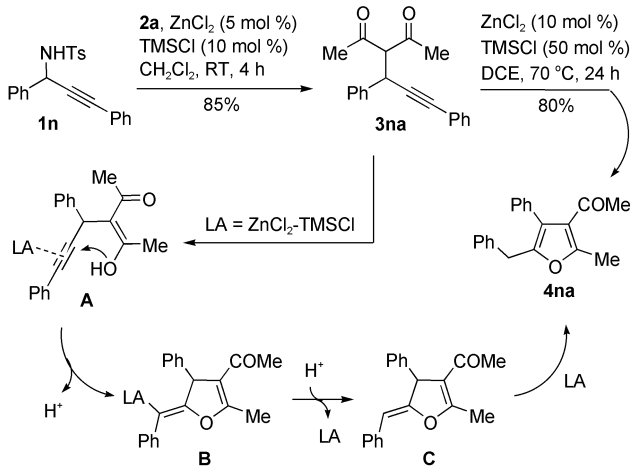
R¹-NHTs (**1**) + H–R² (**2**) → R¹-R² (**3**)

	1	**2**	Product, **3**		*t* [h]	Yield [%][b]
1	**1a**	**2b**,		**3ab**	1	96
2	**1a**	**2c**, R = Me		**3ac**	2	94
3	**1a**	**2d**, R = Ph		**3ad**	5	91
4	**1h**	**2d**		**3hd**	9	88
5[c]	**1a**	**2e**,		**3ae**	48	62
6	**1a**	**2f**, $(NC)_2CH$		**3af**	24	80
7	**1a**	**2g**, R = H		**3ag**	0.5	80
8	**1a**	**2h**, R = Me		**3ah**	1	92
9	**1h**	**2h**		**3hh**	3	89
10	**1j**	**2h**		**3jh**	1.5	91
11	**1af**	**2h**		**3ah**	1	93
12	**1a**	**2i**, PhSMe		**3ai**	20	82
13	**1a**	**2j**, R = H		**3aj**	0.5	82
14	**1a**	**2k**, R = Me		**3ak**	1	90

[a] Reaction conditions: **1** (0.50 mmol), **2** (1.2 equiv), $ZnCl_2$ (5 mol%), TMSCl (10 mol%), CH_2Cl_2 (0.50 mL), RT. [b] Isolated yield. [c] 10 mol% of $ZnCl_2$ and 50 mol% of TMSCl were used.

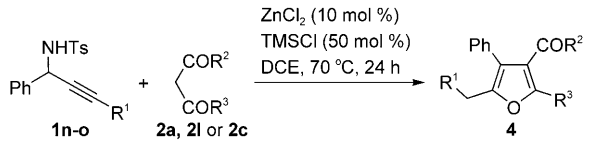
More excitingly, the direct treatment of sulfonamide **1n** and acetyl acetone (**2a**) with 10 mol% of $ZnCl_2$ and 50 mol% of TMSCl at 70°C resulted in formation of tetrasubstituted furan **4na** in good yield (Table 4, entry 1). Furthermore, this one-step procedure for the cross-coupling reaction of 1,3-dicarbonyl compounds with benzylic propargylic amine derivatives has proved to be useful for the construction of several other tetrasubstituted furans (Table 4, entries 2–4).

Similarly, the cross-coupling reaction of *para*-substituted phenols with benzylic propargylic amine derivatives was successfully applied to the one-step synthesis of polysubstituted benzofurans, such as compound **4nj** (Scheme 3). As indicated by the appearance of intermediate **3nj** at an early stage

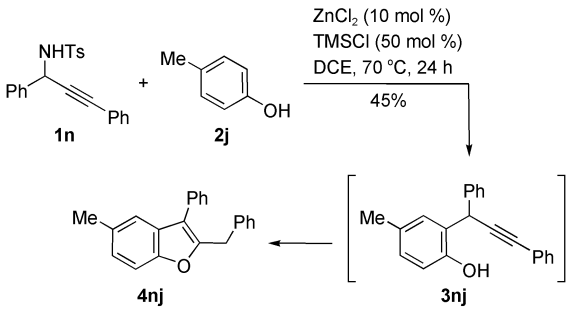


Scheme 2. Cycloisomerization of β-alkynyl diketone **3na** to generate furan **4na**.

Table 4. One-step synthesis of tetrasubstituted furans.



	1, R^1	**2**, R^2, R^3	**4**	Isolated Yield [%]
1	**1n**, Ph	**2a**, Me, Me	**4na**	65
2	**1n**	**2l**, Ph, Ph	**4nl**	63
3	**1n**	**2c**, OEt, Me	**4nc**	47
4	**1o**, *n*Bu	**2a**	**4oa**	61

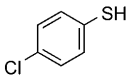
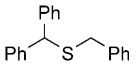
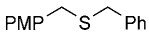
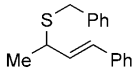
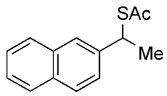
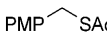
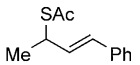
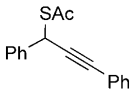


Scheme 3. One-step synthesis of benzofuran **4nj**.

of the reaction, benzofuran **4nj** should be formed in a reaction pathway that is analogous to that for tetrasubstituted furans.[11]

To expand the scope of protic nucleophiles, we found that mercapto-substituted arenes were also able to couple with tosyl-activated benzylic and allylic amines, but the reaction gave the corresponding thioethers instead of *C*-alkylation products. For example, the cross-coupling reaction of *N*-tosyl benzhydrylamine (**1a**) with 2-methylthiophenol (**5a**) in the presence of 5 mol% of $ZnCl_2$ and 10 mol% of TMSCl proceeded smoothly at room temperature to give thioether **6a** in 99% yield (Table 5, entry 1). Likewise, thioether **6b** was obtained from the reaction of 4-chlorothiophenol (**5b**) with *N*-tosyl benzhydrylamine (**1a**) in excellent yield (Table 5, entry 2). The overwhelming selectivity of *S*-alkylation over *C*-alkylation in the reaction of mercapto-substituted arenes with sulfonamides prompted us to investigate more protic sulfur nucleophiles to synthesize diverse sulfur-containing compounds. As expected, aliphatic thiols were found to serve as excellent substrates in the cross-coupling reaction with tosyl-activated benzylic and allylic amines (Table 5, entries 3–6). Further investigation showed that readily available thioacetic acid reacted well with a range of tosyl-activated benzylic and allylic amines to afford the corresponding thioesters in good to excellent yields (Table 5, entries 7–12).

Table 5. Catalytic alkylation of protic sulfur nucleophiles with sulfonamides.[a]

	1	**5**	Product, **6**		*t* [h]	Yield [%][b]
1	**1a**	**5a**,		**6a**	1	99
2	**1a**	**5b**,		**6b**	1	98
3	**1a**	**5c**, $PhCH_2SH$		**6c**	1	92
4	**1a**	**5d**,		**6d**	1.5	99
5	**1h**	**5c**		**6e**	2	93
6	**1j**	**5c**		**6f**	2	94
7	**1a**	**5e**, AcSH		**6g**	0.5	91
8	**1e**	**5e**		**6h**	2	93
9	**1g**	**5e**		**6i**	1	83
10	**1h**	**5e**		**6j**	2	56
11	**1j**	**5e**		**6k**	0.5	96
12	**1n**	**5e**		**6l**	1	81

[a] Reaction conditions: **1** (0.50 mmol), **5** (1.2 equiv), $ZnCl_2$ (5 mol%), TMSCl (10 mol%), CH_2Cl_2 (0.50 mL), RT. [b] Isolated yield. Ac = acetyl.

Conclusion

We have developed, for the first time, a highly efficient benzylic and allylic alkylation of protic carbon and sulfur nucleophiles with sulfonamides through double Lewis acid catalyzed cleavage of sp^3 carbon–nitrogen bonds at room temperature. In the presence of a catalytic amount of inexpensive $ZnCl_2$-TMSCl, 1,3-diketones, β-keto esters, β-keto amides, malononitrile, aromatic compounds, thiols, and thioacetic acid are able to couple with a broad range of tosyl-activated benzylic and allylic amines to give diversely functionalized products in good to excellent yields and with high regioselectivity. Furthermore, the cross-coupling reaction of 1,3-dicarbonyl compounds with benzylic propargylic amine derivatives has been successfully applied to the one-step synthesis of polysubstituted furans and benzofurans.

Experimental Section

General procedure for the catalytic alkylation of protic nucleophiles with sulfonamides: To a solution of sulfonamide **1** (0.50 mmol) in dichloromethane (0.50 mL) were added protic nucleophile **2** or **5** (0.60 mmol), TMSCl (5.4 mg, 6.3 μL, 0.050 mmol), and $ZnCl_2$ (3.4 mg, 5 mol%). The resulting mixture was stirred at room temperature until no further transformation was observed by using thin layer chromatography (TLC) analysis, and then purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (200:1 to 10:1), to give product **3** or **6** (Tables 2, 3 and 5).

General procedure for the one-step synthesis of tetrasubstituted furans: To a solution of sulfonamide **1n** (or **1o**, 0.50 mmol) in 1,2-dichloroethane (0.50 mL) were added protic carbon nucleophile **2a** (**2c** or **2l**, 0.60 mmol), TMSCl (27.2 mg, 31.5 μL, 0.25 mmol), and $ZnCl_2$ (6.8 mg, 10 mol%). The resulting mixture was stirred at 70 °C for 24 h, cooled to room temperature, and purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (200:1 to 50:1), to give product **4** (Table 4).

Acknowledgement

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[8] For recent reviews, see: a) S. F. Kirsch, *Org. Biomol. Chem.* **2006**, *4*, 2076–2080; b) R. C. D. Brown, *Angew. Chem.* **2005**, *117*, 872–874; *Angew. Chem. Int. Ed.* **2005**, *44*, 850–852.

[9] For a review, see: B. A. Keay, P. W. Dibble in *Comprehensive Heterocyclic Chemistry II*, (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon Press, Oxford, **1996**, *Vol. 2*, pp. 395–436.

[10] Neither $ZnCl_2$ alone nor TMSCl alone was able to catalyze the cycloisomerization of β-alkynyl diketone **3na**.

[11] The treatment of compound **3nj** with 10 mol% of $ZnCl_2$ and 50 mol% of TMSCl at 70 °C resulted in formation of benzofuran **4nj** in 75% yield.

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