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Iron-Catalyzed Ring-Opening Azidation and Allylation of *O*-Heterocycles

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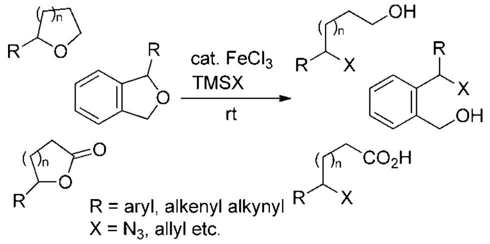
ABSTRACT



We have established the first catalytic C–C and C–N bond formation reactions of *O*-heterocycles (e.g., tetrahydrofuran, phthalane, and lactone derivatives) using iron trichloride as a catalyst in the presence of $TMSN_3$ or allylsilanes accompanied by the ring opening of *O*-heterocycles. The reactions smoothly proceeded at room temperature to give the corresponding primary saturated alcohols from the 2-substituted tetrahydrofurans, *ortho*-substituted benzyl alcohols from phthalanes, and saturated carboxylic acids from lactones in high yields.

The tetrahydrofuran ring represented as *O*-heterocycles can be a useful organic backbone source composed of four carbons and one oxygen atom, namely the 1-butanol unit, by cleavage of the carbon (C)–oxygen (O) bond of the tetrahydrofuran ring due to the easy availability of various tetrahydrofuran derivatives.[1–5] However, a very small number of carbon and nitrogen (N) atom introduction reactions accompanied by the ring opening (C–O bond cleavage) of tetrahydrofurans have been reported in the literature and required more than a chemical equivalent of Lewis acids and/or harsh reaction conditions [$TiCl_4$ (1.2 equiv) at −78 °C,[6] $Sc(OTf)_3$ (2 equiv) at 100 °C using a microwave apparatus[7]] in the presence of allylslilanes or $TMSN_3$ as a nucleophile. We now report the efficient and mild iron(III) chloride catalyzed C–N and C–C bond formations of tetrahydrofuran derivatives (e.g., 2-aryl,[2] alkenyl,[3] and alkynyl[2] substituents), additionally phthalanes[4] and lactone[5] derivatives associated with the ring-opening reaction. The present method could afford the corresponding highly functionalized alcohols and carboxylic acids at room temperature.

We have recently discovered that Lewis acids, such as the $AuCl_3$ or $FeCl_3$ catalyst, could activate the C–O bond of 2-aryl-2,5-*dihydro*furan substructure-containing substrates to give the ring-opened intermediate, and the subsequent

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(1) Related references are cited in a recent paper; see: Mulvey, R. E.; Blair, V. L.; Clegg, W.; Kennedy, A. R.; Klett, J.; Russo, L. *Nat. Chem.* **2010**, *2*, 588–591.

(2) For preparation of 2-aryl and -alkynyl tetrahydrofurans, see: Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *13*, 4293–4308.

(3) For preparation of 2-alkenyl tetrahydrofurans, see: (a) Jang, Y.-J.; Shih, Y.-K.; Liu, J.-Y.; Kuo, W.-Y.; Yao, C.-F. *Chem.—Eur. J.* **2003**, *9*, 2123–2128. (b) Liu, Z.-Q.; Sun, L.; Wang, J.-G.; Han, J.; Zhao, Y.-K.; Zhou, B. *Org. Lett.* **2009**, *11*, 1437–1439.

(4) For preparation of phthalane derivatives, see: Yoshioka, M.; Osawa, H.; Fukuzawa, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 877.

(5) For preparation of lactone derivatives, see: Dohi, T.; Takenaga, N.; Goto, A.; Maruyama, A.; Kita, Y. *Org. Lett.* **2007**, *9*, 3129–3132.

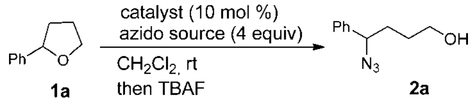
(6) Oku, A.; Homoto, Y.; Harada, T. *Chem. Lett.* **1986**, *15*, 1495–1498.

(7) Qin, H.-L.; Lowe, J. T.; Panek, J. S. *J. Am. Chem. Soc.* **2007**, *129*, 38–39.

10.1021/ol402511r

functionalizations using allylTMS and $TMSN_3$ efficiently provided the corresponding useful unsaturated linear or arene products.[8] Our next challenge was the application of these methodologies to the ring-opening C–C and C–N bond formations using the thermodynamically more stable *tetra*hydrofurans in a catalytic manner. The azidative[9] ring opening of 2-phenyltetrahydrofuran (**1a**) using $TMSN_3$ (4 equiv) was first examined in the presence of 10 mol % of a Lewis acid in CH_2Cl_2 at room temperature (Table 1). $HAuCl_4 \cdot 3H_2O$ and $AuCl_3$ as gold(III) catalysts, which are effective catalysts for the ring opening of dihydrofurans,[8a] effectively promoted the desired azidation within 5 min to give the 4-azido-4-phenylbutan-1-ol (**2a**) in high yields (entries 1 and 2).[10] The use of $(Ph_3P)AuCl/AgSbF_6$ as a Au(I) species, AgOTf, $BF_3 \cdot Et_2O$, TMSOTf, $ZnCl_2$, and $FeCl_2 \cdot 4H_2O$ as Lewis acids, and TFA as a Brønsted acid led to low or no reaction efficiencies (entries 3–9). It is noteworthy that $FeCl_3$ and $FeBr_3$ as cheaper iron(III) catalysts most effectively facilitated the azidative ring-opening reaction to give **2a** in efficient yields (entries 10 and 11). Additionally, the decrement of $FeCl_3$ (5 mol % from 10 mol %) and $TMSN_3$ (1.5 equiv from 4 equiv) could also retain the reaction efficiency to give **2a** in a high yield (entry 12). The reaction using NaN_3 or diphenylphosphoryl azide (DPPA) as an azido source never proceeded (entries 13 and 14), and the use of other solvents (e.g., $CHCl_3$, toluene, dioxane, and THF) was less effective for promoting the present reaction (see Supporting Information).

Table 1. Lewis Acid Catalyzed Azidative Ring Opening of 2-Phenyltetrahydrofuran (**1a**)



entry	catalyst	azido source	time	yield (%)
1	$HAuCl_4 \cdot 3H_2O$	$TMSN_3$	5 min	81
2	$AuCl_3$	$TMSN_3$	5 min	79
3	$(Ph_3P)AuCl/$ $AgSbF_6$	$TMSN_3$	1 h	38
4	AgOTf	$TMSN_3$	24 h	NR
5	$BF_3 \cdot Et_2O$	$TMSN_3$	24 h	trace
6	TMSOTf	$TMSN_3$	24 h	trace
7	$ZnCl_2$	$TMSN_3$	24 h	68
8	$FeCl_2 \cdot 4H_2O$	$TMSN_3$	24 h	53
9	TFA	$TMSN_3$	24 h	trace
10	$FeCl_3$	$TMSN_3$	5 min	87
11	$FeBr_3$	$TMSN_3$	5 min	88
12[a,b]	$FeCl_3$	$TMSN_3$	15 min	85
13	$FeCl_3$	NaN_3	24 h	NR
14	$FeCl_3$	DPPA	24 h	NR

[a] 5 mol % of $FeCl_3$ and 1.5 equiv of $TMSN_3$ were used. [b] Reactions in other solvents (e.g., $CHCl_3$, toluene, dioxane, THF) gave inefficient results (see Supporting Information).

The $FeCl_3$-catalyzed ring-opening azidation could be adapted to various substrates (Table 2).[11] While the 2-aryltetrahydrofurans (**1b**–**d**) bearing electron-donating and -withdrawing groups on the aromatic ring efficiently underwent the azidative ring-opening reaction to give the 4-azidated linear primary alcohols at room temperature (**2b**–**d**) (Table 2, entries 1–3), the 2-alkylated tetrahydrofuran (**1e**) never reacted with $TMSN_3$ even under higher temperature conditions (entry 4).[12] The 2,2-disubstituted tetrahydrofuran (**1f**) was also transformed into the tertiary azido product (**2f**) regardless of the bulkiness of the substrate (entry 5). Furthermore, the 2-alkenyl and alkynyl tetrahydrofurans (**1g**–**i**) efficiently and regioselectively underwent the azidative ring opening at the 2 position to give the corresponding allylic and propargyl azides (**2g** and **2i**) (entries 6–8). It is noteworthy that the mixture of *E*- and *Z*-alkenyl tetrahydrofurans (**1h**) was completely transformed into the corresponding *E*-alkenyl azide (**2g**) (entry 7).[13] The present method was applicable to the azidative ring opening of 2-phenyl tetrahydropyran (**1j**) by the addition of TMSCl as a co-Lewis acid (entry 9).[14] The reaction using 1,4-epoxytetrahydronaphthalene (**1k**) as a substrate allowed the double azidation at the 1 and 4 positions to give the 1,4-diazido product (**2k**) in high yield (entry 10).[15] Furthermore, the present reactions could be adapted for the azidation of the phthalane and lactone derivatives (entries 11–14). 1-Phenyl and alkenyl phthalanes (**1l** and **1m**) were efficiently transformed into *ortho*-substituted benzylalcohols (**2l** and the

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(8) (a) Sawama, Y.; Sawama, Y.; Krause, N. *Org. Lett.* **2009**, *11*, 5034–5037. (b) Sawama, Y.; Kawamoto, K.; Satake, H.; Krause, N.; Kita, Y. *Synlett* **2010**, *14*, 2151–2155. (c) Sawama, Y.; Shishido, Y.; Yanase, T.; Kawamoto, K.; Goto, R.; Monguchi, Y.; Kita, Y.; Sajiki, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 1515–1519. (d) Sawama, Y.; Ogata, Y.; Kawamoto, K.; Satake, H.; Shibata, K.; Monguchi, Y.; Sajiki, H.; Kita, Y. *Adv. Synth. Catal.* **2013**, *355*, 517–528.

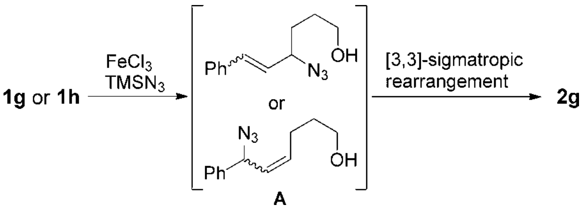
(9) An azide is easily transformed into a triazole by the Huisgen reaction and amine by reduction, etc.; see: (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565–598. (b) Rostovsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (c) Scriven, E. F. V. *Chem. Rev.* **1988**, *88*, 297–368.

(10) While the mixture of 4-azido-4-phenylbutan-1-ol (**2a**) and its TMS ether was obtained during the reaction process, only **2a** was isolated after the deprotection of the TMS group of the TMS ether using TBAF. Alternatively, the quench using 1 M HCl aq. instead of TBAF gave a similar yield.

(11) The usage of $FeCl_3$ and $TMSN_3$ or allylsilanes was optimized for each reaction.

(12) The ring-opening azidation of methyl tetrahydrofuran-2-carboxylate and 4-(2-tetrahydrofuryl)acetophenone also gave no ring-opened products.

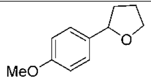
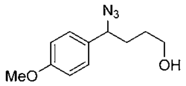
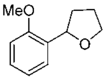
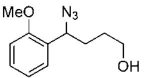
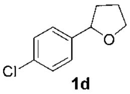
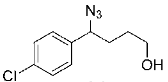
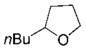
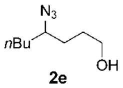
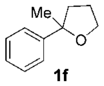
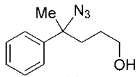
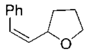
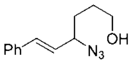
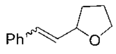
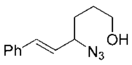
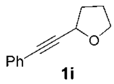
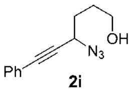
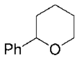
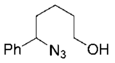
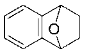
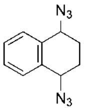
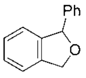
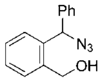
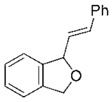
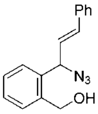
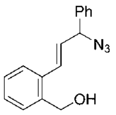
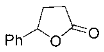
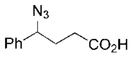
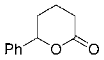
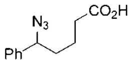
(13) The azidation of **1g** and **1h** could proceed via various intermediates (**A**), which undergo [3,3]-sigmatropic rearrangements of allylic azide moieties to provide only thermodynamically stable **2g**. See the related papers: (a) Lauzon, S.; Tremblay, F.; Gagnon, D.; Godbout, C.; Chabot, C.; Mercier-Shanks, C.; Perreault, S.; DeSève, H.; Spino, C. *J. Org. Chem.* **2008**, *73*, 6239–6250. (b) Craig, D.; Harvey, J. W.; O'Brien, A. G.; White, A. J. P. *Org. Biomol. Chem.* **2011**, *9*, 7057–7061.



(14) TMS halides, such as TMSCl, were reported to activate the Lewis acid such as $InCl_3$; see: Onishi, Y.; Nishimoto, Y.; Yasuda, M.; Baba, A. *Org. Lett.* **2011**, *13*, 2762–2765. In addition, we also discovered that the $AuCl_3$– or $FeCl_3$–TMSCl combination is effective for the ring opening of 1,4-epoxy-1,4-dihydronaphthalenes. See refs 8b and 8c.

Table 2. Scope and Limitation of Ring-Opening Azidation

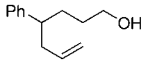
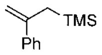
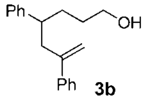
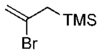
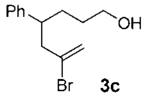
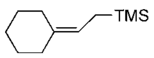
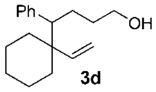
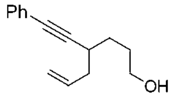
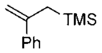
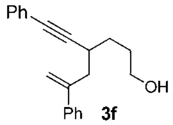
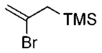
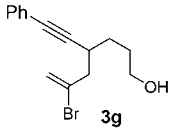
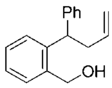
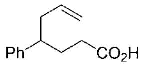
substratre **1** $\xrightarrow[\text{CH}_2\text{Cl}_2\text{, rt then TBAF}]{\text{FeCl}_3\text{,TMSN}_3}$ product **2**

entry	substrate (**1**)	product (**2**)	time (h)	yield (%)
1[a]	 **1b**	 **2b**	0.5	81
2[b]	 **1c**	 **2c**	1	83
3[b]	 **1d**	 **2d**	3	95
4[b]	 **1e**	 **2e**	24	NR
5[b]	 **1f**	 **2f**	6	78
6[b]	 **1g**	 **2g**	6	96
7[b]	 **1h**	 **2g**	6	84
8[c]	 **1i**	 **2i**	3	82
9[d]	 **1j**	 **2j**	6	67
10[c]	 **1k**	 **2k**	2.5	82 (dr = 1 : 1)
11[f]	 **1l**	 **2l**	12	72
12[b]	 **1m**	 **2ma** +  **2mb**	5	70 (2 : 3)
13[g,h]	 **1n**	 **2n**	3	75
14[h]	 **1o**	 **2o**	3	90

[a] $FeCl_3$ (5 mol %) and $TMSN_3$ (1.5 equiv) were used. [b] $FeCl_3$ (5 mol %) and $TMSN_3$ (2 equiv) were used. [c] $FeBr_3$ (10 mol %) and $TMSN_3$ (3 equiv) were used at 0 °C. [d] $FeCl_3$ (10 mol %), $TMSN_3$ (3 equiv), and TMSCl (20 mol %) were used. [e] $FeCl_3$ (10 mol %) and $TMSN_3$ (2 equiv) were used at −40 °C to rt. [f] $FeCl_3$ (10 mol %) and $TMSN_3$ (3 equiv) were used. [g] $FeCl_3$ (1.1 equiv) and $TMSN_3$ (3 equiv) were used. [h] The quench using TBAF was not necessary.

Table 3. Allylative Ring Opening

substratre **1** $\xrightarrow[\text{CH}_2\text{Cl}_2\text{, rt then TBAF}]{\text{FeCl}_3\text{, allysilane}}$ product **3**

entry	allylsilane	product	time (h)	yield (%)
*Ring-opening of **1a***				
1[a]	allylTMS	 **3a**	10	93
2[b]		 **3b**	3	94
3[b]		 **3c**	3	68
4[c]		 **3d**	1	68
*Ring-opening of **1i***				
5[d]	allylTMS	 **3e**	10	66
6[e]		 **3f**	1	90
7[f]		 **3g**	1	62
*Ring-opening of **1l***				
8[g]	allylTMS	 **3h**	1	68
*Ring-opening of **1n***				
9[e,h]	allylTMS	 **3i**	24	97

[a] $FeCl_3$ (10 mol %) and allylsilane (3 equiv) were used. [b] $FeCl_3$ (5 mol %) and allylsilane (2 equiv) were used. [c] $FeCl_3$ (50 mol %) and allylsilane (2 equiv) was used. [d] $FeCl_3$ (50 mol %) and allylsilane (3 equiv) were used. [e] $FeCl_3$ (10 mol %), allylsilane (3 equiv), and TMSCl (1 equiv) were used. [f] $FeCl_3$ (20 mol %) and allylsilane (4 equiv) were used. [g] $FeCl_3$ (10 mol %) and allylsilane (4 equiv) were used. [h] The quench using TBAF was not necessary.

mixture of **2ma** and **2mb**,[16] entries 11 and 12),[17] and also azidated saturated carboxylic acids (**2n** and **2o**) were efficiently obtained by the use of 1-phenyl γ-butyro- and δ-valerolactone (**1n** and **1o**) as substrates (entries 13 and 14).[17]

Moreover, the allylative ring-opening reaction of various tetrahydofuran derivatives, which could construct the highly functionalized C7 linear alcohol skeletons bearing an olefin functionality at the opposite terminal against the hydroxyl group, was investigated (Table 3).[11] The reaction using 2-phenyltetrahydrofuran (**1a**) with various allylsilane derivatives, such as allylTMS, 2-phenyl and bromo-substituted allylsilanes, and [2-(trimethylsilyl)ethylidene]-cyclohexane, was efficiently catalyzed by $FeCl_3$ as the case with the azidation to give the corresponding 6-hepten-1-ols (**3a**–**d**) (entries 1–4) in moderate to excellent yields. The 2-alkynyl tetrahydrofuran (**1i**) could be transformed into 1,5-eneyne[18] products bearing a primary hydroxyl group (**3e**–**g**) (entries 5–7). Furthermore, the ring-opening allylation of the phthalane and lactone derivatives could also proceed to give the corresponding allylated *ortho*-benzylalcohol (**3h**) and saturated carboxylic acid (**3i**) derivatives (entries 8 and 9).[17]

In conclusion, we have established the first catalytic C–C and C–N bond formations associated with the ring-opening reaction of the thermodynamically stable tetrahydrofuran derivatives. The azidation using $TMSN_3$ and allylation using various allylsilanes was efficiently catalyzed by $FeCl_3$ as a cheap and universal iron catalyst at room temperature to afford the corresponding azidated linear primary alcohols in excellent yields. Furthermore, the phthalane and lactone derivatives also underwent the $FeCl_3$-catalyzed ring-opening allylation and azidation to give the corresponding *ortho*-substituted benzylalcohols and the saturated carboxylic acids. These azidated and allylated products can be valuable as small synthetic precursors for a wide variety of functional materials.

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Supporting Information Available. The details of optimization of reaction conditions and the spectroscopic data of new products such as ^1H and ^{13}C NMR and IR were depicted. This material is available free of charge via the Internet at http://pubs.acs.org.

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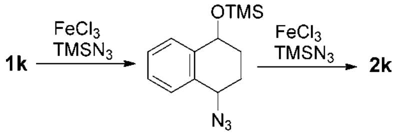
[15] Benzyl TMS ether generated by the first azidation of **1k** was efficiently transformed into the diazido product (**2k**). We have also established the direct azidation of benzyl TMS ether using the $TMSN_3$ and $FeCl_3$ combination; see: Sawama, Y.; Nagata, S.; Yabe, Y.; Morita, K.; Monguchi, Y.; Sajiki, H. *Chem.—Eur. J.* **2012**, *18*, 16608–16611.



[16] **2ma** and **2mb** could not be separated. Each product (**2ma** and **2mb**) was smoothly isomerized during the isolation to the corresponding isomer by the rapid rearrangement of the allylic azido functions.

[17] These are the first examples of the ring-opening azidation and allylation of the phthalane and lactone derivatives.

[18] 1,5-Eneynes are important precursors to construct complicated cyclic compounds. For selected references, see: (a) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858–10859. (b) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328–2334. (c) Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705–9710. (d) Reeds, J. P.; Whitwood, A. C.; Healy, M. P.; Fairlamb, I. J. S. *Chem. Commun.* **2010**, *46*, 2046–2048.

The authors declare no competing financial interest.