ORGANIC
LETTERS

2007
Vol. 9, No. 7
1311−1314

Remarkably Mild and Efficient Intramolecular Friedel–Crafts Cyclization Catalyzed by In(III)

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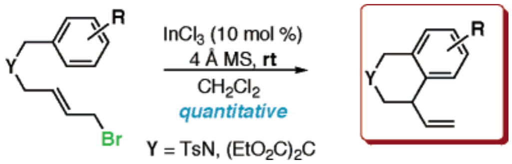
Received January 29, 2007

ABSTRACT



Indium(III) salts were found to be highly effective catalysts for the intramolecular Friedel–Crafts reaction of simple allylic bromides and arenes. In(III) salts appear to be the most general and possess unique halophilic properties as a Lewis acid for this reaction among the catalysts evaluated to date. Deactivated arenes possessing chloride, bromide, and fluoride underwent smooth reaction when activated by InCl$_3$.

More than 125 years after its inception, electrophilic aromatic substitution (the Friedel−Crafts (FC) reaction)[1] still remains an important method for C−C bond formation and is the subject of continued investigation today. FC reactions traditionally require a stoichiometric amount of strong Lewis acid and severe conditions.[2] Original conditions have been replaced by milder and more environmentally friendly procedures. While great strides have been made in catalytic FC reactions, there remain several challenges. Particularly reactions with electron-deficient arenes are a continued problem with very few solutions. Therefore, new efficient, mild, and catalytic methods to activate electrophiles for Friedel−Crafts reactions are highly significant.

Lately, the utility of indium(III) Lewis acids in organic synthesis has received a great deal of interest due to their relatively low toxicity, stability in air and water, and recyclability.[3] There are a number of examples of catalytic indium(III) salts utilized in Friedel−Crafts reactions including electrophilic aromatic substitution with carbonyl compounds,[4] sulfuryl chloride,[5] electron-deficient alkene,[6] alkyne,[7] aziridine,[8] and epoxide.[9] These examples are all activated

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10.1021/ol070235g CCC: $37.00

by Lewis acid coordination to strong Lewis basic functionality such as oxygen and nitrogen. Arene additions to allylic halides catalyzed by Lewis acids and indium metal have been shown;[10] however, these reactions require an excess amount of arene to obtain useful yields. Examples of direct halide activation by catalytic Lewis acid are rare; however, as in Friedel and Crafts' original reports, stoichiometric variants have been reported. Alkylation of aromatics with *exo*-2-chloro and 7-chloronorbornane with a stoichiometric amount of Lewis acids ($SnCl_4$, $AlCl_3$, BF_3, and SbF_5) has been demonstrated,[11] and zinc(II) salts have been reported to activate allyl chlorides for cycloaddition onto alkynes.[12] Because of the difficulty in achieving catalytic activation of halides, their use in FC reactions has been limited.

We have recently demonstrated a mild and efficient atom transfer cyclization catalyzed by In(III) salts.[13] Importantly, we found that the reaction was driven by cationic activation of allyl bromide by a catalytic amount of $InCl_3$. As shown in Scheme 1, treatment of **1** with catalytic indium chloride in dichloromethane at room temperature resulted in the efficient formation of the atom transfer cyclization product **2**. This product arose via electrophilic allylation of the alkyne via the polarized species **A** or the cationic species **B**. Reasoning that this allylic activation would be amenable to FC reactions, we undertook a study to ascertain the effectiveness of In(III) Lewis acids on this reaction. Herein, we disclose a remarkably mild and efficient intramolecular FC cyclization of allylic halide onto a variety of arenes, both electron rich and electron poor, catalyzed by In(III) salts.

Scheme 1

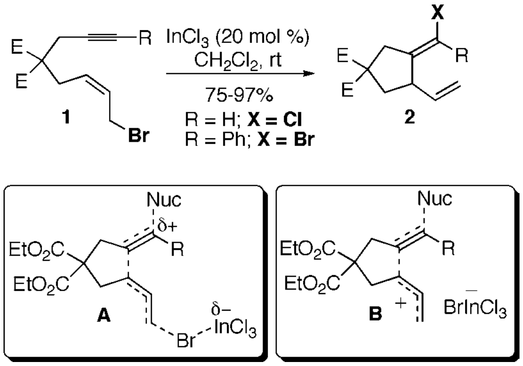
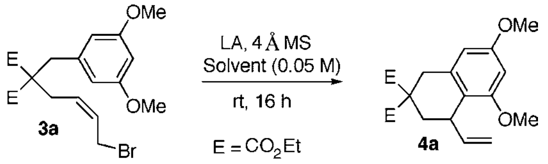


Table 1. Lewis Acid Catalyzed Friedel−Crafts Cyclization[a]



entry	LA (mol %)	solvent	yield[b]
1	$InCl_3$ (5)	CH_2Cl_2	**79%**
2	$InCl_3$ (5)	toluene	**81%**
3	$InCl_3$ (10)	CH_2Cl_2	**88%**
4	$InCl_3$ (10)	toluene	**87%**
5	$InCl_3$ (10)	CH_2Br_2	**91%**
6	$InCl_3$ (10)	$ClCH_2CH_2Cl$	**76%**
7	$InBr_3$ (10)	CH_2Cl_2	**84%**
8	$In(OTf)_3$ (10)	CH_2Cl_2	**82%**
9	$In(NO_3)_3$ (10)	CH_2Cl_2	**77%**
10	InI (10)	CH_2Cl_2	trace[c]
11	InF_3 (10)	CH_2Cl_2	trace[c]
12	$In(OAc)_3$ (10)	CH_2Cl_2	trace[c]
13	$AlCl_3$ (20)	CH_2Cl_2	0%[c]
14	$Sc(OTf)_3$ (20)	CH_2Cl_2	0%[c]
15	$Cu(OTf)_2$ (20)	CH_2Cl_2	0%[c]
16	$Mg(OTf)_2$ (20)	CH_2Cl_2	0%[c]
17	$ZrCl_4$ (20)	CH_2Cl_2	0%[c]
18	$Y(OTf)_3$ (20)	CH_2Cl_2	0%[c]
19	AgOTf (20)	CH_2Cl_2	0%[c]
20	$La(OTf)_3$ (20)	CH_2Cl_2	0%[c]
21	$Sm(OTf)_3$ (20)	CH_2Cl_2	0%[c]
22	$SnCl_4$ (20)	CH_2Cl_2	80%
23	$Fe(ClO_4)_3$ (20)	CH_2Cl_2	75%
24	$Zn(OTf)_2$ (20)	CH_2Cl_2	95%

[a] Substrate, solvent, 4 Å MS, and catalyst were stirred together at rt in a screwcap scintillation vial for 16 h. [b] Yield of isolated product. [c] Starting material was recovered intact.

We have discovered that 10 mol % of $InCl_3$ in dichloromethane (0.05 M) at room temperature in the presence of molecular sieves efficiently catalyzed the FC cyclization of allylic bromide onto electron-rich arene with excellent yield (Table 1, entries 1−6). In the absence of molecular sieves, the substrate decomposed. The sieves are thought to be performing the role of a neutral acid scavenger.[14] Optimal efficiency was observed with 10 mol % catalyst loading, although 5 mol % performed with only slightly diminished yield. The reaction proceeded well in noncoordinating solvents such as dichloromethane, dibromomethane, or toluene but failed in other common solvents ($CHCl_3$, THF, MeCN, $MeNO_2$, EtOH, MeOH, acetone, H_2O). Application of In(I) salts, InF_3, and $In(OAc)_3$ in the reaction resulted in the formation of only a trace of product with recovery of unreacted starting material (entries 10−12).

We next screened a variety of common Lewis acids. Most completely failed to promote the cyclization (Table 1, entries 13−21). However, $SnCl_4$, $Fe(ClO_4)_3$, and $Zn(OTf)_2$ showed success in the catalytic activation of **3a** (entries 22−24). It is important to note that only indium(III) Lewis acids catalyzed the reaction of arenes that were less electron rich than **3a**. Zn(II), Fe(III), or Sn(IV) Lewis acids were ineffective at promoting the cyclization of the activated monomethoxyarene **3b**. Thus, of the Lewis acids examined,

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(10) (a) Ichihara, J. *Chem. Commun.* **1997**, 1921. (b) Lim, H. J.; Keum, G.; Kang, S. B.; Kim, Y. *Tetrahedron Lett.* **1999**, *40*, 1547.

(11) (a) Olah, G. A.; Lee, C. S.; Prakash, G. K. S.; Moriarty, R. M.; Rao, M. S. C. *J. Am. Chem. Soc.* **1993**, *115*, 10728. (b) Olah, G. A.; Lee, C. S.; Prakash, G. K. S. *J. Org. Chem.* **1994**, *59*, 2590.

(12) Miller, A.; Moore, M. *Tetrahedron Lett.* **1980**, *21*, 577.

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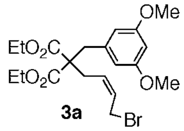
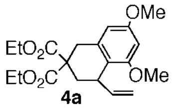
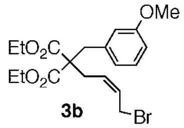
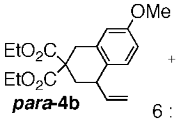
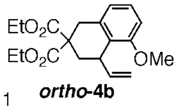
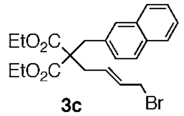
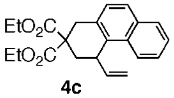
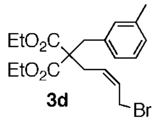
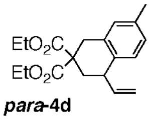
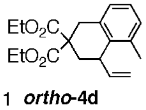
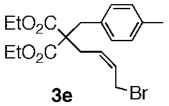
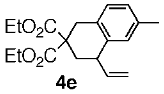
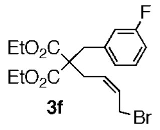
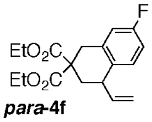
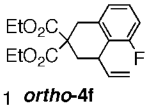
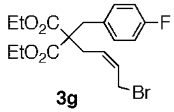
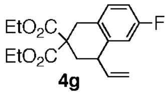
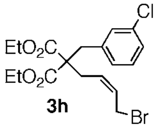
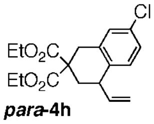
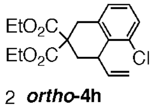
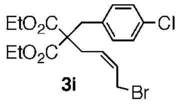
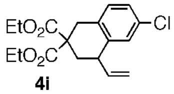
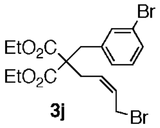
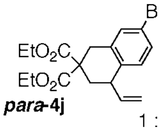
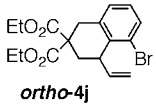
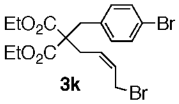
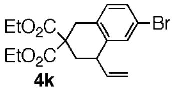
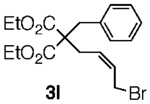
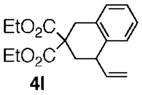
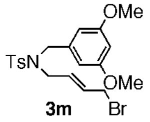
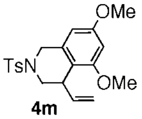
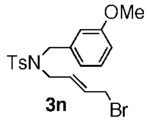
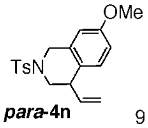
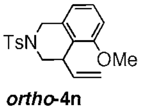
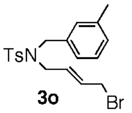
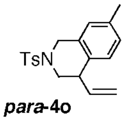
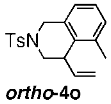
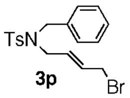
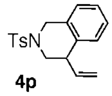
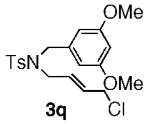
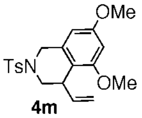
Table 2. Substrate Scope in the Lewis Acid Catalyzed Friedel−Crafts Cyclization[a]

entry	substrate	yield[b]	product
1	 **3a**	88%	 **4a**
2	 **3b**	93%	 ***para*-4b** +  ***ortho*-4b** 6 : 1
3	 **3c**	87%	 **4c**
4	 **3d**	98%	 ***para*-4d** +  ***ortho*-4d** 2 : 1
5	 **3e**	97%	 **4e**
6	 **3f**	96%[c]	 ***para*-4f** +  ***ortho*-4f** 4 : 1
7	 **3g**	93%[d]	 **4g**
8	 **3h**	98%	 ***para*-4h** +  ***ortho*-4h** 1 : 2
9	 **3i**	80%[e]	 **4i**
10	 **3j**	92%	 ***para*-4j** +  ***ortho*-4j** 1 : 2
11	 **3k**	89%[d]	 **4k**
12	 **3l**	97%	 **4l**
13	 **3m**	97%	 **4m**
14	 **3n**	98%	 ***para*-4n** +  ***ortho*-4n** 9 : 1
15	 **3o**	100%	 ***para*-4o** +  ***ortho*-4o** 2 : 1
16	 **3p**	87%[f]	 **4p**
17	 **3q**	95%[e]	 **4m**

[a] $InCl_3$ (10 mol %), 4 Å MS, CH_2Cl_2 (0.05 M), 16 h, rt. [b] Yield of isolated product. [c] 30 mol % of catalyst, 16 h. [d] 20 mol % of catalyst, 48 h. [e] 20 mol % of catalyst, 72 h. [f] 20 mol % of catalyst, 16 h.

In(III) salts were unique in their mildness and activity for this FC reaction.

The substrate scope of the reaction under the optimized conditions was investigated, and the results are summarized in Table 2. The reaction was amenable to a wide variety of aromatic rings for the synthesis of benzocarbocycles.[15] When *meta*-substituted arenes were employed, regioisomeric products resulted from both *para*- and *ortho*-attack of the electrophile. Remarkably, to our great satisfaction, under In(III) catalysis, even electron-deactivated arenes possessing a chlorine, fluorine, or bromine substituent cyclized smoothly and cleanly in high yield (entries 7−12). However, electron-withdrawing groups as strong as CF_3 were ineffective in this Friedel−Crafts cyclization. Nitrogen linkers in the tether were agreeable to the FC cyclization as well. Thus, isoquinolone derivatives[16] were formed in quantitative yields. These reactions performed equally well when other In(III) salts were employed including $InBr_3$, $In(OTf)_3$, and $In(NO_3)_3$. Although slightly higher catalyst loads (25 mol %) and longer reaction times were required, incredibly, even allyl chlorides could

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(15) (a) Palmer, D. C.; Strauss, M. J. *Chem. Rev.* **1977**, *77*, 1. (b) *Dictionary of Natural Products*; Chapman & Hall: London, 1994; Vol 1, p 812. (c) Kuramoto, M.; Yamada, K.; Shikano, M.; Yazawa, K.; Arimoto, H.; Okamura, T.; Uemura, D. *Chem. Lett.* **1997**, 885.

(16) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic: Amsterdam, 1998.

be activated by $InCl_3$. This was exemplified by the smooth cyclization of substrate **3q** in 95% isolated yield (entry 18).

In conclusion, we have demonstrated a remarkably mild and efficient Friedel−Crafts cyclization catalyzed by In(III) salts. The reaction was driven by cationic activation of allylic bromide by a substoichiometric amount of Lewis acid. In(III) salts appear to be the most general and possess unique halophilic properties as a Lewis acid for this reaction among the catalysts evaluated to date. We are currently examining the scope and limitations of this catalytic activation of halides by indium(III) salts and other metals to gain further insight into this distinctive reactivity.

Acknowledgment. We are grateful to the National Science Foundation (NSF-CHM-0616485) and the NDSU NIH Center for Protease Research (NCRR-P20-RR15566) for financial support of this project.

Supporting Information Available: Cyclization experimental procedures, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070235G