Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters

Tetrahedron Letters 48 (2007) 7085–7087

Intermolecular Friedel–Crafts reaction catalyzed by $InCl_3$

Miho Kaneko, Ryuji Hayashi and Gregory R. Cook*

Department of Chemistry and Molecular Biology, North Dakota State University, Fargo, ND 58105, USA

Received 30 July 2007; accepted 1 August 2007

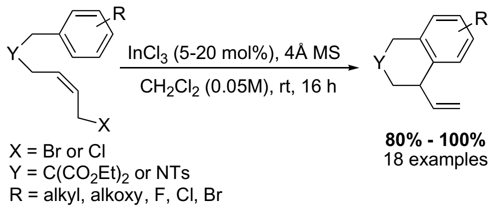
Abstract—Our recent discovery that In(III) salts were able to activate halides catalytically under mild conditions for the intermolecular Friedel–Crafts cyclization prompted us to explore this highly efficient activation in intermolecular Friedel–Crafts reactions. The alkylation of *p*-xylene with allylic and benzylic halides was demonstrated under catalytic and mild condition to afford in some cases quantitative yields of the monoalkylated products without the need to employ large excesses of reactants.

Since Friedel and Crafts discovered addition of alkyl halides to aromatic compounds in the presence of stoichiometric amount of Lewis acids in 1877, electrophilic aromatic substitutions (FC-reactions[1]) have been one of the most important C–C bond formations in the field of organic synthesis. In general, because nucleophilicity of aromatic compounds are relatively low compared to other typical nucleophiles, severe conditions[2] for the intermolecular process with alkyl halides are classic problems in FC-reactions. These reactions typically require stoichiometric amounts of Lewis acids, high temperatures, and large excess of arenes. To overcome these limitations in the intermolecular FC-reaction there has been growing interest in methods that are catalytic, mild, and more environmentally friendly.

In(III) Lewis acids have distinct advantages[3] over other Lewis acids including their relatively low toxicity, stability in the air, and recyclability. In(III) Lewis acid catalysis has been utilized in FC-reactions employing electrophiles such as carbonyl compounds,[4] sulfuryl chloride,[5] electron deficient alkenes,[6] alkynes,[7] aziridines,[8] and epoxides.[9] In nearly all these examples the Lewis acid coordinates to strong Lewis basic functionality including oxygen and nitrogen in order to activate the electrophile. In order to directly activate organohalides stoichiometric quantities of Lewis acid are required. Examples include *exo*-2-chloro and 7-chloronorbornane activated with various Lewis acids ($SnCl_4$, $AlCl_3$, BF_3, and SbF_5).[10] Additionally, Zn(II) salts have been reported to activate allyl chlorides for cycloaddition onto alkynes.[11] While there are examples of direct allylation catalyzed by a Lewis acid such as $AlCl_3$, the reaction affords a complex mixture of products.[2a] There are also arene additions to allylic halides catalyzed by a few Lewis acids. However, large excess (20–140 equiv) of arenes were required for successful reaction.[14] Additionally, indium metal[15] has been known to catalyze intermolecular FC-reactions with allyl chlorides, however this reaction required the use of 10–15 equiv of arene, 80 °C, and strongly basic conditions.

Recently, we discovered Lewis acids such as In(III) and Bi(III) were capable of selectively activating allylic halides catalytically.[12] We have succeeded in developing an efficient, mild, and catalytic intramolecular FC-reaction[13] to synthesize a variety of benzocycles (Scheme 1). Herein, we report the development of intermolecular FC-reactions via catalytic halide activation by In(III) under mild conditions.

In order to optimize the conditions, we examined *p*-xylene (5 equiv) as the nucleophilic arene and benzyl bromide as the electrophile. Previously we discovered that In and Bi Lewis acids were optimal for activating



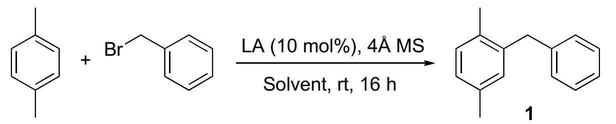
Scheme 1. Ring-closing FC-reaction via catalytic halide activation.

---

* Corresponding author. Tel.: +1 701 231 7413; fax: +1 701 231 1057; e-mail: Gregory.Cook@ndsu.edu

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.08.011

Table 1. Solvent effect and screen of Lewis acids

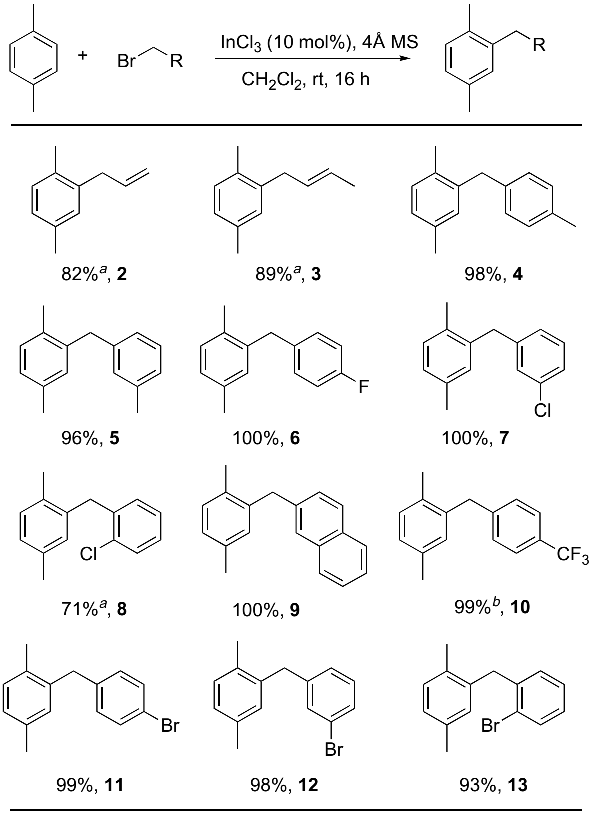


Entry	LA	*p*-Xylene (equiv)	Solvent	Yield (%)
1	$InCl_3$	5	CH_2Cl_2	100
2	$InCl_3$	5	THF	0[a]
3	$InCl_3$	5	MeCN	0[a]
4	$InCl_3$	5	EtOH	0[a]
5	$InCl_3$	5	*i*-PrOH	0[a]
6	$InBr_3$	5	CH_2Cl_2	97
7	$In(OTf)_3$	5	CH_2Cl_2	88[b]
8	$In(NO_3)_3$	5	CH_2Cl_2	69[b]
9	InI	5	CH_2Cl_2	94[b]
10	$BiCl_3$	5	CH_2Cl_2	99[b]
11	$Bi(OTf)_3$	5	CH_2Cl_2	79[b]
12	$InCl_3$	1.5	CH_2Cl_2	Mixture[c]

[a] Starting material recovered.
[b] NMR yield.
[c] Mixture of polyalkylated products (ratio could not be determined).

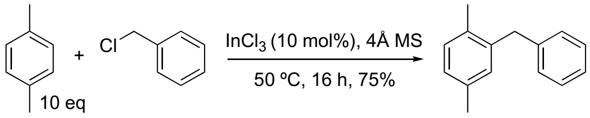
organohalides catalytically. Thus we screened a variety of In and Bi salts under a range of conditions (Table 1). 4 Å molecular sieves played the role of a neutral base[16] in the reaction. Under $InCl_3$ catalysis in CH_2Cl_2, a quantitative yield of desired product **1** was obtained (entry 1). We screened several solvents that posses donor atoms (O or N) and found them to be detrimental to the reaction (entries 2–5). Other Lewis acids such as $InBr_3$, $In(OTf)_3$, InI, and $BiCl_3$ were suitable catalysts (entries 6, 7, 9, and 10) affording excellent yields of monoalkylated products. Employing $In(NO_3)_3$ and $Bi(OTf)_3$ worked as well with slightly diminished yields (entries 8 and 11). Utilizing only 1.5 equiv of *p*-xylene resulted in an efficient reaction, however, mixtures of polyalkylated products were obtained (entry 12). It should be pointed out that although the reaction was optimal at 5 equiv of arene, this is significantly less than catalytic intermolecular FC-reactions previously reported. General optimal conditions were found to employ 10 mol % of the catalyst, 5 equiv of the arene in non-coordinating CH_2Cl_2 at room temperature.[17]

Next we turned our attention to the scope and limitation of the electrophile in the intermolecular FC-reaction and the results are summarized in Scheme 2. In addition to benzyl bromide, we found a variety of benzylic and allylic halides reacted with high efficiency. Under $InCl_3$ catalysis, electrophilic aromatic substitution of *p*-xylene with allyl or crotyl bromide yielded our desired products **2** and **3** in high yields. Methyl-substituted benzyl bromides yielded **4** and **5** in excellent yields. Benzylic bromides possessing electron withdrawing halogen substituents performed admirably in the reaction to afford compounds **6**, **7**, **11**, **12**, and **13**. Only the *o*-substituted substrates afforded a yield of was not essentially quantitative (71%, **8** and 93%, **13**). Product **10** was obtained in excellent yield, however, the *p*-CF_3-substituted benzyl bromide required higher temperature and 10 equiv of *p*-xylene for reaction to complete.



[a]NMR yield. [b]10 equiv xylene, 70 °C, neat.

Scheme 2. Electrophile scope and limitations.



Scheme 3. Intermolecular FC-reaction with benzyl chloride.

Intermolecular FC-reaction with benzyl chloride was also achieved using $InCl_3$ catalysis. Performing the reaction with 10 equiv of *p*-xylene at 50 °C resulted in 75% yield of the desired product (Scheme 3).

In conclusion, we have demonstrated a catalytic and efficient intermolecular FC-reaction with allyl and benzyl halides under mild conditions. As compared to previous reports, our general protocol required less arene (only 5 equiv) and lower temperatures. Quantitative yields of monoalkylated products were obtained. We are currently examining the scope and limitation of this catalytic activation of halides by halophilic Lewis acids and other metals in order to gain further insight into this distinctive reactivity.

Acknowledgments

We are grateful to the National Science Foundation (NSF-CHM-0616485) for financial support of this project. We also thank Pfizer for an undergraduate summer fellowship for M.K.

References and notes

1. (a) Friedel, C.; Crafts, J. M. *C.R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1392; (b) Friedel, C.; Crafts, J. M. *C.R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1450.
2. (a) Olah, G. A. *Friedel–Crafts and Related Reactions*; Wiley: New York, 1963; (b) Olah, G. A. *Friedel–Crafts Chemistry*; Wiley: New York, 1973; (c) Roberts, R. M.; Khalaf, A. A. *Friedel–Crafts Alkylation Chemistry*; Marcel Dekker: New York, 1984; (d) Olah, G. A.; Krishnamurti, R.; Surya Prakash, G. K. In *Comprehensive Organic Synthesis*, 1st ed.; Pergamon: New York, 1991; Vol. 3, pp 293–339; (e) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550–556; (f) Bandini, M.; Emer, E.; Tommasi, S.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2006**, 3527.
3. Reviews for indium Lewis acids: (a) Frost, C. G.; Chauhan, K. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015; (b) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Curr. Org. Chem.* **2003**, *7*, 1661; (c) Frost, C. G.; Hartley, J. P. *Mini-Rev. Org. Chem.* **2004**, *1*, 1.
4. (a) Babu, G.; Sridhar, N.; Perumal, P. T. *Synth. Commun.* **2000**, *30*, 1609; (b) Chapman, C. J.; Frost, C. G.; Hartley, J. P.; Whittle, A. J. *Tetrahedron Lett.* **2001**, *42*, 773; (c) Nagarajan, R.; Perumal, P. T. *Tetrahedron* **2002**, *58*, 1229.
5. (a) Frost, C. G.; Hartley, J. P.; Whittle, A. J. *Synlett* **2001**, 830; (b) Frost, C. G.; Hartley, J. P.; Griffin, D. *Tetrahedron Lett.* **2002**, *43*, 4789.
6. (a) Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Synthesis* **2001**, 2165; (b) Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Tetrahedron Lett.* **2001**, *42*, 8063; (c) Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 5386; (d) Bandini, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Synthesis* **2002**, 1110.
7. Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, Y. *Chem. Commun.* **2000**, 1573.
8. (a) Yadav, J. S.; Reddy, B. V. S.; Abraham, S.; Sabitha, G. *Tetrahedron Lett.* **2001**, *42*, 8067; (b) Yadav, J. S.; Reddy, B. V. S.; Mahesh Kumar, G.; Madan, C. *Synlett* **2001**, *11*, 1781.
9. (a) Yadav, J. S.; Reddy, B. V. S.; Mahesh Kumar, G.; Madan, C. *Synlett* **2001**, *11*, 1781; (b) Yadav, J. S.; Reddy, B. V. S.; Parimala, G. *Synlett* **2002**, *7*, 1143.
10. (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.
11. Miller, A.; Moore, M. *Tetrahedron Lett.* **1980**, *21*, 577.
12. Cook, G. R.; Hayashi, R. *Org. Lett.* **2006**, *8*, 1045.
13. Hayashi, R.; Cook, G. R. *Org. Lett.* **2007**, *9*, 1311.
14. Ichihara, J. *Chem. Commun.* **1997**, 1921.
15. Lim, H. J.; Keum, G.; Kang, S. B.; Kim, Y. *Tetrahedron Lett.* **1999**, *40*, 1547.
16. Padwa, A.; Ginn, J. D.; Bur, S. K.; Eidell, C. K.; Lynch, S. M. *J. Org. Chem.* **2002**, *67*, 3412.

17. *General experimental procedure*: $InCl_3$ (0.05 mmol) and 4 Å MS (250 mg) were placed in a small screw-cap scintillation vial equipped with a magnetic stir bar. *p*-Xylene (2.5 mmol), dicholoromethane (1 mL) and halide (0.5 mmol) were added. The reaction was stirred under room temperature. Upon completion of the reaction (~16 h), the mixture was filtered through a small pad of silica gel and rinsed with ethyl acetate. After removing solvent in vacuo, analytically pure alkylated products were obtained. (For some examples, 1, 2, 3-trimethoxy benzene was used as an internal standard for NMR yields.) All products afforded satisfactory spectral data for their structure identification.