

Reaction Mechanism for the LiCl-Mediated Directed Zinc Insertion: A Computational and Experimental Study

Ching-Yuan Liu,^[a, b] Xuan Wang,^[a] Taniyuki Furuyama,^[a] Shuji Yasuike,^[a, b] Atsuya Muranaka,^[a] Keiji Morokuma,^[c] and Masanobu Uchiyama^[a, b]

In situ generation of organozinc reagents and their integration into C–C bond-forming processes are of continuing interest because of the characteristically high chemo- and stereoselectivity.^[1] In 2006, Knochel and co-workers discovered that the oxidative insertion of zinc dust into aryl halides is drastically accelerated in the presence of LiCl, thereby opening up a practical and efficient preparation method for aryl- and alkylzinc reagents.^[2] This protocol was successfully used for chemo- and regioselective Zn insertion^[3] (also termed directed *ortho* insertion (DoI)), and is now widely employed. Koszinowski et al. detected $\text{Li}^+\text{ZnRClHal}^-$ (Hal = halide), which had been proposed by Knochel as the active species for the LiCl-mediated zinc insertion,^[2] in the reaction mixture by using ESI-MS.^[4,1f] However, the reaction pathway and mechanism of $\text{Li}^+\text{ZnRClHal}^-$ formation are still far from being settled. Herein, we report an experimental/computational study on the LiCl-mediated zinc insertion, and we address the questions of the generation mechanism of $\text{Li}^+\text{ZnRClHal}^-$, the role of LiCl, and the origin of the regioselectivity in the reaction.

Firstly, DoI reactions of 1-functionalized 2,4-dibromoaryls **1a–c** in the absence/presence of LiCl were examined under various (kinetic and thermodynamic) conditions in order to elucidate the influence of functional groups and the effect of LiCl on the activation energy and regioselectivity (Table 1).

Some important aspects of the reactivity and regioselectivity of this Zn insertion can be drawn from the data in the Table 1.

Table 1. DoI reaction of zinc into functionalized dibromoaryls.

1: FG = CO₂Et, OMe, CN

	Zn ^[a]		Zn + LiCl ^[a]	
	55 °C, 12 h	RT, 12 h	55 °C, 12 h	55 °C, 48 h
FG = CO ₂ Me (1a)	79:21 (2 %)	98:2 (94 %)	96:4 (95 %)	95:5 (96 %)
FG = OMe (1b)	– (<0.1 %)	– (<0.1 %)	92:8 (3 %)	89:11 (4 %)
FG = CN (1c)	– (<0.1 %)	– (<0.1 %)	75:25 (1 %)	72:28 (1 %)

[a] Ratio (**2:3**)/Yield (**2+3**, values in parentheses) determined by gas chromatography (GC).

[a] Dr. C.-Y. Liu, X. Wang, T. Furuyama, Prof. Dr. S. Yasuike, Dr. A. Muranaka, Prof. Dr. M. Uchiyama
Advanced Elements Chemistry Laboratory
Advanced Science Institute, RIKEN
2-1 Hirosawa, Wako-shi, Saitama 351-0198 (Japan)
Fax: (+81)48-467-2879
E-mail: liu@riken.jp
uchiyanama@riken.jp

[b] Dr. C.-Y. Liu, Prof. Dr. S. Yasuike, Prof. Dr. M. Uchiyama
Department of Pharmaceutical Sciences
Hokuriku University, Ho-3, Kanagawa-machi
Kanazawa, Ishikawa 920-1181 (Japan)

[c] Prof. Dr. K. Morokuma
Cherry L. Emerson Center for Scientific Computation and
Department of Chemistry, Emory University
Atlanta, Georgia, 30322 (USA)
Fax: (+1)404-727-7412
E-mail: morokuma@euch4e.chem.emory.edu

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.200902957>.

1) **Reactivity:** In all cases, acceleration of Zn insertion by LiCl was thermodynamically and kinetically confirmed. For instance, **1a** reacted very slowly with zinc powder at 55 °C over 12 h to afford **2+3** in only 2 % yield, whereas in the presence of LiCl (2.0 equiv), zinc insertion proceeded rapidly at 55 °C (also even at room temperature) furnishing the products in excellent total yield. In contrast, the MeO (**1b**) or CN (**1c**) derivatives fail to behave likewise and the zinc insertions occurred in low yields even with LiCl, and required a longer reaction time (48 h).

2) **Regioselectivity:** the COOMe and OMe groups exhibited high *ortho*-selectivities. As evidenced by **1a**, with the assistance of the LiCl, *ortho*-selectivity was enhanced. Surprisingly, **1c** underwent the zinc insertion with LiCl to give the products in low yield with poor selectivity.

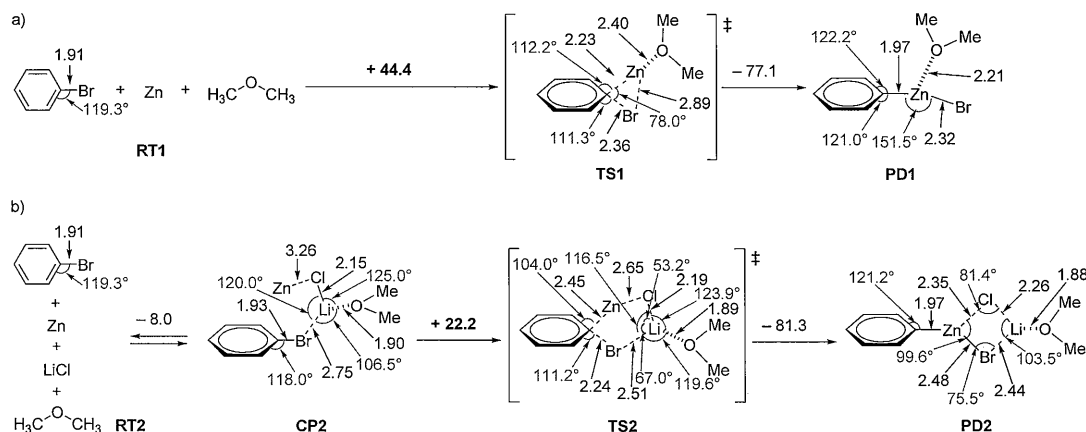


Figure 1. Plausible reaction pathways of zinc insertion into bromobenzene: a) without LiCl; b) with LiCl. Energy changes at the B3LYP/631SVP level are shown in kcal mol⁻¹ on the arrows and bond lengths are shown in angstrom.

Since the CN group is classified as an electron-withdrawing group (EWG), one would expect it to facilitate oxidative metal insertion^[2] and DoI reactions. Thus, it is of interest to seek the reason for the origin of the acceleration of Zn insertion by LiCl and the DoI selectivity.

DFT calculations (B3LYP/631SVP)^[5] were performed to investigate the reaction pathway of the LiCl-mediated zinc insertion using bromobenzene (Figure 1). In the absence of LiCl, we could not find any energetically plausible initial complex and zinc insertion takes place directly from the reactants **RT1** through the distorted “triangular TS” **TS1** with an energy loss of 44.4 kcal mol⁻¹. This large energy loss is a result of the cleavage of the stable C–Br bond and of the rather small energy gain to form the triangle bond.

In the presence of LiCl, reactants **RT2** form an association complex **CP2** first with an energy gain (8.0 kcal mol⁻¹). The Zn atom can migrate very smoothly from **CP2**, along the intrinsic reaction coordinate,^[6] to the phenyl carbon atom with a small activation energy (22.2 kcal mol⁻¹) to afford a five-membered ring in **TS2**. Zn metal then inserts into the Ph–Br bond to produce the adduct **PD2**. The stabilization energy is very large (–81.3 kcal mol⁻¹) because of the formation of the stable halogen ate complex, and this provides a driving force for the insertion reaction and energy for successive reaction of the intermediate **PD2**. These computational results are in good agreement with the experimental facts that the additive LiCl substantially facilitates the zinc insertion and that Li⁺ZnRClHal⁻ is generated as the active species in the reaction system.^[2–4]

As judged from the degree of elongation of the C–Br bond, as well as the forming Zn–C bond in the TSs, we consider **TS2** to be significantly earlier in the reaction pathway than **TS1**. This was also confirmed by natural population analysis (NPA) and natural resonance theory (NRT) (Figure 2 and Supporting Information);^[7] the positive charge of the Zn atom increases monotonously from **CP2** to **PD2**, while the negative charge of the phenyl carbon and Br

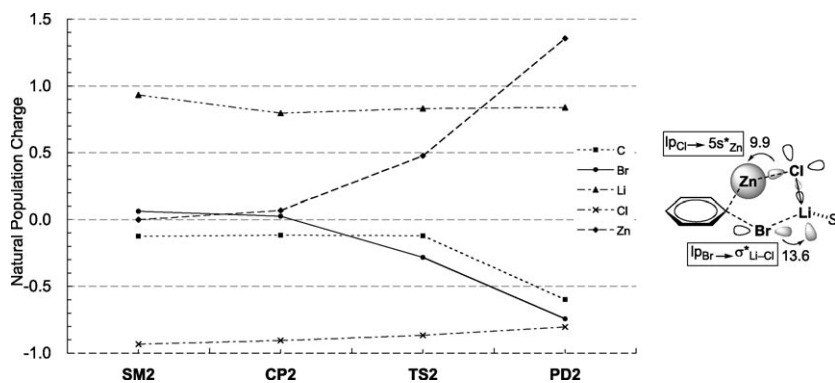


Figure 2. Charge changes (left) and NBO donor–acceptor interactions (right) of **TS2** (energy shown in kcal mol⁻¹).

atoms decreased monotonously toward –1 in the product. The exchange of electrons occurs exclusively among the three atoms, and the charges of the Li and the Cl atoms remain essentially constant during the reaction, indicating that LiCl does not participate in any oxidation/reduction process.

The origin of the LiCl effect was then investigated by natural bond orbital (NBO) analysis.^[7] Second-order perturbation analysis of **TS2** indicates two large stabilization energies due to the push–pull interactions of LiCl (9.9 kcal mol⁻¹ (push)/13.6 kcal mol⁻¹ (pull)), corresponding to the secondary orbital interactions between the lone pair of Cl (donor NBO) and the vacant 5s* orbital of Zn (acceptor NBO),

and between the lone pair of Br (donor NBO) and the unoccupied s orbital of Li atom (acceptor NBO), respectively. These results strongly suggest that the LiCl stabilizes the zinc insertion TS sterically and electronically.

Finally, we focused on the origin of the regioselectivity. The B3LYP/631SVP-optimized TSs for zinc insertions of *ortho/para*-functionalized bromobenzenes are shown in Supporting Information (Figure S1 for no LiCl TSs) and Figure 3 (for LiCl-assisted TSs).

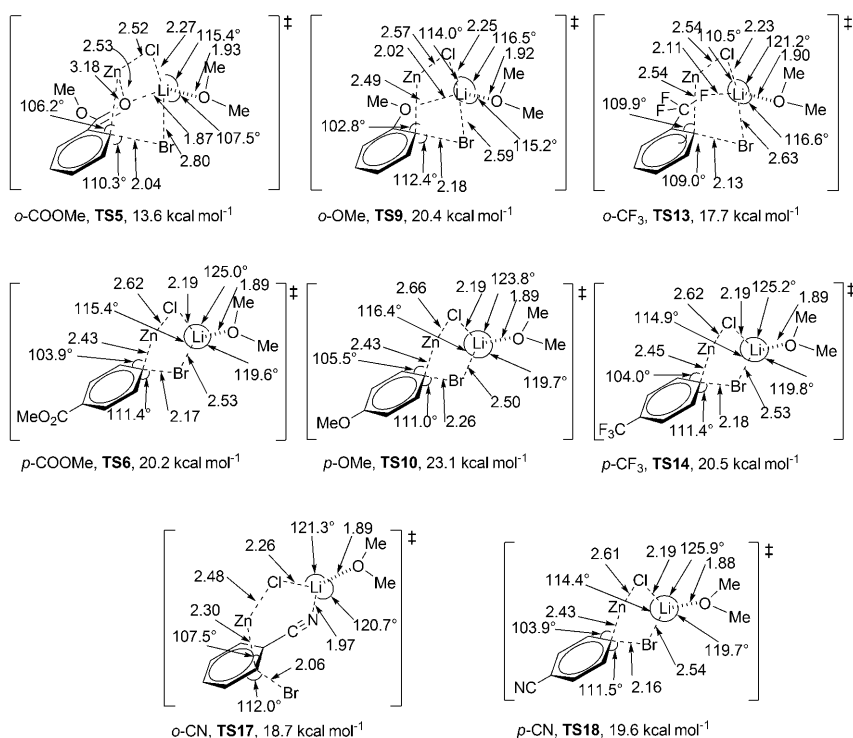
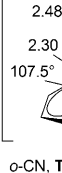


Figure 3. TS structures and activation energies of LiCl-mediated zinc insertion reactions of ortho/para functionalized bromobenzenes at the B3LYP/631SVP level.

- 1) **Reactivity:** All activation energies with LiCl are considerably lower than those without LiCl (ca. 19–22 kcal mol⁻¹), in accordance with the experimental facts.^[8]
- 2) **DoI selectivity:**^[9] *ortho*-Functional groups such as ester, alkoxy, and CF₃ groups can facilitate DoI reactions through an active interaction/contribution to the five-membered “push-pull” TSs. Among them, the *ortho*-substituted ester (*o*-CO₂Me) is proved to be the most efficient as a directing and activation group mainly due to the best interaction/combination between ester and the five-membered zinc insertion TS. In order to obtain spectroscopic information about the metalation process and the regioselectivity, an in situ FT-IR study was then performed with ethyl *ortho/para*-iodobenzoates as model substrates. The zinc insertion of the *para*-derivative with Zn/LiCl scarcely proceeded at room temperature for 30 min (Supporting Information, Figure S2), whereas the metalation process of the *ortho* isomer under the same reaction conditions was rapid and efficient (Figure 4). An IR band at 1733 cm⁻¹ in the spectrum of ethyl *ortho*-iodobenzoate quickly diminished in intensity as the reaction proceeded and the newly generated red-shifted absorption at around 1675 cm⁻¹ increased during the course of the metalation. These observations are in good agreement with the computed C=O stretching frequencies of the *ortho*-substrate (1786 cm⁻¹) and the metalated intermediate (1680 cm⁻¹) (Supporting Information). However, in the absence of LiCl, zinc insertion scarcely proceeds and no band shift was observed (Supporting Information, Figure S3).
- 3) **CN group:** Interestingly, **TS17** shows a completely different form from those of others (**TS5**, **TS9**, and **TS13**). The reaction pathway of LiCl-mediated zinc insertion of 2-
- 
- Figure 3. TS structures and activation energies for *ortho*-substituted bromobenzenes at the

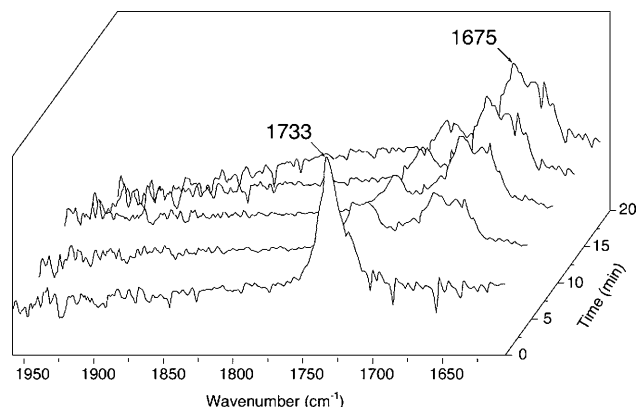


Figure 4. In situ FT-IR monitoring of the LiCl-mediated zinc insertion of ethyl *ortho*-iodobenzoate.

ciano bromobenzene is depicted in detail in Figure 5. The reactants initially form an association complex **CP17** with a reasonable stabilization energy (17.1 kcal mol⁻¹). The Zn atom then reaches the *ipso*-phenyl carbon, while maintaining the CN⁻Li coordination; thus, the *ortho*-Br atom cannot coordinate to the Li atom. Lack of coordination of the Br atom to the Li atom in **TS17** causes an overall energy loss of 18.7 kcal mol⁻¹ (this would be greater for EWG-containing substrates). Therefore, the activation energies of **TS17** and **TS18** stay about the same. The unique cylindrical symmetry of the CN group

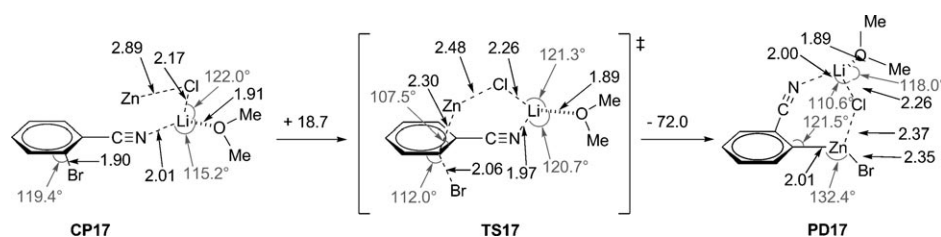


Figure 5. Plausible reaction pathways of zinc insertion into 2-cyanobromobenzene with LiCl. Energy changes at the B3LYP/631SVP level are shown in kcal mol⁻¹ on the arrows and bond lengths are shown in angstrom.

prohibits DoI selectivity and efficient activation of Zn insertion by LiCl.

In summary, DFT calculations, kinetic/thermodynamic competitive experiments, and an in situ FT-IR study of LiCl-mediated directed zinc insertion have been performed. The following aspects were addressed:

- 1) Reaction pathways of zinc insertion reactions in the presence of LiCl with (functionalized) halobenzenes, including the formation mechanism of Li⁺ZnRClHal⁻, which Koszinowski et al. recently detected in the reaction medium.
- 2) Role of LiCl in the oxidative insertion of zinc metal into aryl halides and the reason why LiCl facilitates the reaction, including some unprecedented findings, such as the 5-membered ring TS including LiCl, and secondary orbital interaction among phenyl halide substrates, Zn atom, and LiCl.
- 3) Origin of the directed *ortho* selectivity of the zinc insertion reaction.
- 4) General requirements for functionalized phenyl halide compounds to accept zinc insertion smoothly and regioselectively.

The theoretical analysis delineated above further advances the understanding of recent zinc insertion chemistry^[1–3] and should contribute to rational design for efficient preparation of functionalized arylzinc reagents and its application to useful synthetic transformations. Further extensions of this work are currently under way in our laboratory.

Experimental Section

Typical procedure for the directed zinc insertion of 1a–1c (Table 1): Lithium chloride (258 mg, 6 mmol) was placed in an argon-flushed flask and dried for 10 min at 200 °C (heat gun) under vacuum (1 mbar). Zinc powder (390 mg, 6 mmol) was added under argon and the mixture was dried again for 10 min at 200 °C under vacuum (1 mbar). The reaction flask was evacuated and refilled with argon twice. THF (2.5 mL) was added and the zinc was activated with BrCH₂CH₂Br (5 mol%) and Me₃SiCl (5 mol%). Compounds **1a**, **1b**, or **1c** (3 mmol) was added neat at room temperature and the reaction mixture was then heated at room temperature or 55 °C for 12–48 h. After cooled to room temperature, the solution of the corresponding arylzinc bromide was carefully separated from the remaining zinc powder by using a syringe and transferred to an-

other argon-flushed flask followed by the addition of saturated aqueous NH₄Cl solution (5 mL). The aqueous phase was extracted with ether (2 × 10 mL) and the combined organic phases were washed with brine (20 mL), dried over MgSO₄ and concentrated in vacuo. The crude mixture (**2+3**) was then submitted to GC/MS analyses.

Acknowledgements

We gratefully acknowledge financial support from Hoansha, the Naito foundation, Mochida memorial foundation and KAKENHI (Young Scientist (A), Houga, and Priority Area No. 459) (to M.U.), the Frontier Organization of Hokuriku University (to M.U., S.Y., and C-Y.L.), and a JSPS Research Fellowship for Young Scientists (to T.F.). The calculations were partially performed on the RIKEN Super Combined Cluster (RSCC).

Keywords: density functional calculations • insertion • lithium chloride • reaction mechanisms • regioselectivity • zinc

- [1] a) *Handbook of Functionalized Organometallics, Vol. 1* (Ed.: P. Knochel), Wiley-VCH, Weinheim, **2005**, p 251; b) *Organozinc Reagents* (Eds.: P. Knochel, P. Jones), Oxford University Press, New York, **1999**; c) H. Ren, G. Dunet, P. Mayer, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 5376–5377; d) A. Metzger, M. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107–1110; e) A. Metzger, M. Schade, G. Manolikakes, P. Knochel, *Chem. Asian J.* **2008**, *3*, 1678–1691; f) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem.* **2007**, *119*, 3876–3899; *Angew. Chem. Int. Ed.* **2007**, *46*, 3802–3824.
- [2] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem.* **2006**, *118*, 6186–6190; *Angew. Chem. Int. Ed.* **2006**, *45*, 6040–6044.
- [3] N. Boudet, S. Sase, P. Sinha, C.-Y. Liu, A. Krasovskiy, P. Knochel, *J. Am. Chem. Soc.* **2007**, *129*, 12358–12359.
- [4] a) K. Koszinowski, P. Böhrer, *Organometallics* **2009**, *28*, 771–779; b) K. Koszinowski, P. Böhrer, *Organometallics* **2009**, *28*, 100–110; c) R. Bilow, S. Deuerlein, T. Stey, R. Herbst-Irmer, H. Gornitzka, D. Stalke, *Z. Naturforsch. B* **2004**, *59*, 1471–1479.
- [5] The basis set denoted 631SVP consists of Ahlrichs' SVP all-electron basis set for the zinc and bromine atoms and 6-31+G* for the other atoms. For details of theoretical methods and chemical models, see: a) F. E. Häffner, C. Sun, P. G. Williard, *J. Am. Chem. Soc.* **2000**, *122*, 12542–12546; b) M. Uchiyama, S. Nakamura, T. Ohwada, M. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 10897–10903; c) M. Uchiyama, Y. Matsumoto, S. Usui, Y. Hashimoto, K. Morokuma, *Angew. Chem.* **2007**, *119*, 944–947; *Angew. Chem. Int. Ed.* **2007**, *46*, 926–929.
- [6] a) K. Fukui, *Acc. Chem. Res.* **1981**, *14*, 363–368; b) K. Ishida, K. Morokuma, A. Komornicki, *J. Chem. Phys.* **1977**, *66*, 2153–2156.
- [7] NPA, NRT and NBO analysis were carried out by using NBO 3.0 program on Gaussian 03. NBO analysis was performed using “CHOOSE” keywords in order to standardize the resonance structure representations of each TS. The details are given in the Supporting Information; Gaussian 03 (Revision E.01), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G.

Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **2004**.

- [8] Direct zinc insertion reactions into *ortho*-, or *para*-substituted ($-\text{CO}_2\text{Me}$, $-\text{OMe}$, $-\text{CF}_3$, $-\text{CN}$) bromobenzenes were also carried out to study the influence of different functional groups and the effect of LiCl on the substrate reactivity and regioselectivity (see the Supporting Information, TP2, Table S2, for details).
- [9] B3LYP/6-31++G** (TZVP for Zn and Br) and MP2/6-31++G** (TZVP for Zn and Br) single point energies of activation (298.15 K, kcal mol^{-1}) are as follows: **TS5**, 15.1, 13.6; **TS6**, 21.0, 20.4; **TS9**, 22.1, 20.0; **TS10**, 24.2, 25.0; **TS13**, 18.7, 17.6; **TS14**, 21.4, 20.2, respectively. These calculations do not change the conclusions of the above analysis.

Received: October 26, 2009
Published online: January 11, 2010