Aryl Ether as a Negishi Coupling Partner: An Approach for Constructing C-C Bonds under Mild Conditions

Chao Wang,*^[a, b] Takashi Ozaki,^[a, b] Ryo Takita,^[a, b] and Masanobu Uchiyama*^[a, b]

Owing to their high efficiency and broad applicability to form C–C/C–X bonds, transition-metal-catalyzed cross-coupling reactions have long been regarded as a pillar of organic synthesis.^[1] Various organometallics, catalysts, and activators have been developed for these transformations, and have found wide application both academically and industrially. The electrophiles principally exploited in these reactions have been organic iodides and bromides,^[1] and in more recent years, inert halides such as chlorides,^[2] fluorides,^[3] or pseudo-halides (nitriles)^[4]. In addition, hetero-atom-containing compounds, particularly oxygen-based substrates, have been employed.^[5] As depicted in Scheme 1, many O-based



Scheme 1. O-based substrates applied as electrophiles in cross-coupling reactions.

leaving groups, such as sulfonate,^[5] phosphate,^[5] and carboxylate,^[5–8] facilitate the coupling process because the adjacent hetero-atom moiety stabilizes the intermediate/transition state, or polarizes/activates the targeted C–O bond.^[8] Very recently, the cross-coupling of phenolic salts has also been advanced.^[9]

However, the development of efficient functionalization of the C–O bond in simple aryl ethers has remained an important challenge.^[5,10–12] Ethers are generally unreactive, and are found widely in natural products, bioactive compounds, pharmaceuticals, and functional materials. Since the pioneering work of Wenkert et al. as early as in 1979,^[9a] there were

[a] Dr. C. Wang, T. Ozaki, Prof. Dr. R. Takita, Prof. Dr. M. Uchiyama Advanced Elements Chemistry Research Team Advanced Science Institute, RIKEN 2–1 Hirosawa, Wako-shi, Saitama, 351-0198 (Japan) Fax: (+81)3-5841-0732 E-mail: chaowang@riken.jp
[b] Dr. C. Wang, T. Ozaki, Prof. Dr. R. Takita, Prof. Dr. M. Uchiyama Graduate School of Pharmaceutical Sciences The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku Tokyo 113-0033 (Japan)

E-mail: uchiyama@mol.f.u-tokyo.ac.jp

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201103784.

only several reports on transition-metal-catalyzed cross-coupling C–C bond formation reactions with aryl alkyl ethers, involving the Kumada–Tamao–Corriu (KTC)-type^[10] and the Suzuki–Miyaura (SM)-type of reactions (Scheme 2).^[11]



Scheme 2. Cross-coupling of aryl ether with different organometallics.

However, as inspiring as these results are, their application to the elaboration of complex organic structures has still been limited because of narrow functional group tolerance (KTC-type) or the need for harsh reaction conditions and additional efforts for preparation of boronic reagents (SMtype). Hence, the development of new methodologies complementary to the KTC-type and SM-type reactions for functionalization of the aryl ether C-O bond would be practically very useful. Organozinc reagents are excellent transmetalation reagents with several advantages, such as broad functional-group compatibility, high reactivity/selectivity and easy preparation,^[1,13] but to our knowledge, cross-coupling between organozinc and aryl alkyl ether (i.e., Negishi-type) has never been reported. Here, we describe the first crosscoupling reaction of aryl alkyl ethers with dianion-type zincates through selective cleavage of etheric C(sp²)-O bond, affording biaryls under mild conditions.

We started by screening suitable organozinc reagents, using the nickel-tricyclohexylphosphine (Ni-PCy₃) system as a model catalyst, because this catalyst system has the highest activity toward O-based electrophiles, such as carboxylates,^[5–8] phenolic salts,^[9] or ethers.^[10–12] Initially, several attempts to couple 2-methoxynaphthalene (1a) with PhZnX (X = Cl, Br, or Ph) under various conditions afforded no product, but only recovered starting materials. Our next approach capitalized on the high reactivity and wide chemoselectivity of organozincate reagents, which allow flexible design and fine-tuning by modification of the ligation environment. Several attempts to use monoanion-type zincates^[14-15] such as PhZnMe₂Li (readily generated through an exchange reaction between iodobenzene and Me₃ZnLi) proved unsuccessful in terms of yield. Although utilization of dianion-type zincate^[14-15] PhZnMe₃Li₂ (2a) in N,N-dimethylacetamide (DMA) also failed to provide any coupling

3482

COMMUNICATION

Table 1. Optimization of reaction conditions for nickel-catalyzed crosscoupling of aryl ether 1aa with zincate 2a.



[a] $[NiCl_2(PCy_3)]$ (4 mol%) or $[Ni(cod)_2]$ (4 mol%)/PCy₃ (8 mol%) was used as a catalyst with the same activity. Lowering either the catalyst loading or the amount of zincate reduced the yields. [b] Isolated product yield. DMA = *N*,*N*-dimethylacetamide.

product (Table 1, entry 1), surprisingly, in THF the expected coupling product 2-phenylnaphthalene (**3aa**) was obtained, albeit in low yield (entry 2). We then tested nBu_2O and toluene as typical less polar solvents and they turned out to promote the cross-coupling reaction and give better yields of **3aa** (Table 1, entries 3–4). Interestingly, as the reaction temperature was lowered, the yield of **3aa** rose to 82%, and the reaction in toluene at room temperature gave the best result (Table 1, entries 4–8).^[16] It should be mentioned that the byproduct, 2,2'-binaphthalenyl, presumably formed by homocoupling of **1a**, was also observed, and its amount decreased markedly as the temperature was decreased.

Having established effective procedures for cross-coupling of aryl ether, we proceeded to explore the scope of this reaction between assorted aryl methyl ethers and zincates; the results are summarized in Scheme 3. A variety of aryl zincates, easily generated by means of exchange reactions of aryl iodides with Me₄ZnLi₂, were treated with 1aa in the presence of a Ni catalyst. Zincates bearing electron-donating groups (2b-g) afforded biaryl compounds in high yields. Intriguingly, the methoxy group in the anisole moiety of the zincates 2e-f remained entirely intact. Zincates 2h and 2i bearing silvloxy groups presented no difficulty. The electron-withdrawing, base-sensitive amide functionality in 2j was also compatible with these conditions. Coupling reactions with zincates having expanded aromatic frameworks (21-m), such as biphenyl and naphthalenyl, proceeded successfully, indicating good potential for the application of these reactions in building large π -conjugated systems. Moreover, 2-methoxynaphthalenes bearing diverse functionalities (1b-f) underwent this reaction in good yields. 1-Methoxynaphthalene (1g) could couple with zincate 2g in an analogous trend at a slightly elevated temperature. As with the SM-type reaction developed by Tobisu and Chatani et al.,^[11] the simple anisole derivative **1h** showed lower reactivity than 1a in our method. Finally, heterocycles 1i-j also underwent this reaction, albeit in lower yield. Thus, many functional groups, including alkoxy, silvloxy, amino, silvl,



Scheme 3. Cross-coupling of aromatic ethers with aryl zincates. [a] $[NiCl_2(PCy_3)]$ (4 mol%) or $[Ni(cod)_2]$ (4 mol%)/PCy₃ (8 mol%) was used as a catalyst. Isolated product yields are given in brackets. [b] The reaction was performed at 50 °C.

amide, and heterocylic, were compatible with the conditions of this reaction.

Aryl ethers are widely used in pharmaceuticals, agrochemistry and related areas. For instance, the (+)-naproxen is a non-steroidal anti-inflammatory drug usually employed for reduction of pain fever, and inflammation.^[17] As an example of the utility for this cross-coupling method, Scheme 4 shows the phenylation of (+)-naproxen amide **1k**. This C–C bond formation was achieved efficiently, under very mild conditions, at a methoxy group that is generally regarded as unreactive, and further, without racemization at



Scheme 4. Introducing the phenyl group into (+)-naproxen amide without racemization.

Chem. Eur. J. 2012, 18, 3482-3485

www.chemeurj.org

the sensitive benzylic and α -ketonic positions. These results demonstrate the potential applicability of this method for late-stage derivatization of functional molecules. These advantageous properties are considered to be due to the unique properties of the zincate reagents, which possess

A EUROPEAN JOURNAL

good nucleophilicity and poor basicity.^[14-15] To investigate the chemoselectivity of this coupling, the reactivities of various ethers **1aa–1ac** and pivalate **1ad** were next examined (Scheme 5). Substrates with bulkier substituents showed lower reactivity, probably because the steric re-



Scheme 5. Reactivity of various ethers toward coupling with zincate (isolated product yields are given in all cases).

pulsion from the large groups prevents either the insertion of the Ni catalyst into the etheric C–O bond or the transmetalation to replace the alkoxy group. In the competitive reaction between ethers **1aa** and **1ac**, the coupling takes place on **1aa** with high selectivity (Scheme 6). This result suggests that the steric character of the alkyl substituents in the aryl ether strongly influences the facility of this reaction.

In summary, we have demonstrated the first Ni-catalyzed cross-coupling of aromatic ether and organozinc species



Scheme 6. Competitive experiment for coupling reaction with zincate between ethers **1aa** and **1ac** (GC yields are given in brackets, internal standard: *n*-dodecane).

through cleavage of the etheric C–O bond. The usage of dianion-type zincates, which have high nucleophilicity and low basicity, allows the use of mild reaction conditions, especially room temperature, and the reaction is compatible with a broad range of functional groups. Experimental and theoretical studies to extend the scope of the reaction, to develop synthetic applications, to elucidate the mechanism, and to investigate new coupling strategies are in progress.

Acknowledgements

This research was partly supported by the Mochida Memorial Foundation, the Naito Foundation, the Hoansha Foundation, and the Takeda Science Foundation. We thank Prof. Motomu Kanai and Mr. Harunobu Mitsunuma (The University of Tokyo) for the chiral HPLC measurement. C. W. also gratefully acknowledges the receipts of JSPS Fellowship and RIKEN-FPR Fellowship.

Keywords: C–O activation • cross-coupling • ethers • nickel • zincates

- Representative reviews: a) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* 2011, 111, 1417; b) J.-P. Corbet, G. Mignani, *Chem. Rev.* 2006, 106, 2651; c) F. Diederich, A. Meijere, in *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, 2004; d) E.-I. Negishi, L. Anastasia, *Chem. Rev.* 2003, 103, 1979; e) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* 2002, 102, 1359; f) K. Tamao, N. Miyaura, *Top. Curr. Chem.* 2002, 219, 1.
- [2] Recent reviews: a) A. Littke, in Metal-catalyzed coupling Reactions with Aryl Chlorides, Tosylates and Fluorides, in Modern Arylation Methods, (Eds.: L. Ackermann), Wiley-VCH, Weinheim, 2009, pp. 25-67; b) G. C. Fu, Acc. Chem. Res. 2008, 41, 1555; c) R. Martin, S. L. Buchwald, Acc. Chem. Res. 2008, 41, 1461.
- [3] Recent reviews: a) A. D. Sun, J. A. Love, *Dalton Trans.* 2010, *39*, 10362; b) H. Amii, K. Uneyama, *Chem. Rev.* 2009, *109*, 2119. Also see: ref. [2a].
- [4] M. Tobisu, N. Chatani, Chem. Soc. Rev. 2008, 37, 300.
- [5] Recent reviews: a) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* 2011, 111, 1346; b) B.-J. Li, D.-G. Yu, C.-L. Sun, Z.-J. Shi, *Chem. Eur. J.* 2011, 17, 1728; c) D.-G. Yu, B.-J. Li, Z.-J. Shi, *Acc. Chem. Res.* 2010, 43, 1486.
- [6] Reports on cross-coupling of carboxylates: a) K. Muto, J. Yamaguchi, K. Itami, J. Am. Chem. Soc. 2012, 134, 169; b) G. A. Molander, F. Beaumard, Org. Lett. 2010, 12, 4022; c) T. Shimasaki, M. Tobisu, N. Chatani, Angew. Chem. 2010, 122, 2991; Angew. Chem. Int. Ed. 2010, 49, 2929; d) B.-J. Li, Y.-Z. Li, X.-Y. Lu, J. Liu, B.-T. Guan, Z.-J. Shi, Angew. Chem. 2008, 120, 10278; Angew. Chem. Int. Ed. 2008, 47, 10124; e) B.-T. Guan, Y. Wang, B.-J. Li, D.-G. Yu, Z.-J. Shi, J. Am. Chem. Soc. 2008, 130, 14468; f) K.-W. Quasdorf, X. Tian, N. K. Garg, J. Am. Chem. Soc. 2008, 130, 14422.
- [7] Reports on the cross-coupling of carbamates, carbonates, and other similar compounds: a) K. W. Quasdorf, A. Antoft-Finch, P. Liu, A. L. Silberstein, A. Komaromi, T. Blackburn, S. D. Ramgren, K. N. Houk, V. Snieckus, N. K. Garg, J. Am. Chem. Soc. 2011, 133, 6352; b) L. Xi, B.-J. Li, Z.-H. Wu, X.-Y. Lu, B.-T. Guan, B.-Q. Wang, K.-Q. Zhao, Z.-J. Shi, Org. Lett. 2010, 12, 884; c) A. Antoft-Finch, T. Blackburn, V. Snieckus, J. Am. Chem. Soc. 2009, 131, 17750; d) N. Yoshikai, H. Matsuda, E. Nakamura, J. Am. Chem. Soc. 2009, 131, 9590; e) F.-H. Poree, A. Clavel, J.-F. Betzer, A. Pancrazi, J. Ardisson, Tetrahedron Lett. 2003, 44, 7553; f) C. Dallaire, I. Kolber, M. Gingras, Org. Synth. 2002, 78, 42; g) A. F. Brigas, R. A. W. Johnstone, J. Chem. Soc. Perkin Trans. 1 2000, 1735; h) S. Sengupta, M. Leite, D. S. Raslan, C. Quesnelle, V. Snieckus, J. Org. Chem. 1992, 57, 4066; i) P. Kocienski, N. J. Dixon, Synlett 1989, 52; j) R. A. W. Johnstone, W. N. McLean, Tetrahedron Lett. 1988, 29, 5553.
- [8] Z. Li, S.-L. Zhang, Y. Fu, Q.-X. Guo, L. Liu, J. Am. Chem. Soc. 2009, 131, 8815. Also see: ref. [7a] and ref. [7e].
- [9] The first report on cross-coupling of phenolic salts: a) E. Wenkert,
 E. L. Michelotti, C. S. Swindell, J. Am. Chem. Soc. 1979, 101, 2246;
 Recent developments: b) D.-G. Yu, B.-J. Li, S.-F. Zheng, B.-T. Guan,
 B.-Q. Wang, Z.-J. Shi, Angew. Chem. 2011, 123, 7235; Angew. Chem.
 Int. Ed. 2011, 50, 7097; c) G.-J. Chen, X. Huang, L.-X. Gao, F.-S.
 Han, Chem. Eur. J. 2011, 17, 4038; d) D.-G. Yu, B.-J. Li, S.-F. Zheng,

www.chemeurj.org

3484

COMMUNICATION

B.-T. Guan, B.-Q. Wang, Z.-J. Shi, Angew. Chem. 2010, 122, 4670; Angew. Chem. Int. Ed. 2010, 49, 4566.

- [10] For the first report on the cross-coupling of aryl/vinyl ethers, see ref. [9a]. Reports on Kumada-type reactions: a) L.-G. Xie, Z.-X. Wang, Chem. Eur. J. 2011, 17, 4972; b) B.-T. Guan, S.-K. Xiang, T. Wu, Z.-P. Sun, B.-Q. Wang, K.-Q. Zhao, Z.-J. Shi, Chem. Commun. 2008, 1437; c) J. W. Dankwardt, Angew. Chem. 2004, 116, 2482; Angew. Chem. Int. Ed. 2004, 43, 2428; d) E. Wenkert, E. L. Michelotti, C. S. Swindell, M. Tingoli, Org. Chem. 1984, 49, 4894; Recently, methylation of benzyl ether was also reported, see: e) B. L. H. Taylor, E. C. Swift, J. D. Waetzig, E. R. Jarvo, J. Am. Chem. Soc. 2011, 133, 389; f) B.-T. Guan, S.-K. Xiang, B.-Q. Wang, Z.-P. Sun, Y. Wang, K.-Q. Zhao, Z.-J. Shi, J. Am. Chem. Soc. 2008, 130, 3268.
- [11] Reports on a Suzuki-type reaction of aryl/vinyl ether: a) T. Shimasaki, Y. Konno, M. Tobisu, N. Chatani, Org. Lett. 2009, 11, 4890; b) M. Tobisu, T. Shimasaki, N. Chatani, Angew. Chem. 2008, 120, 4944; Angew. Chem. Int. Ed. 2008, 47, 4866; c) S. Ueno, E. Mizushima, N. Chatani, F. Kakiuchi, J. Am. Chem. Soc. 2006, 128, 16516; d) F. Kakiuchi, M. Usui, S. Ueno, N. Chatani, S. Murai, J. Am. Chem. Soc. 2004, 126, 2706.
- [12] Reports on a Ni-catalyzed reduction of the etheric C–O bond:
 a) A. G. Sergeev, J. F. Hartwig, *Science* 2011, 332, 439; b) M. Tobisu,
 K. Yamakawa, T. Shimasaki, N. Chatani, *Chem. Commun.* 2011, 47, 2946; c) P. Álvarez-Bercedo, R. Martin, *J. Am. Chem. Soc.* 2010, 132, 17352; Report on Ni-catalyzed amination of etheric C–O bond:
 d) M. Tobisu, T. Shimasaki, N. Chatani, *Chem. Lett.* 2009, 38, 710.
- [13] a) E.-I. Negishi, Angew. Chem. 2011, 123, 6870; Angew. Chem. Int. Ed. 2011, 50, 6738; Angew. Chem. 2011, 123, 6870; b) P. Knochel, T. Thaler, C. Diene, Isr. J. Chem. 2010, 50, 547; c) V. B. Phapale, D. J. Cardenas, Chem. Soc. Rev. 2009, 38, 1598; d) E.-I. Negishi, Z. Huang, G. Wang, S. Mohan, C. Wang, H. Hattori, Acc. Chem. Res.

2008, 41, 1474; e) Z. Rappoport, I. Marek, in *The Chemistry of Organozinc Compounds*, Wiley-VCH, New York, 2006.

- [14] For recent reviews, see: a) R. E. Mulvey, Acc. Chem. Res. 2009, 42, 743; b) S. Nakamura, M. Yonehara, M. Uchiyama, Chem. Eur. J. 2008, 14, 1068; c) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, Angew. Chem. 2007, 119, 3876; Angew. Chem. Int. Ed. 2007, 46, 3802; d) A. E. H. Wheatley, New J. Chem. 2004, 28, 435.
- [15] For reports on reactions and applications of zincates from our group, see: a) K. Snegaroff, S. Komagawa, F. Chevallie, P. C. Gros, S. Golhen, T. Roisnel, M. Uchiyama, F. Mongin, *Chem. Eur. J.* 2010, *16*, 8191; b) T. Furuyama, M. Yonehara, S. Arimoto, M. Kobayashi, Y. Matsumoto, M. Uchiyama, *Chem. Eur. J.* 2008, *14*, 10348; c) M. Uchiyama, Y. Kobayashi, T. Furuyama, S. Nakamura, Y. Kajihara, T. Miyoshi, T. Sakamoto, Y. Kondo, K. Morokuma, *J. Am. Chem. Soc.* 2008, *130*, 472; d) S. Nakamura, M. Uchiyama, M. Kobayashi, Y. Matsumoto, K. Tanaka, *J. Am. Chem. Soc.* 2006, *128*, 8404; f) S. Nakamura, M. Uchiyama, T. Ohwada, *J. Am. Chem. Soc.* 2005, *127*, 13116; g) S. Nakamura, M. Uchiyama, T. Ohwada, *J. Am. Chem. Soc.* 2004, *126*, 11146; h) M. Uchiyama, M. Kameda, O. Mishima, N. Yokoyama, M. Koike, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.* 1998, *120*, 4934.
- [16] We screened a variety of commonly used ligands and Ni sources, but most showed little or no activity, and those described here, [NiCl₂-(PCy₃)] and [Ni(cod)₂]/PCy₃, gave the best results. Further studies to find improved catalysts/ligands for reactions of this type are in progress.
- [17] P. J. Harrington, E. Lodewijk, Org. Process Res. Dev. 1997, 1, 72.

Received: December 2, 2011 Published online: February 28, 2012