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Regioselective, Transition Metal-Free C−O Coupling Reactions Involving Aryne Intermediates

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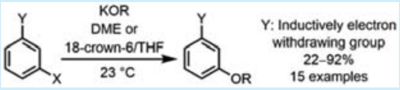
Ⓢ *Supporting Information*



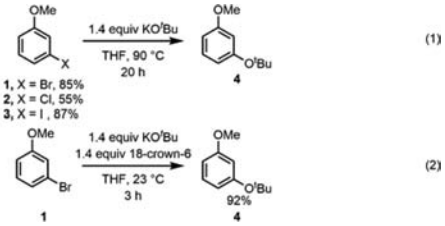
ABSTRACT: A new transition-metal-free synthetic method for C−O coupling between various aryl halides and alkoxides is described. This type of transformation is typically accomplished using palladium catalysts containing a specialized phosphine ligand. The reactions reported here can be performed under mild, ambient conditions using certain potassium alkoxides and a range of aryl halides, with iodide and bromide derivatives giving the best results. A likely mechanistic pathway involves the *in situ* generation of an aryne intermediate, and directing groups on the aryl ring inductively control regioselectivity.

Aryl ethers are an important class of compounds that include many examples of important pharmaceuticals and natural products.[1] Consequently, a great deal of research has focused on the synthesis of these compounds. Current common methods for the preparation of aryl ethers include the Williamson ether synthesis,[2a] nucleophilic substitution on electron-deficient aryl rings (S_NAr),[2b−d] the Mitsunobu reaction,[2e,f] and the transition-metal catalyzed cross-coupling of an aryl halide with an alcohol.[1a,3] Despite the success of palladium- and copper-catalyzed aryl C−O coupling reactions, transition-metal-free methods for aryl C−O bond formation are desirable in many applications where tolerance for heavy metals in the final products is low, as in the pharmaceutical industry.[4]

One approach to transition-metal-free aryl C−O bond formation involves the addition of an alcohol to an aryne intermediate, and many related carbon−heteroatom coupling reactions have been reported.[2g−l,5] While this approach has been known for a long time, the reported syntheses require forcing conditions for the generation of the aryne intermediate, and are limited by low regioselectivities. Recently, the availability of more efficient aryne precursors has allowed utilization of milder conditions and significant improvements in selectivity.[5,6a] However, this approach relies on the synthesis of silyl triflate arenes with appropriate substitution patterns. Herein, we present a transition-metal-free synthesis of aryl−alkyl ethers that features good yields and regioselectivities, using simple alkoxide and aryl halide starting materials. The reaction is shown to proceed via aryne intermediates that are generated at ambient temperature and selectively trapped by the alkoxide.

Initial efforts to discover a new synthetic method for aryl C−O coupling catalysis involved screening candidate first-row transition metal catalysts. Interestingly, control experiments suggested that 3-haloanisoles efficiently couple with potassium *tert*-butoxide in the absence of transition-metal catalysts at 90 °C in THF (Scheme 1). Further exploration of this reaction revealed that while potassium *tert*-butoxide is an efficient coupling partner for 3-haloanisoles, sodium *tert*-butoxide does not produce any C−O coupled product under the same conditions.

Scheme 1. Transition-Metal-Free C−O Coupling Using KO^{t}Bu



Given the significant difference in reactivity between potassium and sodium *tert*-butoxide, we sought to further examine the influence of the cation on the reaction. Thus, 18-crown-6 and 15-crown-5 were added to the reactions of potassium and sodium *tert*-butoxide, respectively, in an attempt to sequester the cation and mitigate any effect it might have on the reaction. However, while the addition of 15-crown-5 had no effect on the sodium *tert*-butoxide reaction, the addition of 18-crown-6 to the potassium *tert*-butoxide reaction resulted in a substantial increase in reactivity. In the presence of the crown ether, the reaction proceeded at ambient temperature and resulted in an increased yield (Scheme 1).

On the basis of the outcomes of the these reactions, three possible mechanisms were envisioned: (1) catalysis by a trace amount of a metal impurity;[7] (2) the intermediacy of an aryne intermediate;[5,8] (3) initiation of a chain reaction by a single electron transfer (SET) process (Scheme 2).[8]

To investigate the first possibility, careful control experiments were carried out to ensure that the reaction was in fact transition-metal free. Since iron is found as an impurity in

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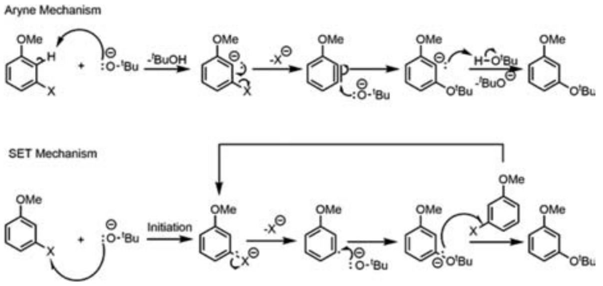
Scheme 2. Possible Pathways for ArO^{t}Bu Formation

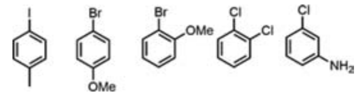


potassium *tert*-butoxide,[9] the reaction was carried out with and without additional $FeCl_2$ (10 mol %) and monitored over time (Supplementary Figure 1, SI, Supporting Information). The reaction exhibited no change in the rate or the yield of product.

As an additional control, the reaction was carried out using independently sourced reagents. Potassium *tert*-butoxide and 3-bromoanisole (**1**) purchased from different sources (Strem and Sigma-Aldrich) were observed to provide identical results. The reaction was also carried out using both sublimed and unsublimed potassium *tert*-butoxide purchased from Sigma-Aldrich; both reactions resulted in the same overall conversion. On the basis of these results, the possibility of a trace amount of metal impurity as a catalyst for the reaction was eliminated.

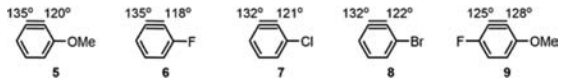
To distinguish between the aryne and SET mechanisms, coupling reactions with the *ortho* and *para* regioisomers of bromoanisole were examined. The C−O coupling reaction was found to occur only when the methoxy group was *meta* to the bromine. This outcome may be attributed to the acidic proton between the inductively electron-withdrawing halide and methoxy groups. Presumably, the presence of a doubly activated proton is required for generation of the aryne intermediate by deprotonation with potassium *tert*-butoxide. This is further supported by the failure of aryl halides lacking an inductively electron-withdrawing group *meta* to halogen to react with potassium *tert*-butoxide (Scheme 3). For 3-chloroaniline, coupling is presumably inhibited by competing deprotonation to the corresponding anilide.

Scheme 3. Substrates That Failed To Couple with KO^{t}Bu



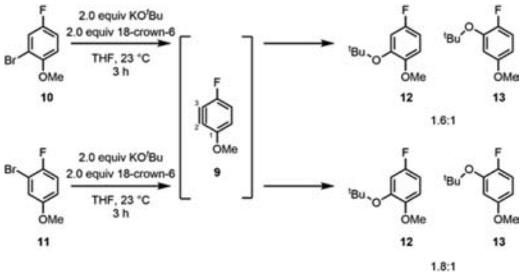
An interesting aspect to the observed reaction (2) concerns its high regioselectivity, and possible implications for the proposed aryne-based mechanism.[8] Relevant results from density functional calculations, published recently by Garg and co-workers, predict the regioselectivity of nucleophilic attack onto 3-substituted benzynes by comparing the distortion angle present in the rings of geometry-optimized structures (Scheme 4).[6] In particular, it is suggested that aryne carbons associated with the largest deviation of the C−C−C bond angle from 120° are more likely to undergo attack by the nucleophile. The prediction from this study is that bond angle differences of greater than 4° for the two aryne carbons should lead to high levels of regioselectivity.[6]

Scheme 4. DFT Computationally Optimized Strutures[6]



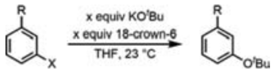
Thus, the 15° difference in angles for **5** appears to explain the high regioselectivity of reaction (2). A further test of this hypothesis, and of the proposal of an aryne intermediate, was based on reactions of potassium *tert*- butoxide with 2-bromo- (**10**) and 3-bromo-4-floroanisole (**11**) (Scheme 5). Assuming a mechanism involving an aryne intermediate, the two substrates should give the same intermediate (**9**), and due to the small calculated difference in angles (3°, Scheme 4), the same product distribution is expected for both reactions (Scheme 5). Indeed, product ratios of 1.6:1 and 1.8:1 were observed with the primary product being derived from an attack at C-2.

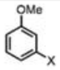
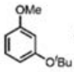
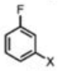
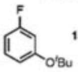
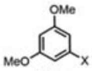
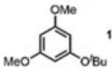
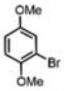
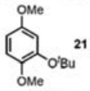
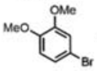
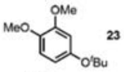
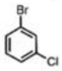
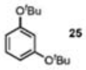
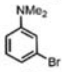
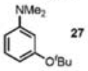
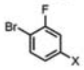
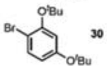
Scheme 5. Evidence for an Aryne Intermediate



On the basis of the assumption that the reaction goes through an aryne intermediate, a series of 3-substituted arylhalides were examined, and these gave the predicted products with good yields and selectivities (Table 1). Note that 3-bromo-*N*,*N*-dimethylaniline **26**, unlike the related 3-

Table 1. Substrates Scope for the Aryl Halides



substrate		amount (equiv)	time (h)	product		yield (%)[a]
	**1**, X=Br **2**, X=Cl **3**, X=I	1.4 2.5 2.0	3 20 3		**4**	92 90 92
	**14**, X=Br **16**, X=I	1.4 1.4	3 3		**15**	92 90
	**17**, X=Br **19**, X=Cl	2.0 2.5	20 20		**18**	86 83
	**20**	2.0	20		**21**	86
	**22**	2.0	20		**23**	79
	**24**	4.0	20		**25**	73
	**26**	4.0	48		**27**	55[b]
	**28**, X=Br **29**, X=Cl	2.0 3.0	20 20		**30**	35 22[c]

[a]Isolated yield. [b]Yield corresponds to a 48 h reaction time and 60% conversion. [c]A second product is 3,5-di-*tert*-butoxy-chlorobenzene (22%).

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chloroaniline, is an effective substrate. Substrates **28** and **29** were chosen to examine selectivities of the coupling for appropriate trihaloarenes. Note that in these cases the flouride is more activated toward S_NAr substitution. For **29** both chloro- and bromo-substituted products are isolated in comparable yields, as a consequence of competing deprotonations from two positions.

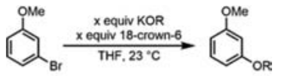
Because of the relatively high price of 18-crown-6, it is desirable to use only catalytic amounts of the crown ether. To investigate this possibility, the conversions associated with four reactions involving different quantities of 18-crown-6 (0 equiv, 0.05 equiv, 0.10 equiv, 1.40 equiv) were examined over time, and the results are shown in Supplementary Figure 2. The reaction proceeded with similar yields when only 0.10 equiv of 18-crown-6 was present in the coupling reaction with **1** (91% versus 95% with an excess amount of crown ether), albeit at a slower rate. In general, larger amounts of 18-crown-6 lead to higher reaction rates and greater overall conversions, with the yield dropping off substantially with less than 0.10 equiv of 18-crown-6 added to the reaction.

Given the results shown above, further studies using DME as the reaction solvent and no 18-crown-6 were conducted, employing selected aryl halides (Supplementary Table 1). It was found that although the reaction rate significantly decreased and more potassium *tert*-butoxide was required, the reactions using substrates **1**, **3**, and **22** in DME resulted in similar overall conversion.

To evaluate the relative reactivities of different 3-haloanisole derivatives under optimized reaction conditions, the conversions of **1**, **2**, and **3** were monitored over time (Supplementary Figure 3). These results indicate that the bromo- and iodo-derivatives generate the aryne intermediate much more rapidly than the corresponding chloride. This is consistent with known trends in aryne-generation reactions, which are distinctly slower with a chloride leaving group.[8] Note that 3-bromofluorobenzene (**14**) was converted exclusively to 1-(*tert*-butoxy)-3-fluorobenzene (**15**), which does not react further with an excess of potassium *tert*-butoxide under the reaction conditions. Thus, as expected, fluoride is an even poorer leaving group for aryne formation.

To examine the scope of possible oxygen-based coupling partners for this reaction, various potassium reagents were examined (Table 2). Although the more basic potassium alkoxides generally give acceptable to excellent yields of the C−O coupled products, potassium hydroxide, potassium methoxide, and potassium 3,5-di-*tert*-butylphenoxide did not provide product under the same conditions (Supplementary Table 2). Use of the sterically demanding alkoxide, potassium fenchyl alkoxide (**36**), results in substantial dehalogenation of **1** and an inseparable 1:10 mixture of the ortho (**37**) and meta (**38**) isomers of the product (Scheme 6). The dehalogenation may occur via a mechanism similar to that of the Meerwein−Pondorf−Verley reduction (Scheme 6).[8,10] In this case, because of steric hindrance, it is difficult for the alkoxide to approach the newly generated aryne, and as a result α-hydrogen transfer is competitive with the addition of the alkoxide to the aryne.

Table 2. Oxygen-Based Coupling Partners



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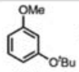
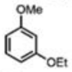
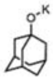
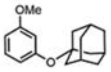
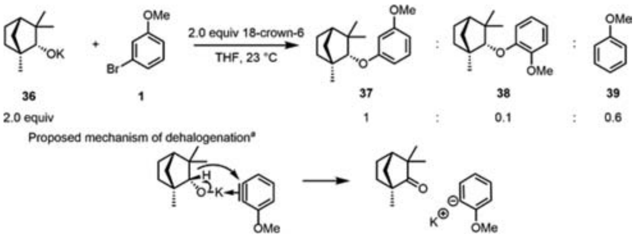
oxygen based coupling partner	amount (equiv)	time (h)	product	yield (%)[a]
KO^{t}Bu **31**	1.4	3	 **4**	92
KOEt **32**	2.2	20	 **33**	90
 **34**	2.2	20	 **35**	85

[a] Isolated yield.

Scheme 6. Reaction with Fenchyl Alkoxide

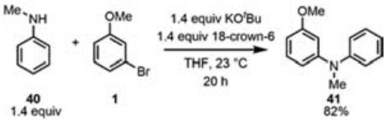


[a] Fenchone is observed in the product mixture using GC−MS.

To further illustrate the potential of this reaction in organic synthesis, comparisons with other synthetic conditions utilizing transition metal catalysts are listed in Supplementary Table 3. These results indicate that for certain combinations of aryl halides and alkoxides, the metal-free reactions described herein are easier to carry out and provide a comparable yield, with no heating or additional reagents; however, transition metal catalyzed C−O coupling reactions have a wider substrate scope of aryl halide and oxygen-based coupling partners.

Preliminary results indicate that the chemistry described above may be extended to additional nucleophiles. The addition of *N*-methylaniline (**40**, 1.4 equiv) to the reaction mixture involving **1** and KO^{t}Bu provided the C−N coupled product in 82% yield (Scheme 7).

Scheme 7. Reaction Involving *N*-Methylaniline



In conclusion, a highly regioselective transition-metal-free C−O coupling method that proceeds at ambient temperature through an aryne intermediate has been developed. This reaction appears to be generally useful for the introduction of alkoxy substituents *meta* to an inductively electron-withdrawing group (e.g., −OMe, −F, −Cl), for a relatively wide range of aryl halides. Reactions employing other nucleophiles (e.g., *N*-methylanilide) are possible, and further studies will explore this possibility.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00183.

Experimental details, data, and spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (b) Cai, Q.; He, G.; Ma, D. *J. Org. Chem.* **2006**, *71*, 5268. (c) Toumi, M.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 572. (d) Sinclair, P. J.; Wong, F.; Wyvratt, M.; Staruch, M. J.; Dumont, F. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1035. (e) Sinclair, P. J.; Wong, F.; Staruch, M. J.; Wiederrecht, G.; Parsons, W. H.; Dumont, F.; Wyvratt, M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2193.

(2) Selected references for transition metal free aryl C−O bond formation: (a) Fuhrmann, E.; Talbiersky, J. R. *Org. Process Res. Dev.* **2005**, *9*, 206. (b) Kingsbury, C. A. *J. Org. Chem.* **1964**, *29*, 3262. (c) Bartoli, G.; Todesco, P. E. *Tetrahedron Lett.* **1968**, *9*, 4867. (d) Henderson, A. S.; Medina, S.; Bower, J. F.; Galan, M. C. *Org. Lett.* **2015**, *17*, 4846. (e) Mitsunobu, O. *Synthesis* **1981**, *1*, 1. (f) Manivel, P.; Rai, N. P.; Jayashankara, V. P.; Arunachalam, P. N. *Tetrahedron Lett.* **2007**, *48*, 2701. (g) Bunnett, J. F.; Hrutfiord, B. J. *J. Am. Chem. Soc.* **1961**, *83*, 1691. (h) Zoratti, M.; Bunnett, J. F. *J. Org. Chem.* **1980**, *45*, 1769. (i) Kumar, A.; Bhakuni, B. S.; Prasad, C. D.; Kumar, S.; Kumar, S. *Tetrahedron* **2013**, *69*, 5383. (j) Cano, R.; Ramon, D. J.; Yus, M. *J. Org. Chem.* **2011**, *76*, 654. (k) Yuan, Y.; Thomé, I.; Kim, S. H.; Chen, D.; Beyer, A.; Bonnamour, J.; Zuidema, E.; Chang, S.; Bolm, C. *Adv. Synth. Catal.* **2010**, *352*, 2892. (l) Cram, D. J.; Rickborn, B.; Knox, G. R. *J. Am. Chem. Soc.* **1960**, *82*, 6412. (m) Lindstedt, E.; Ghosh, R.; Olofsson, B. *Org. Lett.* **2013**, *15*, 6070. (n) Liu, F.; Yang, H.; Hu, X.; Jiang, G. *Org. Lett.* **2014**, *16*, 6408. (o) Jalalian, N.; Petersen, T. B.; Olofsson, B. *Chem. - Eur. J.* **2012**, *18*, 14140. (p) Jalalian, N.; Ishikawa, E. E.; Silva, L. F., Jr.; Olofsson, B. *Org. Lett.* **2011**, *13*, 1552. (q) Sach, N. W.; Richter, D. T.; Cripps, S.; Tran-Dubé, M.; Zhu, H.; Huang, B.; Cui, J.; Sutton, S. C. *Org. Lett.* **2012**, *14*, 3886. (r) Shintou, T.; Mukaiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 7359.

(3) Selected references for Pd or Cu catalyzed C−O coupling reactions: (a) Gowrisankar, S.; Sergeev, A. G.; Anbarasan, P.; Spannenberg, A.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 11592. (b) Bacon, R. G. R.; Rennison, S. C. *J. Chem. Soc. C* **1969**, 312. (c) Marcoux, J. F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539. (d) Wolter, M.; Nordmann, G.; Job, J. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973. (e) Aalten, H. L.; van Koten, C.; Grove, D. M.; Kuilman, T.; Piekstra, O. G.; Hulshof, L. A.; Sheldon, R. A. *Tetrahedron* **1989**, *45*, 5565. (f) Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770. (g) Mann, G.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268. (h) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224. (i) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369. (j) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2498. (k) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 10718. (l) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694.

(4) (a) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889. (b) Rosso, V. W.; Lust, D. A.; Bernot, P. J.; Grosso, J. A.; Modi, S. P.; Rusowicz, A.; Sedergran, T. C.; Simpson, J. H.; Srivastava, S. K.; Humora, M. J.; Anderson, N. G. *Org. Process Res. Dev.* **1997**, *1*, 311.

(5) Recent reviews on the use of aryne in organic synthesis: (a) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (b) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (c) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579. (d) Mehta, V. P.; Punji, B. *RSC Adv.* **2013**, *3*, 11957.

(6) Selected references on the aryne distortion model: (a) Medina, J. M.; Mackey, J. L.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 15798. (b) Picazo, E.; Houk, K. N.; Garg, N. K. *Tetrahedron Lett.* **2015**, *56*, 3511. (c) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G.- Y. J.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 1267. (d) Im, G.-Y. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.-Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, *132*, 17933. (e) Bronner, S. M.; Goetz, A. E.; Garg, N. K. *Synlett* **2011**, *18*, 2599. (f) Goetz, A. E.; Garg, N. K. *J. Org. Chem.* **2014**, *79*, 846.

(7) Thomé, I.; Nijs, A.; Bolm, C. *Chem. Soc. Rev.* **2012**, *41*, 979.

(8) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: United States, 2006.

(9) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. *Nat. Chem.* **2010**, *2*, 1044.

(10) (a) Wilds, A. L. *Org. React.* **1944**, *2*, 178. (b) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* **1994**, *10*, 1007. (c) Cohen, R.; Graves, C. R.; Nguyen, S. T.; Martin, J. M. L.; Ratner, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 14796. (d) Nerdel, F.; Frank, D.; Barth, G. *Chem. Ber.* **1969**, *102*, 395.

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