Organic Chemistry |Hot Paper|

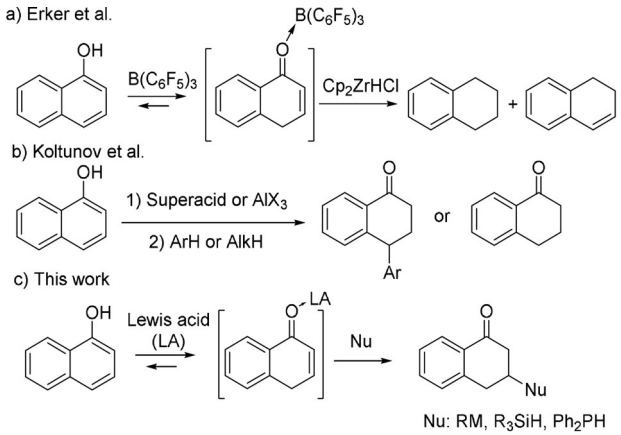
Lewis Acid Promoted Dearomatization of Naphthols

Kirill Kulish, Cosimo Boldrini, Marta Castiñeira Reis, Juana M. Pérez, and Syuzanna R. Harutyunyan*[a]

Abstract: Two-step dearomative functionalization of naphthols promoted by Lewis acids and copper(I) catalysis was developed. Initially, Lewis acid complexation inverted the electronic properties of the ring and established an equilibrium with the dearomatized counterpart. Subsequent trapping of the dearomatized intermediate with organometallics as well as organophosphines was demonstrated and provided the corresponding dearomatized products.

Biologically active natural products and pharmaceutically active compounds often contain a high percentage of sp^3 carbons embedded in cyclic structures, commonly six-membered systems.[1,2] Dearomative strategies allow functionalization of readily available arenes and offer rapid access to complex six-membered alicyclic compounds with substitution patterns that are difficult to achieve in a single reaction step with other methods.[3] As a result, the area of dearomative functionalizations has seen major development in recent years, with reductive,[4] oxidative,[5] transition-metal-mediated,[6] and cycloaddition-based[7] processes having been reported. Nevertheless, dearomative functionalization still represents a challenge, especially in intermolecular processes and with non-activated arenes.[3d]

Building on our recent developments in Lewis acid (LA)-promoted C–C bond forming reactions with organometallic reagents[8] we were interested to adapt these strategies to achieve dearomative functionalization of arenes. This idea was initially triggered by a report of Erker and co-workers from 1999,[9] in which the authors reported that the tautomerization equilibrium of naphthol can be shifted towards the keto form in the presence of a LA, namely $B(C_6F_5)_3$. Although the authors could stabilize naphthalen-1(4*H*)-one with the LA, the dearomatization of naphthol was not regioselective, and the resulting alicyclic compound was not further functionalized (Scheme 1 a).



Scheme 1. a) and b) State of the art; c) this work.

In addition to Erker and co-workers' seminal report, Koltunov et al. reported on the dearomatization of naphthol derivatives using an excess of super acids and/or aluminum-based LAs.[10] In their work, the dearomatization process is followed by an attack of an external nucleophile, such as benzene or toluene, and even cyclohexane when radical processes intervene.[10]

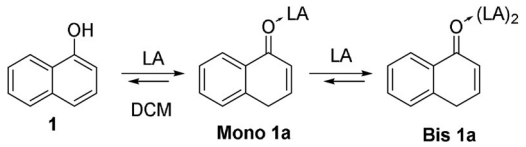
Given these results, we wondered if it is possible to obtain the dearomatized product through the combined use of LA and copper(I)-catalyzed conjugate addition. A major challenge for this strategy is the compatibility between the acidic conditions required for the dearomatization step and the reactive, often basic, nucleophiles needed for the second step.

We started our investigations by assessing the conditions required to shift the keto–enol equilibrium completely to the dearomatized keto-form (Table 1). As a first step we reproduced the experiments reported by Erker and co-workers using $B(C_6F_5)_3$ in toluene.[9] In agreement with the previous report, we found that upon the addition of an equimolar amount of $B(C_6F_5)_3$ to 1-naphthol (**1**) in toluene, the keto–enol equilibrium between **1** and naphthalenone/$B(C_6F_5)_3$ complex **1 a** is established in a 25:75 ratio. We also observed that this ratio is sensitive to the solvent and can be changed to 50:50 by using dichloromethane (DCM) as a solvent instead (entry 2). Other boron-based LAs such as BPh_3, BBr_3, and $B(OiPr)_3$ did not trigger the formation of **1 a**. To maximally shift the equilibrium towards the keto-form other types of LAs were

[a] K. Kulish, C. Boldrini, Dr. M. Castiñeira Reis, Dr. J. M. Pérez, Prof. Dr. S. R. Harutyunyan
Stratingh Institute for Chemistry
University of Groningen
Nijenborgh 4, 9747 AG, Groningen (The Netherlands)
E-mail: s.harutyunyan@rug.nl

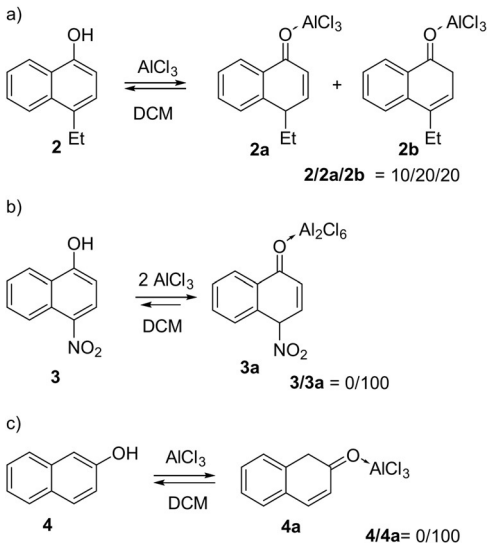
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/chem.202003392.

Table 1. Optimizations for dearomatization.[a]



Entry	LA	Solvent	LA equiv.	Ratio[b] 1/Mono 1a/Bis 1a
1	$B(C_6F_5)_3$	toluene	1	25:75:0
2	$B(C_6F_5)_3$	DCM	1	50:50:0
3[c]	$AlCl_3$	toluene	1	–
4[d]	$AlCl_3$	DCM	1	0:100:0
5[e]	**$AlCl_3$**	**DCM**	**2**	**0:67:33**
6	$AlCl_3$	DCM	3	0:0:100

[a] Reaction conditions: 1-naphthol (**1**) (60 mM in DCM), LA, RT, N_2 atmosphere. [b] Ratio was determined using ^{1}H NMR spectroscopy. [c] Heterogeneous mixture with traces of **1a** (in the solution) was obtained probably due to low solubility of **1a** in toluene. [d] Cloudy yellow solution at RT; suspension with pale-yellow precipitate at 0 °C. [e] Clear red solution at RT and at 0 °C.



Scheme 2. Determination of the keto–enol equilibrium upon addition of $AlCl_3$ to substituted naphthols **2**–**4**. Reaction conditions: 1-naphthol (**1**) (60 mM in DCM), $AlCl_3$ (2 equiv.), RT, N_2 atmosphere. Ratios are determined by ^{1}H NMR spectroscopy.

screened as well, revealing $AlCl_3$ as the most promising candidate for dearomatization purposes (for details see Table S1).

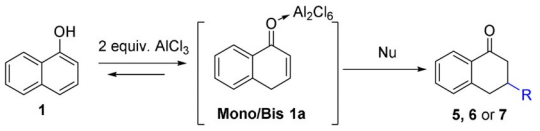
In toluene, the mixture between $AlCl_3$ and 1-naphthol was not fully dissolved, and in the solution only trace amounts of the ketone form **1a** were observed (Table 1, entry 3). In contrast, the mixture is soluble in DCM, with only **1a** being detected (entry 4). Interestingly, we found that addition of an extra equivalent of $AlCl_3$ led to the binding of two molecules of $AlCl_3$ to the 1-naphthol (determined by ^{1}H NMR spectroscopy, see the Supporting Information for further details) and that the resulting complex **Bis 1a** is more soluble than the monocoordinated one (entries 5 and 6). Importantly, in polar coordinating solvents such as THF, methyl *tert*-butyl ether (MTBE), or acetone, only the enol form is present.

We also evaluated the keto–enol equilibrium under the same optimized conditions, when using 1-naphthols substituted at position 4, namely 4-ethylnaphthalen-1-ol **2** and 4-nitronaphthalen-1-ol **3** (Scheme 2a–c). The reaction of 1-naphthol **1** leads to only one species with a methylene group at position 4, whereas in the case of 4-ethylnaphthalen-1-ol **2** two tautomeric ketones were observed (Scheme 2a). In contrast, 4-nitronaphthalen-1-ol **3** forms a complex that is insoluble in DCM upon addition of 1 equiv. of $AlCl_3$. The insolubility is remedied by the addition of a second equiv. of $AlCl_3$ (Scheme 2b). The optimized dearomative conditions were also applied to the regioisomer 2-naphthol **4**, and 2-naphthone **4a** was the only dearomatized species observed by NMR spectroscopy (Scheme 2c).

Therefore, the next question we moved to assess was the nucleophilic functionalization of the in situ-formed **1a**. To this end, we explored how the presence of different classes of nucleophiles affects the LA-assisted tautomerization and the reactivity of the 1-naphthone as a Michael acceptor.

First, we looked at organometallics as potential nucleophiles to functionalize naphthols. There are two important factors that can influence the keto–enol equilibrium in such reactions, when using organometallics: a) the basicity of the reagent and b) the coordinating nature of the original solvent in which the organometallic is prepared. Organometallics are usually stabilized by coordinating solvents, which can be detrimental for the tautomerization. To avoid this problem, we opted for organometallics soluble in solvents such as hexane or its analogues and chose EtLi (1.0 M in hexane/benzene) and Et_2Zn (1.0 M in hexane) as nucleophiles.[12] When using EtLi only traces of the conjugate addition product **5a** were obtained (Table 2, entry 1). On the other hand, we found that the addition of Et_2Zn in the presence of $AlCl_3$ affords **5a** in low yield without

Table 2. Dearomatization followed by nucleophilic addition.[a]



Entry	**5**–**7**, Nu (equiv.)	Solvent	Catalyst (5 mol%)	Time [h]	Yield[b] [%]
1[c]	**5a**, EtLi (2)	toluene	CuCl/dppf	24	–
2	**5a**, Et_2Zn (2)	DCM	–	0.1	7
3	**5a**, Et_2Zn (2)	DCM	CuCl/dppf	0.1	50
4	**6a**, Ph_2PH (1.1)	DCM[d]	–	24	71
5	**6a**, Ph_2PH (1.1)	DCE	–	24	85
6[e]	**6a**, Ph_2PH (1.1)	DCM	–	72	35
7	**6b**, *p*MeO-Ph_2PH (1.1)	DCM	–	24	71
8	**7a**, $HSiEt_3$ (1.2)	DCM	CuCl/dppf	0.1	60

[a] Reaction conditions: 1-naphthol (**1**) (60 mM in DCM), $AlCl_3$ (2 equiv.), RT, N_2 atmosphere. [b] Yields are those for the isolated products. [c] Reaction conditions: 1-naphthol (**1**) (60 mM in toluene), $AlCl_3$ (2 equiv.), 0 °C, N_2 atmosphere. Traces of product. [d] When using toluene as a solvent 73% conversion of **1** towards product **6a** was observed with traces of side products. [e] Reaction with a substoichiometric amount of $AlCl_3$ (0.1 equiv.).

catalyst, but with satisfactory yield when adding 5 mol% of CuCl/dppf (dppf = 1,1′-ferrocenediyl-bis(diphenylphosphine)) as catalyst,[13] at room temperature and with a short (10 min) reaction time (compare Table 2, entries 2 and 3).

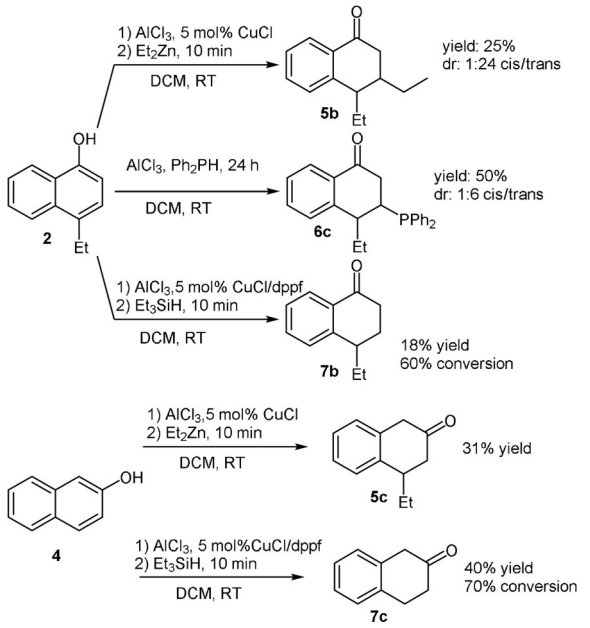
The maximum conversion (and therefore isolated yield) of the reaction, as measured by NMR spectroscopy, is 50%, which could be indicative of the formation of dimers bridged by the LA (see below). After a simple work-up the reaction gives only two products, namely the product of the 1,4-addition to α,β-unsaturated ketone and the starting material (50:50, NMR yields in %). Subjecting this mixture of products again to the reaction conditions resulted in a 75% yield of the desired product and 25% of starting material.

Next, we moved to explore the reactivity of another type of nucleophile, namely phosphines, in the addition reaction to **1**, both with and without copper catalyst. In contrast to the fast reaction time observed with Et_2Zn the phospha-Michael addition requires significantly longer reaction times, providing 71% yield of the addition product in 24 h at room temperature (Table 2, entry 4). Anticipating that weaker coordinating solvents could aid the transformation by increasing LA binding, we decided to screen dichloroethane (DCE) as a solvent for this reaction. In this case, we were able to obtain 85% yield of addition product (entry 5).

Phosphines are less basic than the considered organometallic reagents. This implies that, even though they can deprotonate **1**, an acid/base equilibrium will be established, and it should be possible to use a catalytic amount of $AlCl_3$. Attempting the reaction with 0.1 equiv. of $AlCl_3$ instead of 2 equiv. did indeed allow the phospha-Michael addition to proceed, albeit with a significantly reduced reaction rate (Table 2, entry 6). Finally, *p*-OMe diphenyl phosphine was used as an example of an electron-rich phosphine, resulting in 71% yield of addition product (entry 7).

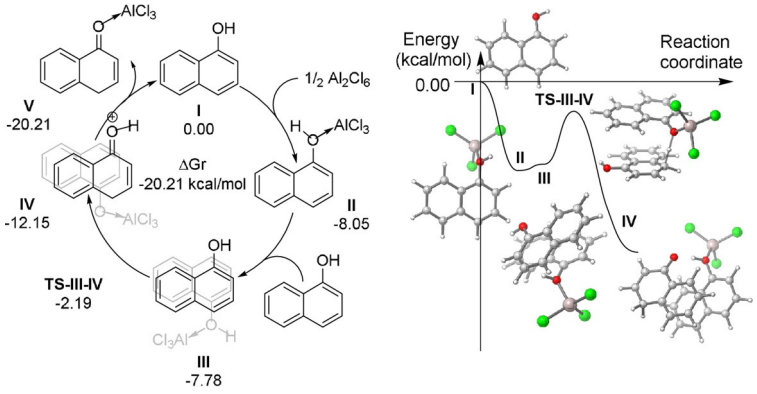
Since the reduction of activated double bonds using silanes is a well-established protocol,[14] we asked ourselves whether we could use this methodology to achieve the formal reduction of naphthol via the unsaturated keto-intermediate **1a**. For this purpose, Et_3SiH was tested in the LA-promoted dearomatization reaction. We were pleased to find that the reduced product could be obtained within 10 min in 60% yield (Table 2, entry 8) in the copper catalyzed reaction (5 mol% of CuCl/dppf). The presence of CuCl is mandatory for the reaction to take place; otherwise a series of radical processes promoted by R_2AlH takes place.[15]

The addition reactions of C-, P- and H-nucleophiles were also examined for naphthol substrates **2** and **4**.[16] A selection of the results is presented (see the Supporting Information for the complete data set) in Scheme 3. We were elated to discover both substrates reacted, although with generally lower yields than those obtained with substrate **1**. Lower yields obtained with naphthol **2** can be rationalized by the formation of the two ketones in equimolar quantities, one of which is less reactive due to the lack of direct conjugation between the double bond and the ketone moiety. In the case of substrate **4** lower yields can be attributed to the lower reactivity of the double bond conjugated to the aromatic ring.



Scheme 3. Dearomatization/nucleophilic addition sequence applied to substrates **2** and **4**.

In order to obtain insight into the mechanism behind this dearomatization protocol we turned to molecular modelling (Scheme 4) and studied it with the assumption that $AlCl_3$ exists in solution as a dimer Al_2Cl_6. We found that in the energetically most feasible pathway naphthol **I** acts, first, as a Lewis base, interacting with Al_2Cl_6 and forming species **II** (−8.05 kcal mol^{-1}). The exergonicity of this step can be rationalized by the high affinity between Al and O. In species **II** the electron density on the naphthol ring is decreased and consequently the acidity of the -OH group increased, thus facilitating its interaction with another naphthol molecule. Once formed, species **II** can interact with a second (non-activated) naphthol molecule in a



Scheme 4. Mechanistic proposal for the intermolecular dearomatization of naphthol. Calculations were performed at the PCM(DCM)/M06/def2svpp computational level. The energies reported correspond to relative Gibbs free energies computed at normal conditions of temperature and pressure and expressed in kcal mol^{-1}.

slightly less exergonic process that yields **III** (Scheme 4). Species (**III**) can exist in different conformations, but once the reactive conformation is in place, it forms the dearomatized species **IV**. This step involves an energy penalty of 5.59 kcal mol^{-1} (**TS-III-IV**). Species **IV** can further reorganize towards species **V**, releasing a naphthol molecule in the process. In this regard, it should be mentioned that **IV** can form species **II** with the concomitant release of a protonated tetralone; however, this process is less favorable than the reorganization of **IV** towards **V** (2.43 vs. −20.21 kcal mol^{-1}, Scheme 4; see the Supporting Information for a more detailed mechanistic discussion and conformational analysis).

In summary, we have shown that it is possible to achieve dearomative functionalization of naphthol derivatives using a protocol in which the oxophilicity of aluminum is used as a reaction trigger and the intrinsic acidity of the naphthol is enhanced and exploited towards copper-catalyzed formation of a tetralone scaffold with C-, P- and H-nucleophiles. Based on molecular modeling we have also proposed mechanistic rational for this Lewis acid promoted dearomatization process. Future studies will be directed towards development of synthetic methodologies using this strategy.

Acknowledgements

Financial support from the European Research Council (S.R.H., C.B. and J.P.G.; Grant No. 773264, LACOPAROM) and the Ministry of Education, Culture, and Science (S.R.H. and K.K.; Gravity program 024.001.035) is acknowledged. M.C.R. thanks the Center for Information Technology of the University of Groningen for providing free access to Peregrine, the Centro de Supercomputacion de Galicia (CESGA) for the free allocation of computational resources and the Xunta de Galicia (Galicia, Spain) for financial support through the ED481B-Axudas de apoio á etapa de formación posdoutoral (modalidade A) fellowship.

Conflict of interest

The authors declare no conflict of interest.

Keywords: copper catalysis · dearomatization · Lewis acids · nucleophilic additions

[1] a) I. Muthukrishnan, V. Sridharan, J. C. Menéndez, *Chem. Rev.* **2019**, *119*, 5057 – 5191; b) L. W. Hernandez, D. Sarlah, *Chem. Eur. J.* **2019**, *25*, 13248 – 13270.

[2] a) N. Hoang Anh, H. Ripperger, A. Porzel, T. Van Sung, G. Adam, *Phytochemistry* **1997**, *44*, 549 – 551; b) L. Liu, W. Li, K. Koike, S. Zhang, T. Nikaido, *Chem. Pharm. Bull.* **2004**, *52*, 566 – 569; c) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257 – 10274; d) F. Giordanetto, C. Jin, L. Willmore, M. Feher, D. E. Shaw, *J. Med. Chem.* **2019**, *62*, 3381 – 3394.

[3] a) S. P. Roche, J. A. Porco, Jr., *Angew. Chem. Int. Ed.* **2011**, *50*, 4068 – 4093; *Angew. Chem.* **2011**, *123*, 4154 – 4179; b) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662 – 12686; *Angew. Chem.* **2012**, *124*, 12834 – 12858; c) L. W. Hernandez, J. Pospech, U. Klöckner, T. W. Bingham, D. Sarlah, *J. Am. Chem. Soc.* **2017**, *139*, 15656 – 15659; d) W. C. Wertjes, E. H. Southgate, D. Sarlah, *Chem. Soc. Rev.* **2018**, *47*, 7996 – 8017; e) J. An, M. Bandini, *Eur. J. Org. Chem.* **2020**, *27*, 4087 – 4097; f) Z.-L. Xia, Q.-F. Xu-Xu, C. Zheng, S.-L. You, *Chem. Soc. Rev.* **2020**, *49*, 286 – 300; g) M. Okumura, D. Sarlah, *Eur. J. Org. Chem.* **2020**, 1259 – 1273.

[4] a) P. W. Rabideau, Z. Marcinow, *Org. React.* **1992**, *42*, 1 – 334, DOI: https://doi.org/10.1002/0471264180.or042.01; b) P. J. Dyson, *Dalton Trans.* **2003**, 2964 – 2974; c) A. Gualandi, D. Savoia, *RSC Adv.* **2016**, *6*, 18419 – 18451; d) B. Chatterjee, C. Gunanathan, *J. Chem. Sci.* **2019**, *131*, 118; e) J. A. Leitch, T. Rogova, F. Duarte, D. J. Dixon, *Angew. Chem. Int. Ed.* **2020**, *59*, 4121 – 4130; *Angew. Chem.* **2020**, *132*, 4150 – 4159.

[5] a) Y. Tamura, T. Yakura, J. Haruta, Y. Kita, *J. Org. Chem.* **1987**, *52*, 3927 – 3930; b) L. Pouységu, D. Deffieux, S. Quideau, *Tetrahedron* **2010**, *66*, 2235 – 2261; c) Q. Ding, Y. Ye, R. Fan, *Synthesis* **2013**, *45*, 1 – 16; d) W.-T. Wu, L. Zhang, S.-L. You, *Chem. Soc. Rev.* **2016**, *45*, 1570 – 1580.

[6] a) A. R. Pape, K. P. Kaliappan, E. P. Kündig, *Chem. Rev.* **2000**, *100*, 2917 – 2940; b) M. Rosillo, G. Dominguez, J. Pérez-Castells, *Chem. Soc. Rev.* **2007**, *36*, 1589 – 1604; c) B. K. Liebov, W. D. Harman, *Chem. Rev.* **2017**, *117*, 13721 – 13755.

[7] a) H.-P. Löffler, *Tetrahedron Lett.* **1974**, *15*, 787 – 788; b) M. Ohashi, Y. Tanaka, S. Yamada, *Tetrahedron Lett.* **1977**, *18*, 3629 – 3632; c) S. J. Hamrock, R. S. Sheridan, *J. Am. Chem. Soc.* **1989**, *111*, 9247 – 9249; d) C. Tang, M. Okumura, H. Deng, D. Sarlah, *Angew. Chem. Int. Ed.* **2019**, *58*, 15762 – 15766; *Angew. Chem.* **2019**, *131*, 15909 – 15913; e) W. C. Wertjes, M. Okumura, D. Sarlah, *J. Am. Chem. Soc.* **2019**, *141*, 163 – 167.

[8] a) R. P. Jumde, F. Lanza, M. J. Veenstra, S. R. Harutyunyan, *Science* **2016**, *352*, 433 – 437; b) M. Rodríguez-Fernández, X. Yan, J. F. Collados, P. B. White, S. R. Harutyunyan, *J. Am. Chem. Soc.* **2017**, *139*, 14224 – 14231; c) R. P. Jumde, F. Lanza, T. Pellegrini, S. R. Harutyunyan, *Nat. Commun.* **2017**, *8*, 2058; d) Y. Guo, J. Kootstra, S. R. Harutyunyan, *Angew. Chem. Int. Ed.* **2018**, *57*, 13547 – 13550; *Angew. Chem.* **2018**, *130*, 13735 – 13738; e) X. Yan, S. R. Harutyunyan, *Nat. Commun.* **2019**, *10*, 3402.

[9] D. Vagedes, R. Fröhlich, G. Erker, *Angew. Chem. Int. Ed.* **1999**, *38*, 3362 – 3365; *Angew. Chem.* **1999**, *111*, 3561 – 3565.

[10] a) K. Y. Koltunov, I. B. Repinskaya, *Russ. J. Org. Chem.* **2002**, *38*, 437 – 442; b) K. Y. Koltunov, G. K. S. Prakash, G. Rasul, G. A. Olah, *J. Org. Chem.* **2002**, *67*, 4330 – 4336; c) K. Y. Koltunov, S. Walspurger, J. Sommer, *Chem. Commun.* **2004**, 1754 – 1755; d) K. Y. Koltunov, *Tetrahedron Lett.* **2008**, *49*, 3891 – 3894.

[11] T.-S. Wu, Y.-L. Tsai, A. G. Damu, P.-C. Kuo, P.-L. Wu, *J. Nat. Prod.* **2002**, *65*, 1522 – 1525.

[12] Another nucleophile we tried was Et_3Al in hexane solution. Using the best conditions for Et_2Zn addition, we could obtain the corresponding product **5a** with 35% yield. Less reactive Me_3Al (hexane solution) provided 55% yield of the dearomatized product **5d** (see the Supporting Information for details).

[13] B. L. Feringa, R. Naasz, R. Imboos, L. A. Arnold, *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**, 224 – 258.

[14] a) B. H. Lipshutz, H. Shimizu, *Angew. Chem. Int. Ed.* **2004**, *43*, 2228 – 2230; *Angew. Chem.* **2004**, *116*, 2278 – 2280; b) M. W. Gribble, Jr., M. T. Pirnot, J. S. Bandar, R. Y. Liu, S. L. Buchwald, *J. Am. Chem. Soc.* **2017**, *139*, 2192 – 2195.

[15] a) E. C. Ashby, A. B. Goel, R. N. DePriest, *Tetrahedron Lett.* **1981**, *22*, 3729 – 3732; b) E. C. Ashby, R. N. DePriest, T. N. Pham, *Tetrahedron Lett.* **1983**, *24*, 2825 – 2828; c) E. C. Ashby, C. O. Welder, *J. Org. Chem.* **1997**, *62*, 3542 – 3551. We were able to prove the occurrence of this radical by-process by GC – MS, which showed multiple products of dichloromethane addition to the naphthol ring.

[16] Importantly, we found that not only naphthols but also amines can undergo dearomatization with subsequent functionalization via hydrophosphination. In particular, we found that the addition of $AlBr_3$ to *N*-Methylnaphthalen-1-amine **8** results in the formation of the corresponding ketimine **8a** that undergoes the addition of Ph_2PH and formation of the dearomatized product **6a** with 60% isolated yield. For details see the Supporting Information, Scheme S2.

Manuscript received: July 20, 2020
Revised manuscript received: September 9, 2020
Accepted manuscript online: September 22, 2020
Version of record online: November 18, 2020