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Nucleophilic Dearomatization of Chloromethyl Naphthalene Derivatives via η^3-Benzylpalladium Intermediates: A New Strategy for Catalytic Dearomatization

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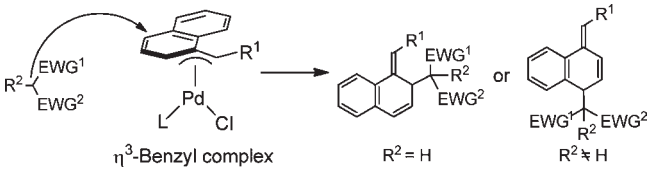
ABSTRACT



Palladium-catalyzed nucleophilic dearomatization of chloromethyl naphthalene derivatives to produce *ortho*- or *para*-substituted carbocycles in satisfactory to excellent yields has been developed. The unprecedented dearomatization reactions proceeded smoothly under mild conditions via η^3-benzylpalladium intermediates.

Dearomatization of aromatic compounds has attracted considerable attention because it provides a simple method to achieve functionalized alicyclic compounds, which can be utilized as synthetic intermediates for the preparation of natural products and bioactive compounds.[1,2] Either electrophilic or nucleophilic dearomatization requires the activation of the aromatic system, which can be achieved by the complexation of the aromatic system to transition metals.[3] The coordination of the aromatic system to the electron-rich, π-basic metal fragment forms [M(η^2-arene)] (M = Os, Re, Mo, and W; Structure **A** in Scheme 1) complexes, which could proceed to electrophilic dearomatization reactions.[4] In contrast, the coordination of the aromatic system to an electron-deficient metal fragment constructs [M(η^6-arene)] (M = Cr, Mn, and Ru; Structure **B** in Scheme 1) complexes, which could undergo a nucleophilic dearomatization reaction.[5] Although these two principal strategies for arene activation have been widely investigated and applied in alicyclic carbocycle synthesis, the required use of stoichiometric amounts of transition metals remains a limitation.

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(1) For selected recent reviews, see: (a) Ortiz, F. L.; Iglesias, M. J.; Fernández, I.; Sánchez, C. A.; Gómez, G. R. *Chem. Rev.* **2007**, *107*, 1580. (b) Quideau, S.; Pouységu, L.; Deffieux, D. *Synlett* **2008**, 467. (c) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (d) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068.

(2) For selected recent references, see: (a) García-Fortanet, J.; Kessler, F.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 6676. (b) Lee, S.; Chataigner, I.; Piettre, S. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 472. (c) Wu, Q.-F.; Liu, W.-B.; Zhuo, C.-X.; Rong, Z.-Q.; Ye, K.-Y.; You, S.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4455 and references therein. (d) Rudolph, A.; Bos, P. H.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 5834. (e) Green, J. C.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2011**, *133*, 1603. (f) Rousseaux, S.; García-Fortanet, J.; Sanchez, M. A. D. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 9282 and references therein.

(3) For a review, see: Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. *Chem. Rev.* **2000**, *100*, 2917.

(4) For transition-metal-mediated electrophilic dearomatization, see: (a) Harman, W. D. *Top. Organomet. Chem.* **2004**, *7*, 95. (b) Ding, F.; Valahovic, M. T.; Keane, J. M.; Anstey, M. R.; Sabat, M.; Trindle, C. O.; Harman, W. D. *J. Org. Chem.* **2004**, *69*, 2257. (c) Surendranath, Y.; Welch, K. D.; Nash, B. W.; Harman, W. H.; Myers, W. H.; Harman, W. D. *Organometallics* **2006**, *25*, 5852 and references therein. (d) Kosturko, G. W.; Graham, P. M.; Myers, W. H.; Smith, T. M.; Sabat, M.; Harman, W. D. *Organometallics* **2008**, *27*, 4513 and references therein. (f) Harrison, D. P.; Sabat, M.; Myers, W. H.; Harman, W. D. *J. Am. Chem. Soc.* **2010**, *132*, 17282 and references therein.

(5) For transition-metal-mediated nucleophilic dearomatization, see: (a) Kündig, E. P.; Pape, A. *Top. Organomet. Chem.* **2004**, *7*, 71. (b) Pearson, A. J.; Vickerman, R. J. *Tetrahedron Lett.* **1998**, *39*, 5931. (c) Pigge, F. C.; Coniglio, J. J.; Dalvi, R. *J. Am. Chem. Soc.* **2006**, *128*, 3498 and references therein. (d) Eloi, A.; Rose-Munch, F.; Rose, E.; Pille, A.; Lesot, P.; Herson, P. *Organometallics* **2010**, *29*, 3876 and references therein.

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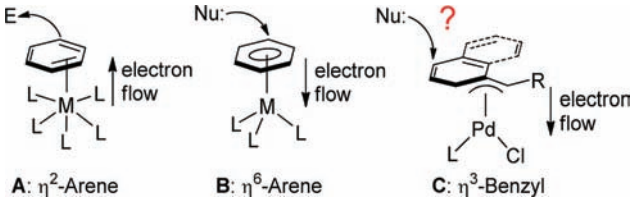
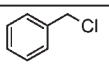
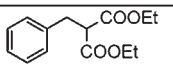
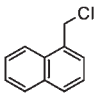
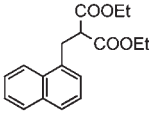
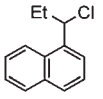
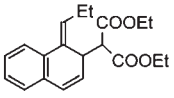
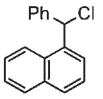
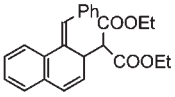
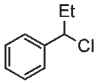
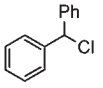
Scheme 1. Structures of η^2-Arene, η^6-Arene, and η^3-Benzyl Complexes



The η^3-benzylpalladium complexes, widely employed in organic synthesis (Structure **C** in Scheme 1),[6,7] possess similar electronic properties as η^6-arene metal complexes. We hypothesize that the reactions of η^3-benzylpalladium complexes with nucleophiles (Tsuji–Trost type reaction) may occur on the benzene ring to yield dearomatization products. Using this strategy, the present work aimed to achieve a transition-metal-catalyzed nucleophilic dearomatization.

To test this hypothesis, several benzyl chloride derivatives were treated with diethyl malonate in the presence of a catalytic amount of $Pd(PPh_3)_4$. The results are shown in Table 1. Initially, the reaction of benzyl chloride (**1a**), the simplest substrate, was attempted at room temperature. A normal nucleophilic substitution reaction took place to give benzylation product **2a** in 64% yield (entry 1). Then, 1-chloromethyl naphthalene (**1b**), a polycyclic analog of **1a**, was employed instead of **1a**. The reaction of **1b** with diethyl malonate proceeded smoothly, yielding a benzylation product **2b** in 91% yield (entry 2). The higher reactivity of **1b** compared with that of **1a** could be attributed to the easy formation of an η^3-benzylpalladium complex from **1b**.[8] If an alkyl or aryl substituent on the benzylic position can stabilize the η^3-benzylpalladium complex generated in situ, then the desired nucleophilic dearomatization can be facilitated. This inference was proved when the dearomatization product **2c** was obtained in 32% yield along with a benzylation product in 40% yield from the reaction of 1-(1-chloropropyl)naphthalene (**1c**) with diethyl malonate (entry 3). Substrate **1c** likewise had a hydrogen atom *beta* to a chlorine atom. No β-hydride elimination product could be observed.[9] Considering these positive results, the reaction of 1-[chloro(phenyl)methyl]-naphthalene (**1d**) having a phenyl group on the benzylic position was examined under the same reaction conditions utilized on **1c**. The dearomatization product **2d** was obtained as the sole product in 85% yield (entry 4). Finally, (1-chloropropyl)benzene (**1e**) and (chloromethylene)-dibenzene (**1f**) were examined, and no reactions were observed (entries 5 and 6). Therefore, 1-[chloro(phenyl)-methyl]naphthalene derivatives were used for intermolecular nucleophilic dearomatization in the subsequent study.

Table 1. Substrate Screening[a]

entry	substrate 1		product 2		yield (%)[b]
1		**1a**		**2a**	64
2		**1b**		**2b**	91
3		**1c**		**2c**	32[c]
4		**1d**		**2d**	85
5		**1e**	--	--	NR[d]
6		**1f**	--	--	NR[d]

[a] Reaction conditions: substrate **1a**–**f** (0.5 mmol), diethyl malonate (0.5 mmol), NaH (1.0 mmol), and $Pd(PPh_3)_4$ (5 mol %) in THF (5 mL) at room temperature under a nitrogen atmosphere. [b] Isolated yield. [c] 40% of benzylation product was also isolated. [d] No reaction.

The intermolecular nucleophilic dearomatization reactions of various chloromethyl naphthalene derivatives with diethyl malonate in the presence of a palladium catalyst were examined, and the results are shown in Scheme 2. The reaction of substrate **1d** was completed within 6 h and produced the desired product **2d** in 89% yield. Substrates **1g** and **1h** bearing a methyl group and bromine atom on the *para* position of the naphthalene ring, respectively, underwent nucleophilic dearomatization smoothly to furnish products **2g** and **2h** in 90% and 71% yields, respectively. These results indicate that the palladium-catalyzed nucleophilic dearomatization is not evidently influenced by the electronic property of a substituent on the *para* position of the naphthalene ring. However, substrate **1i** having a methyl group on the *meta* position of the naphthalene ring was found to be challenging in nucleophilic dearomatization. This substrate produced only a 30% yield of the desired product **2i** along with a 62% yield of benzylation

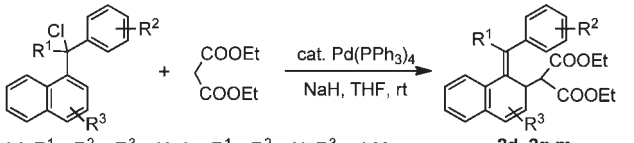
(6) For selected recent references for the use of η^3-benzylpalladium complexes in cross-coupling reactions, see: (a) Lindsell, W. E.; Palmer, D. D.; Preston, P. N.; Rosair, G. M.; Jones, R. V. H.; Whitton, A. J. *Organometallics* **2005**, *24*, 1119. (b) Johns, A. M.; Tye, J. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 16010 and references therein. (c) Larsen, C. H.; Anderson, K. W.; Tundel, R. E.; Buchwald, S. L. *Snylett* **2006**, 2941 and references therein. (d) Kuwano, R.; Kusano, H. *Org. Lett.* **2008**, *10*, 1979 and references therein. (e) Guan, B.; Xiang, S.; Wang, B.; Sun, Z.; Wang, Y.; Zhao, K.; Shi, Z. *J. Am. Chem. Soc.* **2008**, *130*, 3268. (f) Fields, W. H.; Chruma, J. J. *Org. Lett.* **2010**, *12*, 316 and references therein.

(7) For the allylative and propargylative dearomatization via η^3-benzylpalladium intermediates, see: (a) Bao, M.; Nakamura, H.; Yamamoto, Y. J. *Am. Chem. Soc.* **2001**, *123*, 759. (b) Lu, S.; Xu, Z.; Bao, M.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 4366. (c) Peng, B.; Feng, X.; Zhang, X.; Zhang, S.; Bao, M. *J. Org. Chem.* **2010**, *75*, 2619. (d) Peng, B.; Feng, X.; Zhang, X.; Ji, L.; Bao, M. *Tetrahedron* **2010**, *66*, 6013.

(8) For selected references, see: (a) Baird, J. M.; Kern, J. R.; Lee, G. R.; Morgans, D. J., Jr.; Sparacino, M. L. *J. Org. Chem.* **1991**, *56*, 1928. (b) See: Reference 6b and references therein.

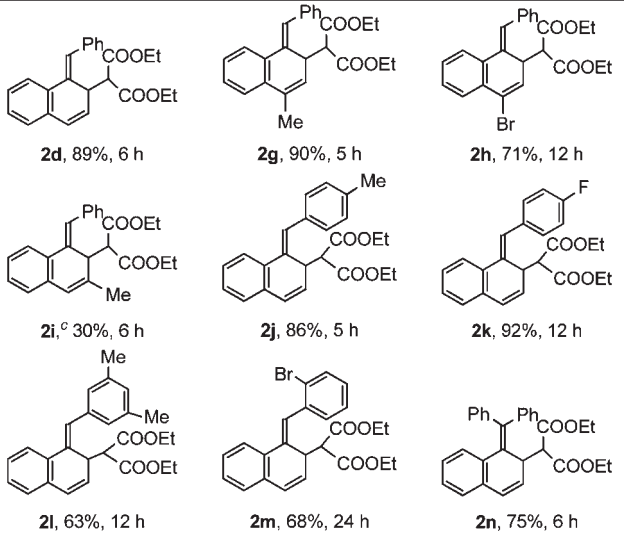
(9) In the cross-coupling reaction of C_{sp^3}–X electrophiles, the β-hydride elimination often took place to give alkenes in preference to coupling. See: (a) Luh, T.-Y.; Leung, M.-k.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187. (b) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384.

Scheme 2. Intermolecular Nucleophilic Dearomatization of Chloromethyl Naphthalene Derivatives with Diethyl Malonate[a,b]



1d: $R^1 = R^2 = R^3 = H$; **1g**: $R^1 = R^2 = H$, R^3 = 4-Me;
1h: $R^1 = R^2 = H$, R^3 = 4-Br; **1i**: $R^1 = R^2 = H$, R^3 = 3-Me;
1j: $R^1 = R^3 = H$, R^2 = 4-Me; **1k**: $R^1 = R^3 = H$, R^2 = 4-F;
1l: $R^1 = R^3 = H$, R^2 = 3,5-diMe; **1m**: $R^1 = R^3 = H$, R^2 = 2-Br;
1n: R^1 = Ph, $R^2 = R^3 = H$.

2d, 2g-m



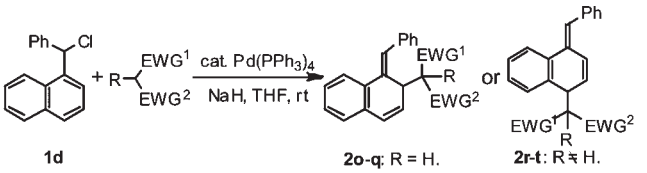
2d, 89%, 6 h; **2g**, 90%, 5 h; **2h**, 71%, 12 h

2i,[c] 30%, 6 h; **2j**, 86%, 5 h; **2k**, 92%, 12 h

2l, 63%, 12 h; **2m**, 68%, 24 h; **2n**, 75%, 6 h

[a] Reaction conditions: substrate **1d**, **1g**–**n** (0.5 mmol), diethyl malonate (0.5 mmol), NaH (1.0 mmol), and $Pd(PPh_3)_4$ (5 mol %) in THF (5 mL) under a nitrogen atmosphere. The reaction progress was monitored by thin layer chromatography (TLC). [b]Isolated yield. [c] A benzylation product was also obtained in 62% yield.

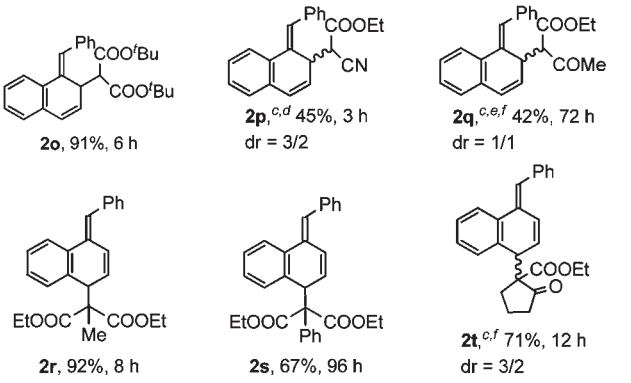
Scheme 3. Intermolecular Nucleophilic Dearomatization of 1-Chloromethyl Naphthalene with Various Activated Methylene Compounds[a,b]



1d

2o-q: R = H.

2r-t: R ≠ H.



2o, 91%, 6 h

2p,[c,d] 45%, 3 h, dr = 3/2

2q,[c,e,f] 42%, 72 h, dr = 1/1

2r, 92%, 8 h

2s, 67%, 96 h

2t,[c,f] 71%, 12 h, dr = 3/2

[a] Reaction conditions: **1d** (0.5 mmol), activated methylene compound (0.5 mmol), NaH (1.0 mmol), and $Pd(PPh_3)_4$ (5 mol %) in THF (5 mL) under a nitrogen atmosphere. The reaction progress was monitored by TLC. [b]Isolated yield. [c]Diastereomeric ratio (dr) was determined by ^1H NMR. [d]A benzylation product was also obtained in 52% yield. [e]A benzylation product was also obtained in 28% yield. [f]The reaction was performed at 50 °C.

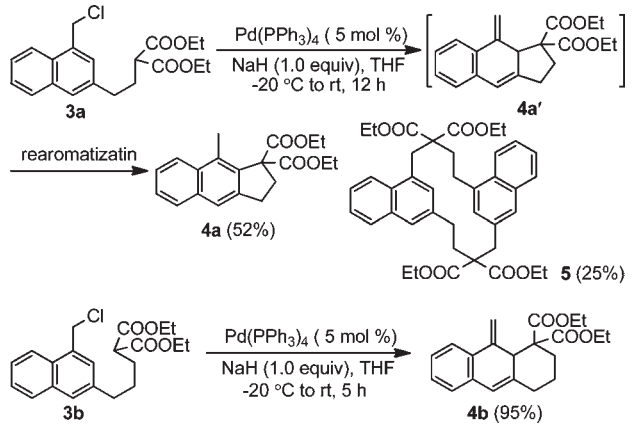
product. This could be due to the steric hindrance of the *meta* methyl group. Reactions of substrates **1j** and **1k** having a methyl group and fluorine atom on the *para* position of the benzene ring, respectively, with diethyl malonate, proceeded smoothly to produce products **2j** and **2k** in 86% and 92% yields, respectively. Substrate **1l** having two methyl groups on the *meta* positions of the benzene ring can also be employed in this type of dearomatization reaction. The desired product **2l** was obtained in 63% yield. The reaction of substrate **1m** having a bromine atom on the *ortho* position of the benzene ring produced the dearomatization product **2m** also in satisfactory yield (68%), but a prolonged reaction time was needed (24 h). The electronic property of a substituent group, as well as its place on the benzene ring, did not strongly influence the substrate reactivity in this type of dearomatization. Bromine atoms remained on the products **2h** and **2m**, suggesting that further manipulation may produce useful compounds. Finally, the reaction of substrate **1n** bearing two phenyl groups at the benzylic position was examined. The product **2n** was obtained in 75% yield.

Scheme 3 shows the results of the investigation on the scope of activated methylene compounds in the palladium-catalyzed nucleophilic dearomatization. Di-*tert*-butyl malonate exhibited almost the same high reactivity and good selectivity as diethyl malonate, producing product **2o** in 91% yield. Poor selectivity was observed in the reaction of **1d** with ethyl 2-cyanoacetate. Product **2p** was obtained in only 45% yield with 3:2 dr and a benzylation product in 52% yield. Ethyl acetoacetate showed lower reactivity than its analogs. The reaction of **1d** with ethyl acetoacetate required an enhanced temperature (50 °C) and prolonged time (72 h) to reach completion. Product **2q** was isolated in only 42% yield with 1:1 dr, and a benzylation product in 28% yield. The use of sterically hindered nucleophiles led to the formation of *para*-substituted dearomatization products. For example, the reactions of **1d** with diethyl 2-methylmalonate, diethyl 2-phenylmalonate, and ethyl 2-oxocyclopentanecarboxylate proceeded under the same reaction conditions and produced *para*-substituted dearomatization products **2r**–**t** in good to excellent yields (92%, 67%, and 71%, respectively).

These successful investigations encouraged us to examine intramolecular nucleophilic dearomatization. The results are shown in Scheme 4. From the reaction of substrate **3a**, product **4a**, a rearomatized product, was isolated in 52% yield along with 25% of dimer **5**. The desired product **4b** was obtained in excellent yield (95%) from the reaction of **3b** without observation of any rearomatized product.

Finally, the dearomatization product **2d** was transformed to tetracyclic compounds **7** and **8** to highlight the usefulness of the dearomatization products obtained

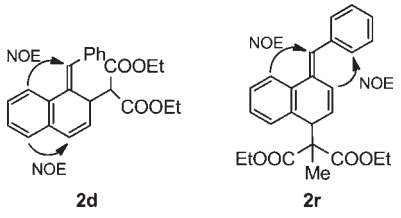
Scheme 4. Palladium-Catalyzed Intramolecular Nucleophilic Dearomatization



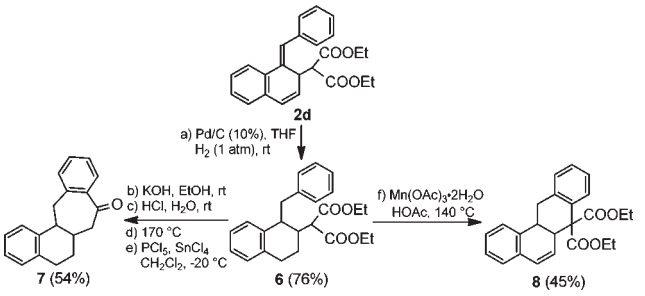
(Scheme 5). Compound **2d** was easily hydrogenated to compound **6**, and compound **7** was subsequently obtained in 54% yield in four steps. Product **8**, a tetracyclic fused ring system, was also obtained, even though the yield was relatively low (45%). All the new products **2c**, **2d**, **2g**–**t**, **4a**, **4b**, and **5**–**8** were identified through their NMR[10] and HRMS data as well as IR spectra.

In conclusion, we demonstrated that the aromatic system can be activated by a palladium catalyst

(10) The structural assignment was based on the analysis of the 1D (^{1}H and ^{13}C) and 2D (^{1}H–^{1}H COSY and NOESY) spectra. For example, the connection and configuration of products **2d** and **2r** were obtained from ^{1}H–^{1}H COSY and NOESY spectra.



Scheme 5. Transformation of Dearomatization Product **2d** to Tetracyclic Compounds



through the η^3-benzylpalladium complex formation to undergo nucleophilic dearomatization. Using the present strategy, chloromethyl naphthalene derivatives can be efficiently transformed to *ortho*- or *para*-substituted carbocycles in satisfactory to excellent yields. With the exception of **4a′**, all the dearomatization products are very stable and could be purified by column chromatography on basic alumina. Further studies focusing on the extension of the reaction scope and the application of dearomatization products are currently underway.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.