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1-Naphthylmethyl and 1-Naphthylmethoxymethyl Protecting Groups: New Members of the Benzyl- and Benzyloxymethyl-Type Family

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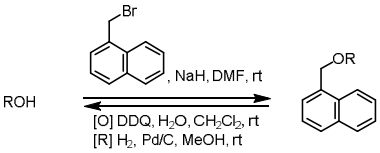
Abstract: 1-Naphthylmethyl (NAP^I) and 1-naphthylmethoxymethyl ($NAPOM^I$) protecting groups were developed as new members of the benzyl- and benzyloxymethyl-type family. NAP^I and $NAPOM^I$ can be introduced under conventional conditions, such as NAP^IBr/NaH/room temperature (rt), or $NAPOM^ICl$/*i*-Pr_2EtN/rt. They can also be removed under conventional conditions, e.g. by oxidation using dichlorodicyanobenzoquinone (DDQ)- or ceric ammonium nitrate (CAN)-mediated, or by hydrogenolysis. The specific advantages of these new protecting groups are: i) a less costly synthesis of $NAPOM^ICl$ compared to $NAPOM^{II}Cl$, ii) the possibility to remove $NAPOM^{II}$ selectively in the presence of $NAPOM^I$ by DDQ-mediated oxidation, and iii) the compatibility with strong acids even in the presence of hard nucleophiles.

As the judicious selection of protecting groups is one of the most important factors for the successful synthesis of complex molecules with several functional groups, numerous protecting groups have been developed to date.[1] For the protection of hydroxy groups, benzyl-type protecting groups such as benzyl (Bn), *p*-methoxybenzyl (PMB), and 2-naphthylmethyl (NAP) groups are especially popular, as they are relatively stable under acidic and basic conditions, and as they can be removed under neutral conditions via Pd-catalyzed hydrogenolysis. In addition, PMB and NAP can also be removed by treatment with oxidants such as dichlorodicyanobenzoquinone (DDQ) or ceric ammonium nitrate (CAN). The introduction of benzyl-type protecting groups is usually achieved under strongly acidic (e.g., $BnOC(NH)CCl_3$ or TfOH)[2] or basic (e.g., NaH/BnBr/DMF or *i*-Pr_2EtN/BnBr/neat/150 °C)[3] conditions.[4] Accordingly, benzyloxymethyl-type groups, such as benzyloxymethyl (BOM), and *p*-methoxybenzyloxymethyl (PMBOM) groups are highly useful for the protection of acid- and/or base-sensitive compounds, as these protecting groups can be installed under weakly basic conditions (e.g. BOMCl/*i*-Pr_2EtN/rt). During our studies on protecting groups for the synthesis of natural products, we have recently developed the 2-naphthylmethoxymethyl (NAPOM)[5,6] group, which can be selectively removed in the presence of other Bn- or BOM-type protecting groups such as PMB, NAP, or BOM. Curiously, 1-naphthylmethyl (NAP^I)[7] and 1-naphthylmethoxymethyl ($NAPOM^I$) groups, which are regioisomers of NAP^{II} and $NAPOM^{II}$,[8] have not yet found widespread applications, despite the potential utility of their characteristic features and the lower costs relative to conventional protecting groups. Herein, we report NAP^I and $NAPOM^I$ as new members of the naphthalene-based protecting group family to increase the pool of available protecting groups for the synthesis of complex molecules, and we demonstrate their unique and highly useful selective removal.

Initially, we examined the protection/deprotection of various alcohols with NAP^I (Table 1). For that purpose, alcohols were treated with NAP^IBr in the presence of NaH in DMF at rt (entries 1-3). For primary (**1a**) and secondary alcohols (**2a**), the reactions proceeded smoothly to afford the corresponding NAP^I ethers **1b** (93%) and **2b** (88%) in good yields. As is often the case with tertiary alcohols such as **1c**, the introduction of NAP^I stopped prematurely at rt, to furnish the protected ether **3b** in 58% yield. In a second step, we attempted to remove the NAP^I group from **1b**-**3b** via oxidative (DDQ, CH_2Cl_2/H_2O = 4/1, rt) or reductive (1 atm H_2, Pd/C, MeOH, rt) conditions. As a result, the free alcohols **1a-3a** were obtained in high yields (97-100%). These results demonstrate the potential of the NAP^I group as a novel member of the Bn-type family protecting groups that can be removed oxidatively.

Table 1. Protection and Deprotection of alcoholic hydroxy groups with NAP^I.

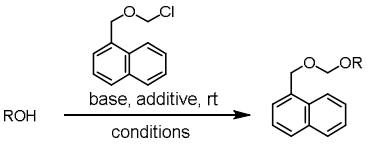


Entry	Substrate and Product	Yield / %[a]		
		Introduction[b]	Removal	
			[O][c]	[R][d]
1	**1a**: Ph, OH **1b**: Ph, $ONAP^I$	93	98	97
2	**2a**: Ph, OH **2b**: Ph, $ONAP^I$	88	quant	99
3	**3a**: Ph, OH **3b**: Ph, $ONAP^I$	58	quant	97

[a] Isolated yields after column chromatography on silica gel. [b] NAP^IBr (1.1 equiv), NaH (1.5 equiv), DMF ([substrate] = 1.0 M), rt, 6-26 h; reactions were monitored by TLC and quenched upon completion or stopping. [c] DDQ (3 equiv),

CH_2Cl_2/H_2O = 4/1, rt, 1.5-6.5 h. [d] H_2 (1 atm), Pd/C (5 mol%), rt, 1.0-1.7 h.

Table 2. Protection of alcoholic hydroxy groups with NAPOM[I].



Entry	Substrate (**1a-6a**) and Product (**1c-6c**)	Reagents[a]	Solvent[b]	Time / h	Yield / %[c]
1	**1a** **1c**: Ph ONAPOM[I]	NAPOM[I]Cl *i*-Pr_2EtN	CH_2Cl_2	7.4	quant
2	**2a** **2c**: Ph ONAPOM[I]	NAPOM[I]Cl *i*-Pr_2EtN	CH_2Cl_2	16	90
3	**3a** **3c**: Ph ONAPOM[I]	NAPOM[I]Cl *i*-Pr_2EtN	CH_2Cl_2	19	96
4	**3a** **3c**	NAPOM[I]Cl *i*-Pr_2EtN	toluene	6	94
5	OAc, Ph, OH **4a** OAc, Ph, ONAPOM[I] **4c**	NAPOM[I]Cl[d] 2,6-lutidine TBAI	CH_2Cl_2	24.5	82
6	**5a**: OH, 7 **5c**: ONAPOM[I], 7	NAPOM[I]Cl *i*-Pr_2EtN	CH_2Cl_2	19	72
7	TBDPSO, O, O, OH, 2 **6a** TBDPSO, O, O, ONAPOM[I], 2 **6c**	NAPOM[I]Cl *i*-Pr_2EtN	CH_2Cl_2	49.5	74

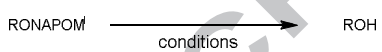
[a] NAPOM[I]Cl (2-6 equiv), *i*-Pr_2EtN (4-12 equiv). [b] [Substrate] = 0.1-0.5 M. [c] Isolated yields after column chromatography on silica gel. [d] NAPOM[I]Cl (6 equiv), 2,6-lutidine (12 equiv), and TBAI (0.5 equiv).

With this encouraging result on NAP[I] in hand, we turned our attention to the NAPOM[I] group. The synthesis of NAPOM[I]Cl was successfully achieved following a procedure similar to that of NAPOM[II]Cl, i.e., a mixture of 1-naphthylmethyl alcohol and paraformaldehyde was treated with gaseous HCl in pentane at -20 °C,[9] which furnished NAPOM[I]Cl in 85% yield.[10] It is noteworthy that 1-naphthylmethyl alcohol is substantially cheaper than 2-naphthylmethyl alcohol, which is required for the preparation of NAPOM[II]Cl.

Subsequently, the protection of alcoholic hydroxy groups with NAPOM[I] was examined (Table 2). A conventional treatment of primary, secondary, or tertiary alcohols (**1a**-**3a**, entries 1-3) with NAPOM[I]Cl and *i*-Pr_2EtN in CH_2Cl_2 at rt, furnished NAPOM[I] ethers **1c**-**3c** in good yields (90-100%). Although the required reaction time is different for primary and tertiary alcohols, a selective installation of the NAPOM[I] group in primary alcohol **1a** in the presence of tertiary alcohol **3a** was not possible under the applied reaction conditions. On the other hand, the reaction time for tertiary alcohol **3a** was shortened in toluene (entry 4), which emerged as one of the best solvents for these reactions[5] without affecting the yield of **3c** (94%). We also attempted to use NAPOM[I] to protect the hydroxy group of a 2-acetoxy-1-ol system (**4a**), whose acetyl group easily migrates under slightly acidic or basic conditions (entry 5). Although acyl migration actually occurred when *i*-Pr_2EtN was used as a base, the use of 2,6-lutidine prevented this unwanted side reaction: treatment of **4a** with NAPOM[I]Cl, 2,6-lutidine, and a catalytic amount of tetrabutyl ammonium iodide (TBAI) in CH_2Cl_2 at rt furnished the desired NAPOM[I] ether (**4c**) in 82% yield. Ester (entry 5), olefin (entry 6), silyl ether and acetal (entry 7) moieties remained unaffected under the applied conditions to install NAPOM[I] to afford **5c** (72%) and **6c** (74%) from **5a** and **6a**,[11] respectively.

Then, we turned our attention to the removal of the NAPOM[I] group (Table 3). Under oxidative conditions using DDQ, NAPOM[I] ethers **1c**-**3c** proved to be unexpectedly resistant, which stands in contrast to the behavior of NAPOM[II].

Table 3. Removal of the NAPOM[I] group from protected hydroxy groups.



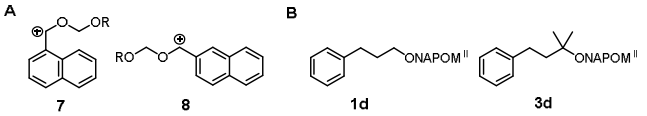
Entry	Substrate (**1c-3c**) and Product (**1a-3a**)	Reagent and Solvent[a]	Temperature	Time / h[b]	Yield / %[c]
1	**1c**: Ph ONAPOM[I] **1a**	DDQ (3 equiv) CH_2Cl_2/H_2O (4/1)	reflux	19.5	0 64[d]
2	**1c** **1a**	CAN (8 equiv) acetone/H_2O (9/1)	rt	149	0 83
3	**1c** **1a**	H_2, Pd/C (5 mol%) MeOH	rt	8	0 81[d]
4	**2c**: Ph ONAPOM[I] **2a**	DDQ (3 equiv) CH_2Cl_2/H_2O (4/1)	reflux	15	0 86[d]
5	**2c** **2a**	CAN (6 equiv) acetone/H_2O (9/1)	rt	121	0 88[e]
6	**2c** **2a**	H_2, Pd/C (5 mol%) MeOH	rt	6.5	0 83[d]
7	**3c**: Ph ONAPOM[I] **3a**	DDQ (3 equiv) CH_2Cl_2/H_2O (4/1)	reflux	27	0 99
8	**3c** **3a**	CAN (4 equiv) acetone/H_2O (9/1)	rt	26.5	0 quant[e]
9	**3c** **3a**	H_2, Pd/C (5 mol%) MeOH	rt	8.5	0 81[d]
10	**1c** **1a**	*p*-TsOH (8 equiv) THF, MeOH	rt	5	97 trace
11	**1c** **1a**	*p*-TsOH (8 equiv) THF, MeOH	reflux	22	0 quant[e]
12	**1c** **1a**	$BF_3{\cdot}OEt_2$ (1 equiv) Et_3SiH (5 equiv) CH_2Cl_2	-78 to -30 °C	3	quant trace

[a] [Substrate] = 0.1 M. [b] Reactions were monitored by TLC and quenched upon completion or the formation of undesired products. [c] Isolated yields after column chromatography on silica gel. [d] Byproducts were observed (for details, see: Supplementary Material). [e] Obtained as an inseparable mixture containing 1-naphthalenemethanol; yields were determined based on the ^{1}H-NMR spectra of the mixture.

The successful removal of NAPOM[I] (entries 1, 4, and 7) required an increased amount of DDQ (3 equiv) in combination with elevated temperatures (reflux), while NAPOM[II] can be removed smoothly using only 1.5 equiv of DDQ at rt. Although the yield of **3a** (99%) was satisfactory, those of **1a** (64%) and **2a** (86%) were not, due to the generation of byproducts, which probably formed on account of the harsh conditions. Therefore, we also examined the milder oxidant CAN (entries 2, 5, and 8). As expected, the yields improved in all cases (83, 88, and 100%, respectively), although prolonged reaction times were required. The reason why NAPOM[I] is

more tolerant toward oxidation than NAPOM^{II} remains unclear at this point.

Chart 1. A. Cationic intermediates during the oxidation of NAPOM^{I} and NAPOM^{II} ethers. **B.** Structures of NAPOM^{II} ethers.



Before our investigations, and based on the conventional electronic theory in organic chemistry, we expected that NAPOM^{I} should be more reactive toward oxidants, given that cationic intermediate **7** should be more stable than cation **8** on account of the resonance effect (Chart 1A). However, the experimental results did not match our expectations. Interestingly, the oxidation potentials of **1c**, **1d**, **3c**, and **3d** (Chart 1B), measured by cyclic voltammetry, could not be used to rationalize the experimental results either, as the oxidation potentials of **1c**, **1d**, **3c**, and **3d** were almost identical (for details, see: Supplementary Material).

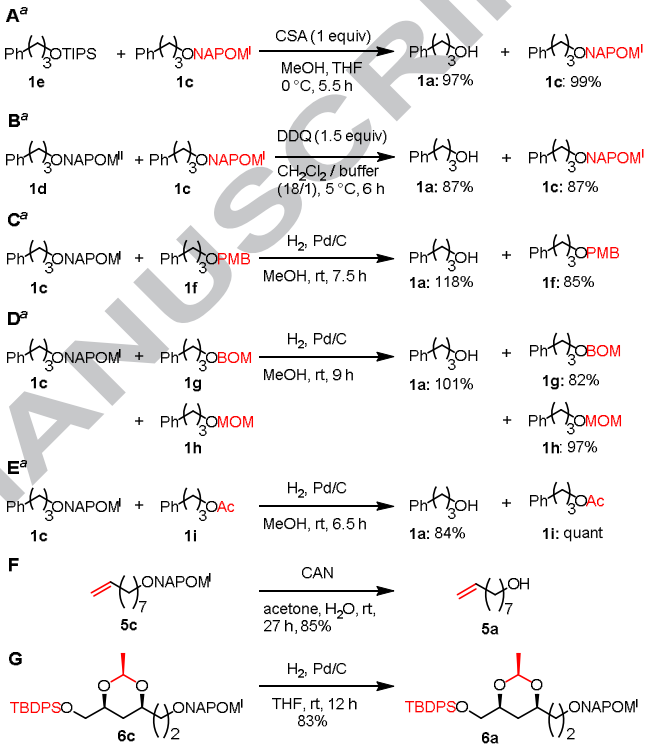
Therefore, we went on to test a hydrogenolytic removal of the NAPOM^{I} group (entries 3, 6, and 9; Table 3). Stirring MeOH solutions of NAPOM^{I} ethers **1c**, **2c**, or **3c** in the presence of Pd/C (5 mol%) under an atmosphere of H_2 (1 atm) provided the deprotected alcohols **1a**, **2a**, and **3a** in 81-83% yields. Again, these reactions were more sluggish than those of the corresponding NAPOM^{II} substrates. Taking the fast hydrogenolytic removal of NAP^{I} (Table 1) into consideration, a possible explanation for the slow hydrogenolysis may be the binding of acetal oxygen atoms of NAPOM^{I} to Pd, resulting in a specific conformation that potentially facilitates the discharge of the naphthalene moiety from the surface of the Pd catalyst.[12]

As the last part of our deprotection experiments, were treated NAPOM^{I} ethers with various acids, in order to determine the stability of the NAPOM^{I} group under acidic conditions. Treatment of NAPOM^{I} ether **1c** with 8 equiv of *p*-TsOH in THF or MeOH at rt did not show any effect (entry 10),[13] whereas the prolonged (22 h) exposure of **1c** to *p*-TsOH at elevated temperatures (reflux) cleaved the NAPOM^{I} group to furnish alcohol **1a** in quantitative yield (entry 11).[13] Combinations of a strong Lewis acid and a hard nucleophile (e.g., $BF_3{\cdot}OEt_2/Et_3SiH$), which are frequently used for reductive etherifications[14] or for the removal of *t*-butoxycarbonyl groups, resulted in the quantitative recovery of **1c**, even at elevated temperatures up to -30 °C (entry 12).[13]

Our results so far have shown that NAP^{I} and NAPOM^{I} can be effectively used as protecting groups. Therefore, we wanted to investigate the possibility of a selective removal of NAP^{I} and NAPOM^{I} in the presence of other protecting groups (Scheme 1).

The characteristic stability of NAPOM^{I} group in acidic media, allowed a treatment of a mixture of **1c** and **1e** with camphor sulfonic acid (CSA) in MeOH at 0 °C, which selectively removed the triisopropylsilyl (TIPS) group from **1e**, but allowed to recover NAPOM^{I} ether **1c** in 99% yield (Scheme 1A). More importantly, the unexpectedly sluggish cleavage of NAPOM^{I} with DDQ can be used to induce a very unique selectivity, i.e., NAPOM^{II} ether **1b** was deprotected by DDQ in the presence of NAPOM^{I} ether **1c** in 87% yield (B). This observation clearly shows that the addition of NAPOM^{I} as a new member of BOM-type protecting group family increases the pool of available protecting groups, especially when oxidatively cleavable protecting groups other than PMB, PMBOM, NAP^{II} and NAAPOM^{II} are required for the synthesis of complex molecules. This notion is supported by the successful cleavage of NAPOM^{I} ethers (**1c**) in the presence of PMB ethers (85% recovery of **1f**; Scheme 1C), as well as BOM (**1g**)[15] and MOM (**1h**)[16] ethers (82% and 97% recovery of **1g** and **1h**; Scheme 1D). Ester (quantitative recovery of **1i**; Scheme 1E), olefin (85% yield of **5a**; Scheme 1F), silyl ether, and acetal (83% yield of **6a**; Scheme 1G) moieties remained unaffected during the cleavage of NAPOM^{I}.

Scheme 1. Selective Removal of NAPOM^{I} Protecting Groups.



[a] A 1:1 (:1) (mol/mol) mixture of substrates was used. For each entry, the protecting and functional groups that remained unaffected are highlighted in red.

Herein, we have reported the development of NAP^{I} and NAPOM^{I} protection groups, i.e., new members of the Bn- and BOM-type family for the protection of hydroxy groups. The specific advantages of the NAPOM^{I} group are: i) the possibility to selectively remove NAPOM^{II} in the presence of NAPOM^{I}, ii) the compatibility with strong Lewis and protic acids, even in the presence of hard nucleophiles, and iii) the possibility to synthesize these protecting groups from cheap commercially available materials. These characteristic should find the NAP^{I} and NAPOM^{I} groups widespread applications in the research communities that are concerned with the synthesis of complex molecules. Application studies involving these NAPOM groups are currently in progress in our laboratory.

Key words

Protecting group; Oxidative cleavage; Benzyl; Benzyloxymethyl; Naphthylmethyl; Naphthylmethoxymethyl; NAP; NAPOM

Supplementary Material

Synthetic procedures, spectral data, and ^{1}H and ^{13}C NMR charts of all new compounds. This material is available free of charge via the Internet.

Acknowledgments

We are grateful to Profs. Ken Sakai and Kosei Yamauchi (Kyushu University) for providing us with access to cyclic voltammetry instrumentation, and to Prof. Masahiko Suenaga (Kyushu University) for invaluable discussions. We also thank Mr. Keiya Yamamoto (Kyushu University) for technical support with cyclic voltammetry measurements. Mr. Naoto Yanai (our laboratory) is acknowledged for providing **6a**. This work was financially supported by a Grant-in-Aid for Young Scientists (B) (No. 15K21210 to K.T.) from the JSPS, and a grant from Wako Pure Chemical Industries (to K.T.), as well as by a Wako Award in Synthetic Organic Chemistry (Japan). K.T. would like to express his deepest gratitude to Ms. Miyoko Ueno, Mr. and Ms. Takaaki and Rumiko Torikai, Mr. Kazuo Fushiki, Ms. Yukiko Ueno, and Mr. and Ms. Motoaki and Michie Yamaoka for their generous financial donations to his project. The authors declare that a patent regarding the use of NAPOMCl for the protection of alcohols and thiols is pending (PCT Int. Appl. WO 2016056448 A1 20160414, 2016).

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(4) Recently, several mild benzylation methods have been developed. For examples, see: (a) Poon, K. W. C.; House, S. E.; Dudley, G. B. *Synlett* **2005**, 3142-3144.; (b) Poon, K. W. C.; Dudley, G. B. *J. Org. Chem*. **2006**, *71*, 3923-3927.; (c) Kotturi, S. R.; Tan, J. S.; Lear, M. J. *Tetrahedron Lett*. **2009**, *50*, 5267-5269. (d) Yamada, K.; Fujita, H.; Kunishima, M. *Org. Lett*. **2012**, *14*, 5026-5029.; (e) Yamada, K.; Fujita, H.; Kitamura, M.; Kunishima, M. *Synthesis* **2013**, *45*, 2989-2997.; (f) Yamada, K.; Tsukada, Y.; Karuo, Y.; Kitamura, M.; Kunishima, M. *Chem.–Eur. J*. **2014**, *20*, 12274-12278.
(5) Sato, T.; Oishi, T.; Torikai, K. *Org. Lett*. **2015**, *17*, 3110-3113. Should a shorter abbreviation for NAPOM be required, the authors propose to use NOM.
(6) Kyushu University, PCT Int. Appl. WO 2016056448 A1 20160414, 2016.
(7) NAP^{I} has previously been used only as a protecting group for carboxy groups, and removed via homogeneous Pd-catalyzed hydrogenolysis. For details, see: Boutros, A.; Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron* **2000**, *56*, 2239-2246. In this paper, the 1-naphthylmethyl group is intentionally abbreviated to NAP^{I}, although it should be 1-NAP when considering precise nomenclature. NAP^{I} has been used in order to minimize the required space in synthetic schemes. Likewise, the 1-naphthylmethoxymethyl group was abbreviated to $NAPOM^{I}$.
(8) In this paper, the 2-naphthylmethyl and 2-naphthylmethoxymethyl groups are abbreviated as NAP^{II} and $NAPOM^{II}$ respectively, to clearly show the difference to $NAPOM^{I}$. It is left to the reader's discretion, which abbreviation to use in the future.
(9) Cooling to -20 °C was critical to suppress side reactions forming 1-chloromethyl naphthalene, which was reported in the following literatures as a main contaminant. (a) Hill, A. J.; Keach, D. W. T. *J. Am. Chem. Soc.* **1926**, *48*, 257-262. (b) Bedford, C. D.; Harris, R. N.; Howd, R. A.; Miller, A.; Nolen, H. W.; Kenley, R. A. *J. Med. Chem.* **1984**, *27*, 1431-1438.
(10) $NAPOM^{I}Cl$ was storable at -20 °C for a minimum of 2 months.
(11) Alcohol **6a** is an intermediate in the synthesis of amphidinol 3; for details, see: Tsuruda, T.; Ebine, M.; Umeda, A.; Oishi, T. *J. Org. Chem*. **2015**, *80*, 859-871.
(12) For a review on the importance of coordination, resulting in the fixation of molecules on the surface of catalysts in hydrogenolysis, see: Mitsui, S. *J. Synth. Org. Chem. Jpn*. **1960**, *18*, 305-317. We envisaged that the coordination of acetal oxygen atoms may be connected in a similar way to the sluggish oxidative removal of $NAPOM^{I}$ with DDQ, i.e., we suspect an interaction between a pair of oxygen atoms and DDQ.
(13) Corresponding $NAPOM^{II}$ ethers afforded similar results (data not shown).
(14) For examples, see: (a) Nicolaou, K. C.; Hwang, C. K.; Nugiel, D. A. *J. Am. Chem. Soc*. **1989**, *111*, 4136-4137.; (b) Torikai, K.; Watanabe, K.; Minato, H.; Imaizumi, T.; Murata, M.; Oishi, T. *Synlett* **2008**, 2368-2372.
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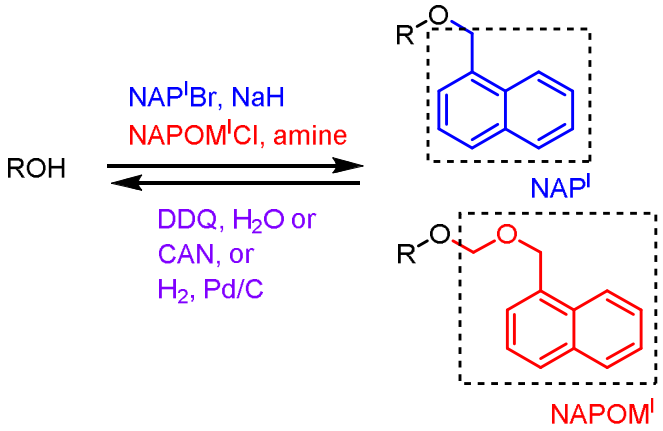
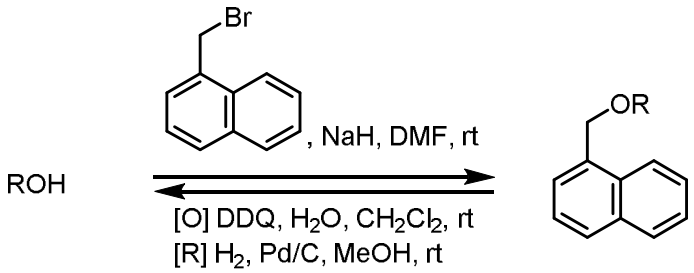
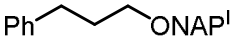
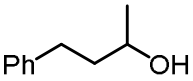
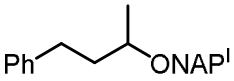
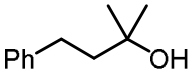
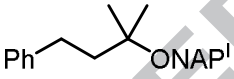


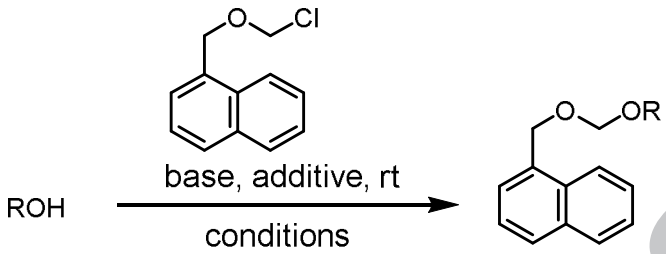
Table 1. Protection and Deprotection of alcoholic hydroxy groups with NAP[I].

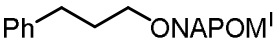
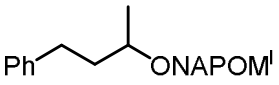
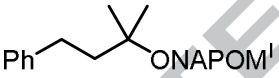
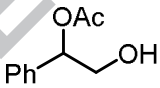
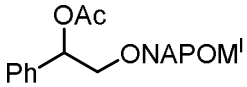
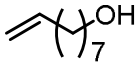
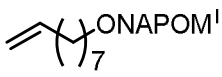


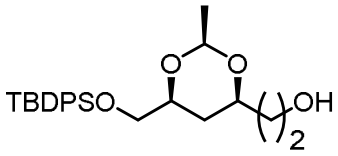
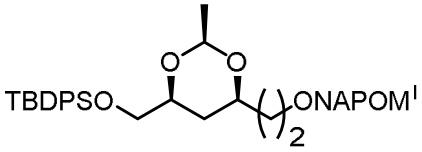
Entry	Substrate and Product		Yield / %[a]		
			Introduction[b]	Removal	
				[O][c]	[R][d]
1	**1a**:		93	98	97
	1b:				
2	**2a**:		88	quant	99
	2b:				
3	**3a**:		58	quant	97
	3b:				

[a] Isolated yields after column chromatography on silica gel. [b] NAP[I]Br (1.1 equiv), NaH (1.5 equiv), DMF ([substrate] = 1.0 M), rt, 6-26 h; reactions were monitored by TLC and quenched upon completion or stopping. [c] DDQ (3 equiv), CH_2Cl_2/H_2O = 4/1, rt, 1.5-6.5 h. [d] H_2 (1 atm), Pd/C (5 mol%), rt, 1.0-1.7 h.

Table 2. Protection of alcoholic hydroxy groups with NAPOM^{I}.

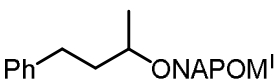


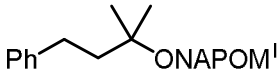
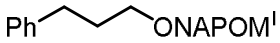
En-try	Substrate (1a-6a) and Product (1c-6c)	Reagents[a]	Solvent[b]	Time / h	Yield / %[c]
1	**1a**	NAPOM^{I}Cl	CH_2Cl_2	7.4	quant
	1c: 	*i*-Pr_2EtN			
2	**2a**	NAPOM^{I}Cl	CH_2Cl_2	16	90
	2c: 	*i*-Pr_2EtN			
3	**3a**	NAPOM^{I}Cl	CH_2Cl_2	19	96
	3c: 	*i*-Pr_2EtN			
4	**3a**	NAPOM^{I}Cl	toluene	6	94
	3c	*i*-Pr_2EtN			
5	**4a**: 	NAPO-M^{I}Cl[d]	CH_2Cl_2	24.5	82
		2,6-lutidine			
	4c: 	TBAI			
6	**5a**: 	NAPOM^{I}Cl	CH_2Cl_2	19	72
		i-Pr_2EtN			
	5c: 				

7	**6a**: 	NAPOM^{I}Cl *i*-Pr$_2$EtN	CH_2Cl_2	49.5	74
	6c: 				

[a] NAPOM^{I}Cl (2-6 equiv), i-Pr$_2$EtN (4-12 equiv). [b] [Substrate] = 0.1-0.5 M. [c] Isolated yields after column chromatography on silica gel. [d] NAPOM^{I}Cl (6 equiv), 2,6-lutidine (12 equiv), and TBAI (0.5 equiv).

Table 3. Removal of the NAPOM^{I} group from protected hydroxy groups.

Entry	**Substrate (1c-3c) and Product (1a-3a)**	**Reagent and Solvent**[a]	**Temperature**	**Time / h**[b]	**Yield / %**[c] **c** **a**
1	**1c**: 	DDQ (3 equiv)	reflux	19.5	0
		CH_2Cl_2/H_2O (4/1)			64[d]
	1a				
2	**1c**	CAN (8 equiv)	rt	149	0
	1a	Acetone/H_2O (9/1)			83
3	**1c**	H_2, Pd/C (5 mol%)	rt	8	0
	1a	MeOH			81[d]
4	**2c:** 	DDQ (3 equiv)	reflux	15	0
		CH_2Cl_2/H_2O (4/1)			86[d]
	2a				

5	**2c**		CAN (6 equiv)	rt	121	0
	2a		Acetone/H_2O (9/1)			88[e]
6	**2c**		H_2, Pd/C (5 mol%)	rt	6.5	0
	2a		MeOH			83[d]
7	**3c**:		DDQ (3 equiv)	reflux	27	0
			CH_2Cl_2/H_2O (4/1)			99
	3a					
8	**3c**		CAN (4 equiv)	rt	26.5	0
	3a		Acetone/H_2O (9/1)			quant[e]
9	**3c**		H_2, Pd/C (5 mol%)	rt	8.5	0
	3a		MeOH			81[d]
10	**1c**:		*p*-TsOH (8 equiv)	rt	5	97
			THF, MeOH			trace
	1a					
11	**1c**		*p*-TsOH (8 equiv)	reflux	22	0
	1a		THF, MeOH			quant[e]
12	**1c**		$BF_3{\cdot}OEt_2$ (1 equiv)	-78 to -30 °C	3	quant
	1a		Et_3SiH (5 equiv)			trace
			CH_2Cl_2			

[a] [Substrate] = 0.1 M. [b] Reactions were monitored by TLC and quenched upon completion or the formation of undesired products. [c] Isolated yields after column chromatography on silica gel. [d] Byproducts were observed (for details, see: Supplementary Material). [e] Obtained as an inseparable mixture containing 1-naphthalenemethanol; yields were determined based on the ^{1}H-NMR spectra of the mixture.

- The 2-Naphthylmethoxymethyl group can be removed in the presence of 1-naphthylmethoxymethyl group with DDQ.
- 1-Naphthylmethoxymethyl chloride is more readily prepared than 2-naphthylmethoxymethyl chloride.
- Naphthylmethoxymethyl groups are compatible with strong acids even in the presence of hard nucleophiles.
