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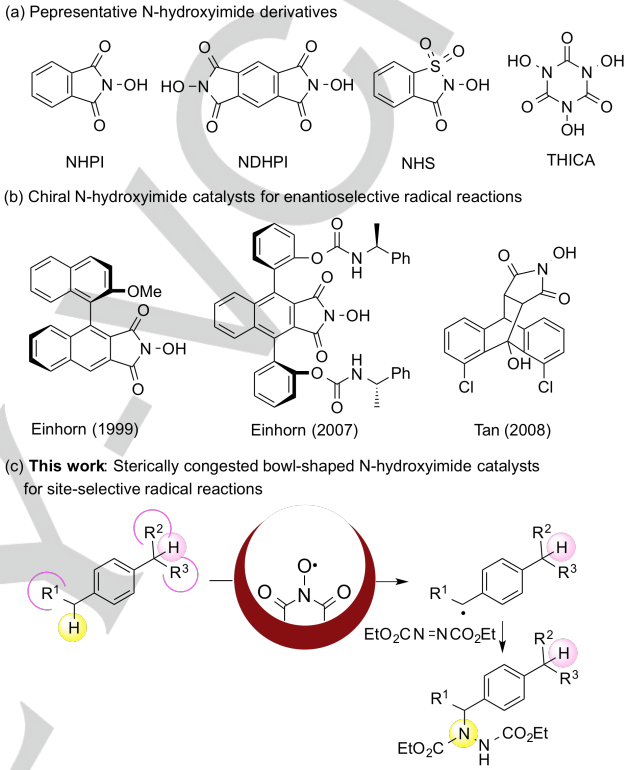
Design of Bowl-Shaped *N*-Hydroxyimide Derivatives as New Organoradical Catalysts for Site-Selective C(sp^3)-H Bond Functionalization Reactions

Terumasa Kato*[a] and Keiji Maruoka*[a],[b],[c]

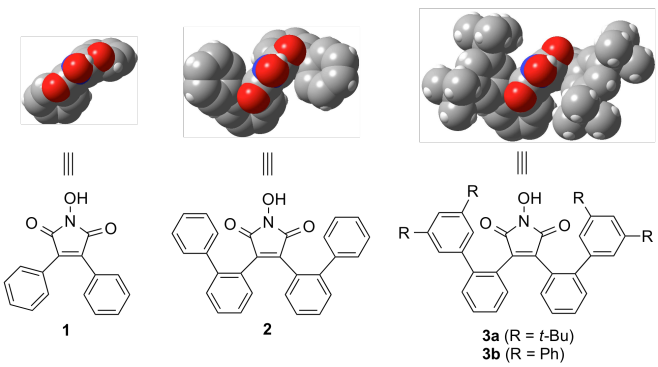
Abstract: A series of new bowl-shaped *N*-hydroxyimide derivatives has been designed and used as selective organoradical catalysts. A number of these bowl-shaped *N*-hydroxyimide derivatives exhibit excellent site-selectivity in the amination of benzylic C(sp^3)-H bonds in aromatic hydrocarbon substrates.

The functionalization of unactivated C(sp^3)-H bonds is one of the most important chemical transformations in organic chemistry, as it offers great potential to simplify synthetic sequences and to add functionality to a wide variety of organic molecules.[1] Unfortunately, such transformations still remain challenging as the high energy of the C(sp^3)-H bond renders it inert toward many reagents and catalysts. Previous attempts to transform such bonds via metal-mediated or -free reactions have often resulted in poor yield and/or low selectivity, thus reducing the practical applicability of those methods.[2] *N*-Hydroxyphthalimide (NHPI), a metal-free *N*-hydroxyimide derivative,[3] and its derivatives such as *N*,*N*'-dihydroxypyromellitimide (NDHPI),[4] *N*-hydroxysaccharin (NHS),[5] and *N,N',N''*-trihydroxyisocyanuric acid (THICA)[6] are well-known organoradical catalysts that can transform various unactivated C(sp^3)-H bonds into the corresponding C(sp^3)-X,[7] C(sp^3)-C,[8] C(sp^3)-O,[9] and C(sp^3)-N[10] bonds (Scheme 1a). Moreover, several chiral NHPI derivatives have been reported in enantioselective radical oxidations (Scheme 1b).[11] However, there are still only few examples of *N*-oxy-type organoradical catalysts/reagents for the site-selective functionalization of unactivated C(sp^3)-H bonds either in the absence or presence of directing groups.[12] Our contribution to this area is based on endowing *N*-oxyimide radical species with a bowl-shaped architecture in order to discriminate between sterically more and less hindered C(sp^3)-H bonds. Herein, we report our initial results on site-selective amination reactions of unactivated C(sp^3)-H bonds by newly designing bowl-shaped *N*-hydroxyimido derivatives with predictable site-selectivity (Scheme 1c).



Scheme 1. Examples of *N*-hydroxyimide-derived organoradical catalysts.

The space-filling models of *N*-hydroxy-3,4-diarylmaleimide derivatives **1~3a** are shown in Scheme 2.[13] The examination of these models suggests that bowl-shaped organoradical catalyst of the type **3** might be appropriate for the site-selective functionalization of hydrocarbons. Accordingly, we prepared various derivatives of *N*-hydroxy-3,4-diarylmaleimide **3**. As shown in Table 1, we evaluated these organoradical catalysts for their efficiency toward the site-selective amination of 1-cyclohexyl-4-ethylbenzene.



Scheme 2. Space-filling models of the *N*-hydroxymaleimide derivatives **1~3a**.

In a control experiment, we treated 1-cyclohexyl-4-ethylbenzene (**7a**) with diethyl azodicarboxylate (DEAD) (0.10 mmol) in 1,2-

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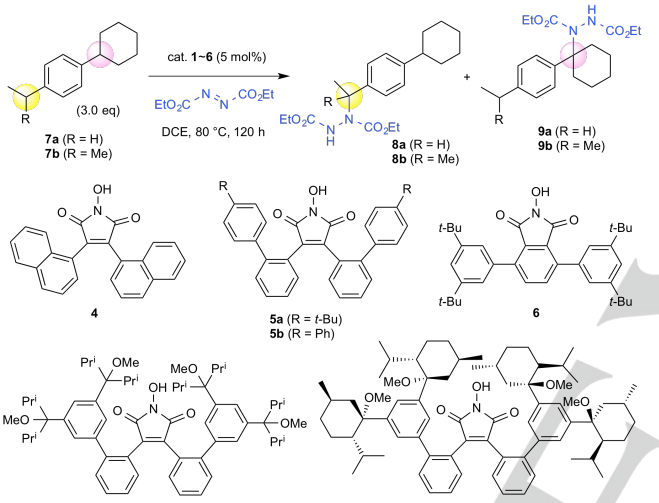
dichloroethane (0.15 M) in the presence of NHPI (5 mol%) at 80 ºC for 120 h, which almost quantitatively afforded a mixture of **8a** and **9a** in a ratio of 53:47 (entry 1).[14] Replacement of the NHPI catalyst with *N*-hydroxy-3,4-diphenylmaleimide (**1**), *N*-hydroxy-3,4-di(1-naphthyl)maleimide (**4**), or *N*-hydroxy-3,4-di(2-phenylphenyl)maleimide (**2**) under otherwise identical conditions furnished mixtures of **8a** and **9a** in ratios of 53:47, 48:52, and 51:49, respectively (entries 2-4). In contrast, the use of *N*-hydroxy-3,4-di(2-(4-*tert*-butyl)phenylphenyl)maleimide (**5a**) and *N*-hydroxy-3,4-di(2-(4-phenyl)phenylphenyl)maleimide (**5b**) enhanced the site-selectivity for the sterically less hindered C(sp^3)-H bonds to 68:32 and 72:28, respectively (entries 5 and 6). The best catalytic performance was observed for *N*-hydroxy-3,4-bis(2-(3,5-di-*tert*-butyl)phenylphenyl)maleimide (**3a**), which resulted in near perfect site-selectivity (entry 7).[15] *N*-Hydroxy-3,4-bis(2-(3,5-diphenyl)phenylphenyl)maleimide (**3b**) produced a slightly lower site-selectivity (entry 8) than **3a**. In contrast, the sterically hindered NHPI derivative **6** showed virtually no site-selectivity (entry 9). The choice of solvents is also highly important for the success of the reaction. Polyhalogenated solvents such as 1,1,2,2-tetrachloroethane and carbon tetrachloride showed excellent site-selectivity (**8**:**9**, 100:0). However, other solvents such as *t*-butyl acetate, acetonitrile, DMSO, chlorobenzene, and heptane were less effective (64:36 to 85:15: *cf.* Supporting Information), which implies that a conformational change could occur in the biphenyl moieties when using these solvents. The results of examining other factors such as the catalyst loading, the substrate ratios, the amount of DEAD used, other DEAD derivatives, the concentration of the reagents, the reaction time, and the reaction temperature are shown in the Supporting Information.

In marked contrast, the reaction of 1-cyclohexyl-4-iropropylbenzene substrate **7b**, which contains sterically similar cyclohexyl and isopropyl substituents, with DEAD (0.10 mmol) in 1,2-dichloroethane (0.15 M) in the presence of **3a** (5 mol%) at 80 ºC for 120 h afforded a mixture of **8b** and **9b** in a ratio of 90:10 (entry 11). In order to achieve an even higher site-selectivity, more sterically hindered *N*-hydroxyimide derivative **3c** was prepared,[15] and applied as a catalyst for the reaction of **7b** in 1,1,2,2-tetrachloroethane. Although the reaction proceeded slowly, it afforded a mixture of **8b** and **9b** in a 95:5 ratio (entry 12). Finally, the *l*-menthyl-derived *N*-hydroxyimide catalyst **3d** exhibited perfect site-selectivity (entry 13).[15]

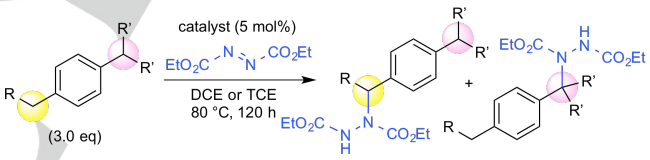
Table1. Optimization of the reaction conditions for the site-selective amination of substrate **7**.[a]

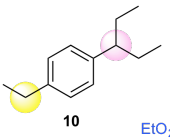
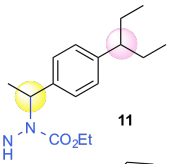
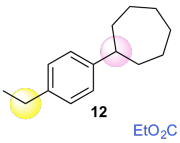
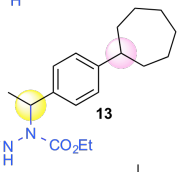
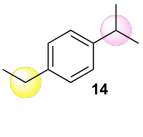
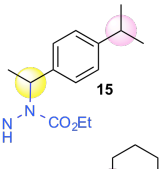
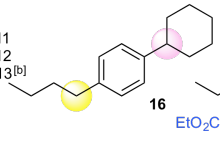
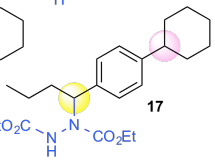


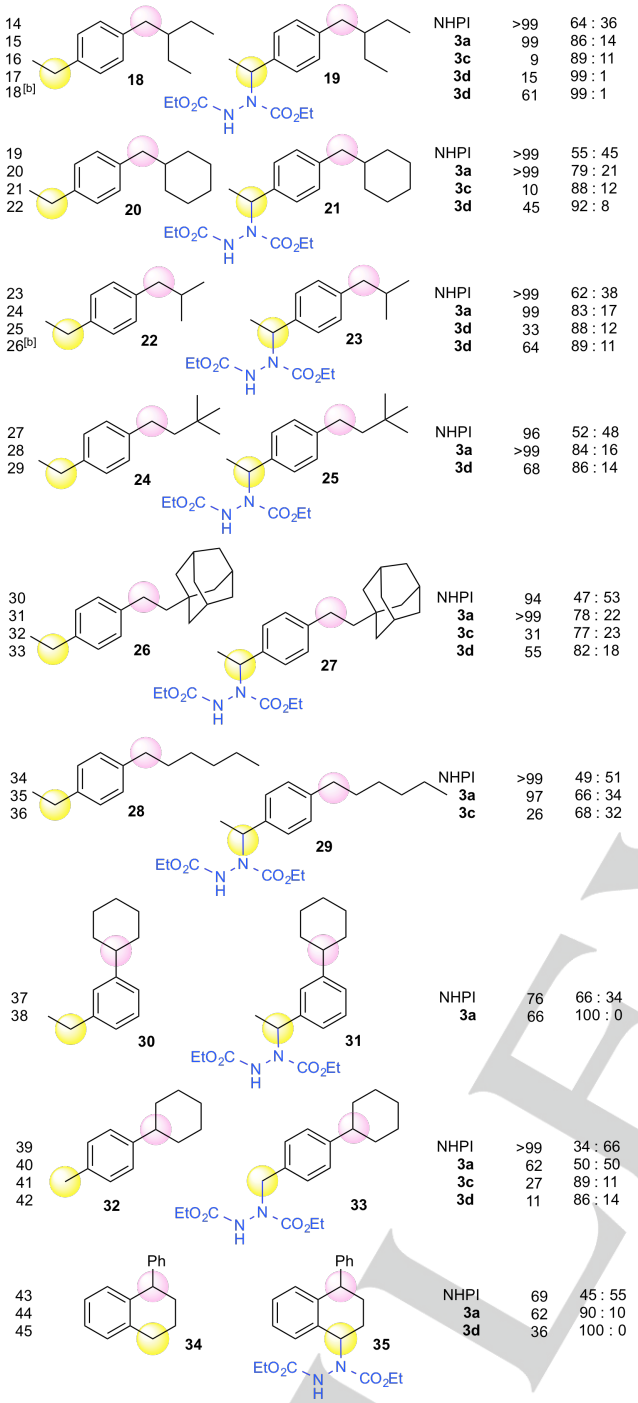
Entry	Substrate	Catalyst	Combined Yield [%][b]	Ratio (**8**:**9**)[b]
1	**7a**	NHPI	>99	53 : 47
2	**7a**	**1**	>99	53 : 47
3	**7a**	**4**	>99	48 : 52
4	**7a**	**2**	>99	51 : 49
5	**7a**	**5a**	>99	68 : 32
6	**7a**	**5b**	72	72 : 28
7	**7a**	**3a**	84 (53)[c]	100 : 0
8	**7a**	**3b**	73	80 : 20
9	**7a**	**6**	>99	55 : 45
10	**7b**	NHPI	>99	53 : 47
11	**7b**	**3a**	76	90 : 10
12[d]	**7b**	**3c**	22	95 : 5
13[d]	**7b**	**3d**	13	100 : 0

[a] Reaction conditions (unless otherwise noted): diethyl azodicarboxylate (DEAD, 0.10 mmol), catalyst (5 mol%) in 1,2-dichloroethane (0.15 M) at 80 ºC for 120 h. [b] The yield and ratio were determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard. [c] Use of DEAD (0.50 mmol). [d] In 1,1,2,2-tetrachloroethane (0.15 M).

Table 2. Scope of the site-selective amination of various substrates.[a]



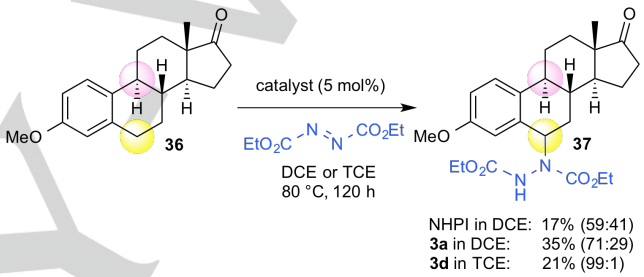
Entry	Substrate	Major Product	Catalyst	Combined Yield [%]	Ratio
1			NHPI	>99	85 : 15
2			**3a**	81	100 : 0
3			NHPI	91	58 : 42
4			**3a**	96	73 : 27
5			**3c**	24	100 : 0
6			**3d**	45	99 : 1
7			NHPI	71	51 : 49
8			**3a**	75	51 : 49
9			**3c**	21	76 : 24
10			**3d**	7	88 : 12
11			NHPI	75	58 : 42
12			**3a**	32	100 : 0
13[b]			**3a**	57	100 : 0



[a] Reaction conditions (unless otherwise noted): diethyl azodicarboxylate (DEAD, 0.10 mmol), catalyst (5 mol%) in 0.15 M of either 1,2-dichloroethane (DCE: for **3a**) or 1,1,2,2-tetrachloroethane (TCE: for **3c** and **3d**) at 80 ºC for 120 h. [b] 6.0 equiv of the substrate used.

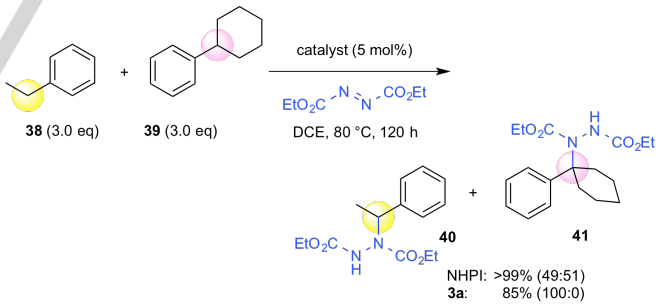
With the optimized conditions in hand, we subsequently examined the scope of the site-selective amination with respect to a series of unsymmetrically substituted benzene substrates (Table 2). The reaction of the ethyl- and 3-pentyl-substituted benzene **10** in the presence of bowl-shaped catalyst **3a** furnished almost exclusively the desired isomer **11**. Ethylbenzene derivatives **12**, **14**, and **16** with different *sec*-alkyl substituents at the *para*-position afforded high to excellent selectivity when using the bowl-shaped catalysts **3c** and/or **3d**. Even more remote control of the site-selectivity was achieved when using bowl-shaped catalysts **3c** and/or **3d** for the reaction of the ethylbenzene derivatives **18**, **20**, and **22**, with different β,β-disubstituted alkyl groups at the *para*-position. The use of excess substrate (6.0 equiv) for the reaction of **18** and **22** enhanced the yield of **19** and **23**, respectively (entries 18 and 26 vs. entries 17 and 25; see also entry 13 vs. entry 12). Substrates **24** and **26**, which contain *β*-(*tert*-alkyl)ethyl substituents at the ethylbenzene *para*-position exhibited high selectivity when using bowl-shaped catalyst **3d**. Notably, even 1-ethyl-4-hexylbenzene (**28**) showed some site-selectivity when using **3c**. 1-Cyclohexyl-3-ethylbenzene (**30**) and 1-cyclohexyl-4-methylbenzene (**32**) exhibited excellent to high site-selectivity when using **3a** or **3c**. This approach also works well for 1-phenyltetrahydronaphthalene (**34**) in the presence of **3d**.

As shown in Scheme 3, the synthetic utility of this approach was demonstrated by the successful site-selective functionalization of estrone 3-methyl ether (**36**).



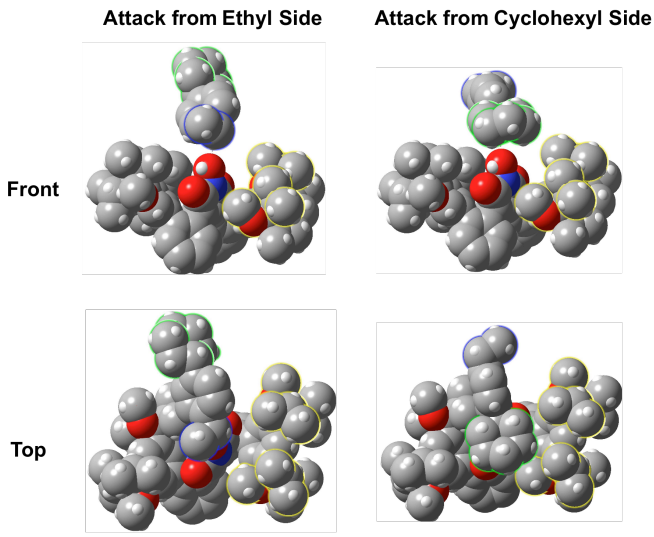
Scheme 3. Site-selective amination of estrone 3-methyl ether (**36**).

The present approach is also applicable to the simultaneous intermolecular site-selective amination of two different substrates **38** and **39** (Scheme 4).



Scheme 4. Intermolecular site-selective amination of **38** and **39**.

The origin of the observed high to excellent site-selectivity can be rationalized by examining the space-filling models of the sterically hindered *N*-hydroxy-3,4-diarylmaleimide derivative **3c** during the site-selective hydrogen abstraction of the benzylic C(sp^3)-H bond of 1-cyclohexyl-4-ethylbenzene (**7a**) (Scheme 5).



Scheme 5. Space-filling models in the site-selective abstraction of the benzylic hydrogen atom at the ethyl side of **7a** with the sterically hindered *N*-hydroxymaleimide derivative **3c**.

In conclusion, we have designed and synthesized a series of novel bowl-shaped *N*-hydroxyimide derivatives as organoradical catalysts for the site-selective amination of benzylic C(sp^3)-H bonds. Further investigations into the applications of bowl-shaped *N*-hydroxyimide catalysts of the type **3c** and **3d** for other C-H activation and functionalization reactions, as well as the design of more efficient bowl-shaped *N*-hydroxyimide catalysts, are currently in progress in our laboratory.

Acknowledgements

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Conflicts of interest

The authors declare no conflict of interests.

Keywords: *N*-hydroxyimide • site-selectivity • amination • diethyl azodicarboxylate • radical reactions

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[13] The geometry of the space-filling models was optimized by the density functional theory (DFT) calculations at the B3LYP/6-31G^{++}(d,p) level of theory using the Gaussian 09 software package. M. J. Frisch, et al., Gaussian 09, Revision A.02, Gaussian, Inc., Wallingford CT, **2009**.

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[15] Catalyst **3** was prepared in 2-step sequence from 1-(benzyloxy)-3,4-dibromo-1H-pyrrole-2,5-dione: Catalyst **3a**: 63% overall yield; catalyst **3c**: 29% overall yield; catalyst **3d**: 39% overall yield (see also Supporting Information). The synthetic pathways of arylboronic acids and their overall yields from the known compounds are described in Supporting Information.

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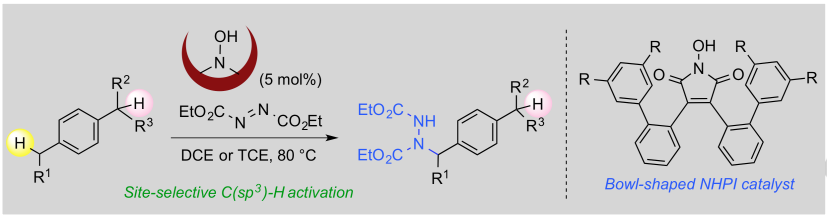

A series of new bowl-shaped *N*-hydroxyimide derivatives has been designed and used as selective organoradical catalysts. A number of these bowl-shaped *N*-hydroxyimide derivatives exhibit high to excellent site-selectivity in the amination of benzylic C(sp^3)-H bonds in aromatic hydrocarbon substrates.

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Design of Bowl-Shaped *N*-Hydroxyimide Derivatives as New Organoradical Catalysts for Site-Selective C(sp^3)-H Bond Functionalization Reactions