Site-selective and Stereoselective C(sp^3)–H Borylation of Alkyl Side Chains of 1,3-Azoles with a Silica-Supported Monophosphine-Ir Catalyst

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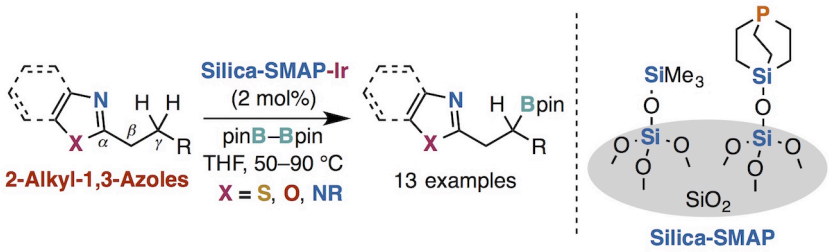

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Abstract Site-selective and stereoselective C(sp^3)–H borylation of alkyl side chains of 1,3-azoles with bis(pinacolato)diboron was effectively catalyzed by a silica-supported monophosphine-Ir catalyst. The borylation occurred under relatively mild conditions (2 mol% Ir, 50–90 °C), affording the corresponding primary and secondary alkylboronates. This system was applicable to a variety of 1,3-(benzo)azoles such as thiazoles, oxazoles, and imidazoles.

Key words 1,3-azole, C–H activation, borylation, Iridium, heterogeneous catalyst

1,3-Azoles are common structures in many biologically active natural compounds, pharmaceuticals and organic functional materials, and many of these molecules have an alkyl substituent at the 2-position (Figure 1).[1] Therefore, functionalization of the alkyl side chain of 1,3-azoles is of great importance for construction of complex molecules containing 1,3-azole scaffolds.[2] Among the methods for functionalization of alkyl groups, C(sp^3)–H borylation is attractive because alkylboron compounds are versatile synthetic intermediates with broad functional group compatibility, and air- and moisture stability.[3,4] Despite recent significant progress in this area, the site-selective borylation of unactivated C(sp^3)–H bonds over potentially more reactive C–H bonds such as C(sp^2)–H bonds remains challenging.[5-10] Moreover, the stereoselective borylation of C(sp^3)–H bonds is underdeveloped.[5e,5g,5h,7,10a]

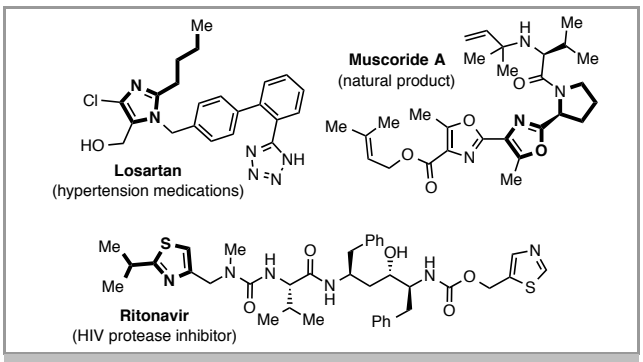


Figure 1. Representative Compounds Containing the 2-Alkyl-1,3-azole Scaffold.

Recently, we have reported the heteroatom-directed borylation of C(sp^3)–H bonds bearing *N*-heteroarenes or carbonyl-based functional groups catalyzed by Rh- or Ir systems based on solid-supported monophosphines with mono-P-ligating features (Figure 2).[10] This strategy allowed site-selective borylation of the N-adjacent[10b] or unactivated[7b,10a,c,d] C(sp^3)–H bonds located γ to N or O atoms on the directing groups. The regioselectivity was due to the proximity effect by the heteroatom-to-metal coordination. In fact, cyclic and acyclic alkyl substituents at the 2-position of pyridines underwent the C(sp^3)–H borylation with excellent site- and stereoselectivities.[10a] Later, we found that 1,3-azoles also worked as suitable directing groups for the C(sp^3)–H boylation of small-ring carbocycles such as cyclopropanes and cyclobutanes.[7b] However, its applicability for linear alkyl groups and normal-sized (five-to-seven membered) carbocycles has not been explored.

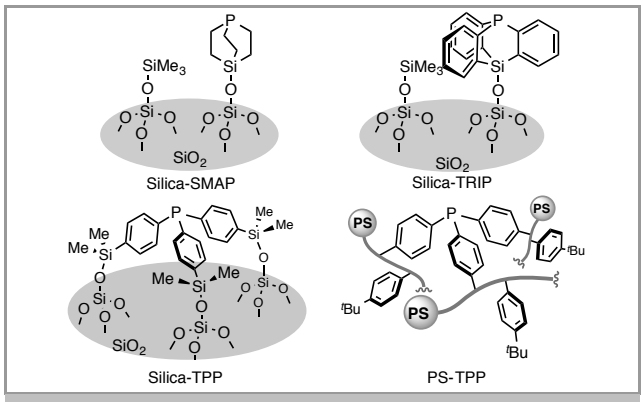


Figure 2. Solid-Supported Monophosphines.

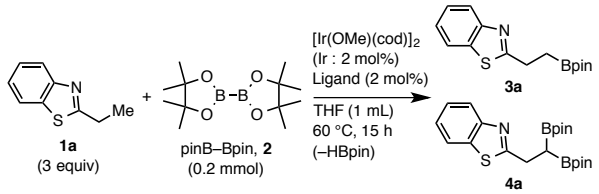
Herein, we report a heteroatom-directed C(sp^3)–H borylation of alkyl side chains of 1,3-azoles with a silica-supported monophosphine-Ir catalyst. Owing to the proximity effect by N-to-Ir coordination, the borylation occurred under relatively mild reaction conditions with high site- and stereoselectivities. This catalytic system was applicable for the reaction of primary and secondary C(sp^3)–H bonds of linear and cyclic alkyl substituents in 1,3-azoles, including thiazoles, oxazoles, and imidazoles.

Initially, we examined the borylation of 2-ethylbenzothiazole (**1a**, 0.6 mmol) with bis(pinacolato)diboron (B_2pin_2) (**2**, 0.2 mmol) in THF at 60 °C for 15 h in the presence of various Ir catalysts (2 mol% Ir), which were prepared *in situ* from $[Ir(OMe)(cod)]_2$ and different ligands. The results are summarized in Table 1.

In contrast to the C(sp^3)–H borylation of 2-alkylpyridines reported previously,[10a] for which all solid-supported monophosphines shown in Figure 1 were effective ligands (Silica-SMAP,[10a] Silica-TRIP,[10b] Silica-TPP[10c] and PS-TPP[10d]), the borylation of **1a** was specifically promoted by commercially available Silica-SMAP, affording the terminal C(sp^3)–H borylation product **3a** and the geminal bisborylation product **4a** in 82% and 32% NMR yields, respectively (Table 1, entry 1).[11,12] The reactivity of the alkyl side chain in **1a** seems to be lower than that in the pyridine analogue. Indeed, 2-ethylpyridine underwent efficient C(sp^3)–H borylation with the Silica-SMAP-Ir system at 25 °C,[10a] while **1a** was intact under identical conditions (data not shown). The ligand specificity of Silica-SMAP in the present borylation reaction may suggest a requirement for the high electron density of the metal and/or sparse nature of the catalytic environment provided by the compact ligand. The total borylation yields over 100% based on B_2pin_2 (**2**) indicated that pinacolborane (HBpin), which was a byproduct of the reaction with B_2pin_2, also served as a borylating reagent, although it was less reactive than **2**. The C(sp^2)–H bonds of the benzothiazole ring and the C(sp^3)–H bonds at the position α to the azole group were intact. A larger-scale reaction (5 mmol for **2**) at 0.5 mol% Ir loading proceeded efficiently at 90 °C to give **3a** in 54% isolated yield (entry 2). The geminal diborylation product **4a** could be obtained as a major product in 89% isolated yield by the reaction with 2 equiv of **2** (2 mol% Ir, 60 °C) (entry 3).

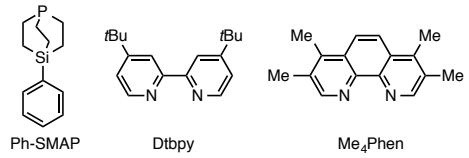
Table 1 also shows the inefficiency of homogeneous catalytic systems. The use of monophosphines such as Ph-SMAP[13] and PPh_3 did not promote the C(sp^3)–H borylation (entries 7 and 8). Bipyridine-based ligands such as Dtbpy and Me_4Phen resulted in only aromatic C–H borylation with lower efficiencies (<4% yields of arylboronates, entries 9 and 10).[14] No reaction occurred without an exogenous ligand (entry 11).

Table 1. Ligand Effects in Ir-catalyzed Borylation of 2-Ethylbenzothiazole (**1a**) with Bis(pinacolato)diboron (**2**)[a]



Entry	Ligand	Yield of **3a** [%][b]	Yield of **4a** [%][b]
1	Silica-SMAP	82[c] (75)[d]	32
2[e]	Silica-SMAP	71 (54)	12
3[f]	Silica-SMAP	2	97 (89)[g]
4	Silica-TRIP	0	0
5	Silica-TPP	0	0
6	PS-TPP	0	0
7	Ph-SMAP	0	0
8	PPh_3	0	0
9[h]	Dtbpy	0	0
10[h]	Me_4Phen	0	0
11	none	0	0

[a] Conditions: **1a** (0.6 mmol), **2** (0.2 mmol), $[Ir(OMe)(cod)]_2$ (2 mol% Ir), ligand (2 mol%), THF (1 mL), 60 °C, 15 h.
[b] ^{1}H NMR yield based on **2**. Isolated yields shown in parentheses.
[c] The C=N reduction product of **1a** (4%) was formed.
[d] The isolated product **3a** was contaminated with **4a** (<1%) and traces of impurities.
[e] **1a** (15 mmol), **2** (5 mmol), $[Ir(OMe)(cod)]_2$ (0.5 mol% Ir), Silica-SMAP (0.5 mol%), THF (5 mL), 90 °C, 24 h.
[f] **1a** (0.2 mmol), **2** (0.4 mmol), $[Ir(OMe)(cod)]_2$ (2 mol% Ir), Silica-SMAP (2 mol%), THF (1 mL), 60 °C, 24 h. Yields of **3a** and **4a** were based on **1a**.
[g] The isolated product **4a** was contaminated with **3a** (2%).
[h] Arylboronates were formed in entries 9 and 10 (4% and 3%, respectively).



The Silica-SMAP-Ir system was applicable to various 1,3-(benzo)azoles **1**, including thiazoles, oxazoles, and imidazoles. Some of the borylation products **3** obtained in this manner were converted into the corresponding alcohols **5** through subsequent oxidation for facile product isolation.[15] The results are summarized in Table 2.

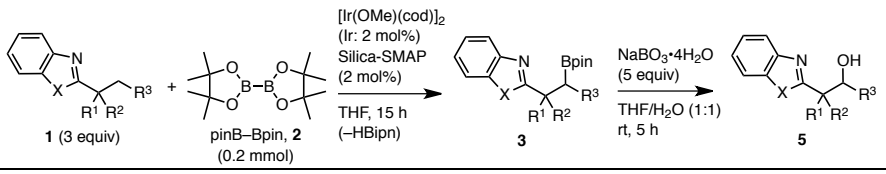
The reaction with 2-ethylbenzoxazole (**1b**) proceeded smoothly at 60 °C to give the monoborylation product **3b** and the geminal diborylation product **4b** in 78% and 26% yields, respectively, with the formation of small amounts of C(sp^2)–H borylation products (5%) (Table 2, entry 1). 2-

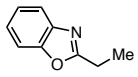
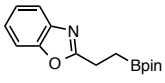
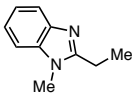
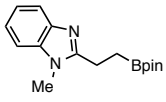
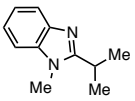
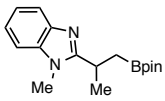
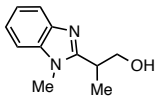
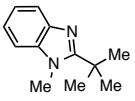
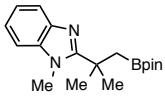
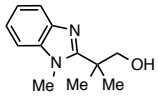
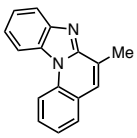
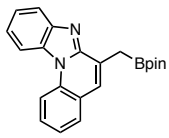
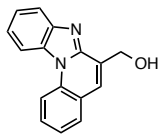
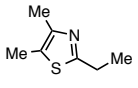
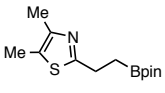
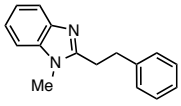
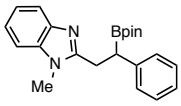
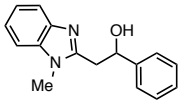
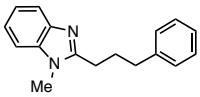
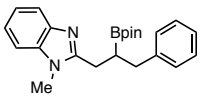
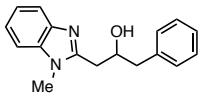
Ethylbenzimidazole (**1c**) was borylated at 50 °C, affording the monoborylation product **3c** and the diborylation product **4c** in 38% and 19% yields, respectively (entry 2). However, the formation of a significant amount of a C=N reduction product of **3c** (structure not determined, ca. 20%) was observed in the ^{1}H NMR spectrum of the crude reaction mixture. The use of cyclooctene as an additive effectively suppressed the C=N reduction of **3c**, resulting in an increase in yields of **3c** and **4c** to 60% and 31%, respectively (entry 3).[16] Benzimidazoles bearing bulky alkyl groups, such as isopropyl (**1d**) and *tert*-butyl (**1e**) groups, at their 2-positions were successfully borylated at the terminal C(sp^3)–H bonds (entries 4 and 5). The methyl C(sp^3)–H borylation of polycyclic compound **1f** gave primary alkylboronate **3f** as a sole product (entry 6). Monocyclic 1,3-thiazole **1g** was also a suitable substrate for the terminal C(sp^3)–H borylation (entry 7).[17]

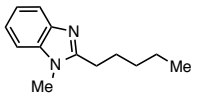
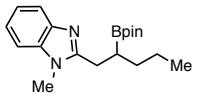
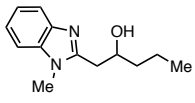
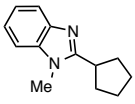
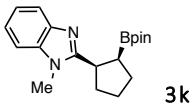
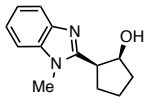
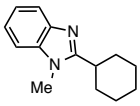
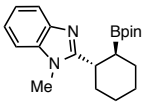
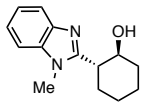
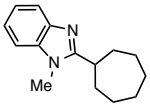
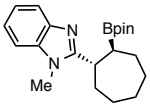
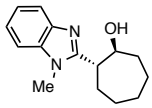
Internal C(sp^3)–H bonds in 2-alkyl-1,3-azoles successfully participated in the borylation with the Silica-SMAP-Ir system under relatively mild conditions (2 mol% Ir, 70–90 °C), affording the corresponding secondary alkylboronates (Table 2, entries 8–13). For example, the reactions of **1h** or **1i** containing a phenyl substituent proceeded with excellent site-selectivity at the C(sp^3)–H bonds located γ to the directing sp^2-hybridized N atoms (entries 8 and 9). The site-selective borylation occurred efficiently with 2-pentylbenzimidazole (**1j**) to provide alkylboronate **3j** (entry 10).

As was the case for the small-sized carbocycles,[7b] normal-sized ring compounds were also borylated site- and stereoselectively. Specifically, the reaction of 2-cyclopentyl-*N*-methylbenzimidazole (**1k**) at 90 °C afforded the borylation product **3k** as a mixture of *cis* and *trans* isomers in a 4:1 ratio (Table 2, entry 11). The cyclohexyl and cycloheptyl groups in **1l** and **1m**, respectively, reacted at 70–80 °C with exceptional *trans* selectivity (entries 12 and 13).

Table 2. Silica-SMAP–Ir Catalyzed C(sp^3)–H Borylation of 2-Alkyl-1,3-azoles **1** with Diboron **2** Followed by Oxidation[a]



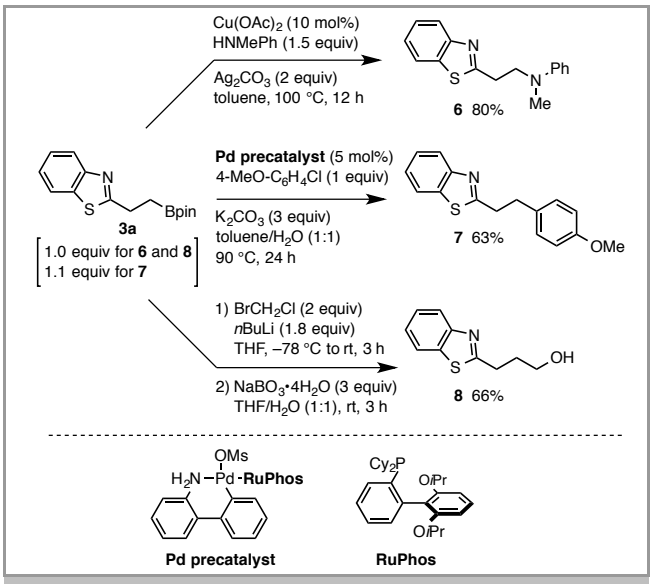
Entry	Substrate 1	Borylation Product 3	Temp (°C)	Yield of 3 (%)[b]	Oxidation Product 5[c]	Yield of 5 (%)[b]
1	 1b	 3b	60	78[c,d,e] (48)[f]	–	–
2	 1c	 3c	50	38[c,d,g]	–	–
3[h]			50	60[c,d] (54)[i]		
4	 1d	 3d	80	83[d]	 5d	(59)
5	 1e	 3e	80	87	 5e	(68)
6	 1f	 3f	70	86	 5f	(71)
7	 1g	 3g	60	80[c] (63)	–	–
8	 1h	 3h	80	81[d,e]	 5h	(69)
9	 1i	 3i	80	89[d,e]	 5i	(70)

10	 **1j**	 **3j**	90	89[d,e]	 **5j**	(74)
11	 **1k**	 **3k** (*cis*:*trans* = 4:1)	90	112[d,e]		**5k** (*cis*): (67) **5k'** (*trans*): (16)[j]
12	 **1l**	 **3l**	70	83[d,e]	 **5l**	(55)[j]
13	 **1m**	 **3m**	80	72[d,e]	 **5m**	(43)[j]

[a] Conditions for C–H borylation: **1** (0.6 mmol), **2** (0.2 mmol), $[Ir(OMe)(cod)]_2$ (2 mol% Ir), Silica-SMAP (2 mol% P), THF (1 mL), 15 h. Conditions for oxidation: the crude products of the C(sp^3)–H borylation (**3**), $NaBO_3{\cdot}4H_2O$ (1 mmol), THF (1 mL), H_2O (1 mL), rt, 5 h.
[b] ^{1}H NMR yield based on **2**. Isolated yields shown in parentheses.
[c] Geminal diborylation products **4** were formed in entries 1, 2, 3 and 7 (26%, 19%, 31%, and 34%, respectively).
[d] The C=N reduction products of **1** were formed in entries 1, 2, 3, 4, 8, 9, 10, 11, 12 and 13 (30%, 64%, 42%, 85%, 40%, 59%, 84%, 35%, 83%, and 41%, respectively).
[e] Arylboronates were formed in entries 1, 8, 9, 10, 11, 12 and 13 (5%, 7%, 6%, 11%, 4%, 8%, and 2%, respectively).
[f] Isolated product was contaminated with arylboronates (9%) and the diborylation product (1%).
[g] The C=N reduction product of **3c** (structure not determined, ca. 20%) was formed.
[h] Cyclooctene (0.2 mmol) was used as an additive.
[i] Isolated product was contaminated with the diborylation product (<1%).
[j] Isolated products in entries 11, 12, and 13 were contaminated with phenol derivatives (1%, 5%, and 2%, respectively), which were derived from the corresponding arylboronates.

To demonstrate the synthetic utility of the present borylation reaction, transformations of alkylboronate **3a** were performed as shown in Scheme 1. The boronate **3a** was converted into tertiary amine **6** through a Cu-catalyzed reaction with *N*-methylaniline in the presence of Ag_2CO_3 as an oxidant.[18] The Suzuki–Miyaura cross-coupling of 4-chloroanisole with a RuPhos-ligated palladacycle precatalyst provided the sp^3–sp^2 coupling product **7**.[19–21] The one-carbon-homologation-oxidation sequence afforded the corresponding primary alcohol **8**.[22]

In summary, a heterogeneous Ir catalyst system with silica-supported cage-type trialkylphosphine Silica-SMAP enabled C(sp^3)–H borylation of alkyl side chains of 1,3-azoles, including thiazoles, oxazoles, and imidazoles, under relatively mild conditions with high site- and stereoselectivities. The borylation occurred not only at terminal C(sp^3)–H bonds but also at internal secondary C(sp^3)–H bonds in linear alkyl groups or carbocyclic rings. The obtained alkylboronates serve as precursors for C–N and C–C bond formation reactions. Thus, this heterogeneous Ir catalysis offers a useful method for rapid access to functionalized molecules with 1,3-azole scaffolds.



Scheme 1. Transformations of **3a**.

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Supporting Information

Experimental details and characterization data for new compounds is available online at **[...]**.

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(11) **Typical Procedure for the C(sp^3)–H Borylation of Alkyl Side Chains on 1,3-Azoles with a Silica-SMAP-Ir Catalyst System (Table 1, Entry 1)**: In a glove box, Silica-SMAP (0.07 mmol/g, 57.1 mg, 0.0040 mmol, 2 mol%), bis(pinacolato)diboron (**2**) (50.8 mg, 0.20 mmol), and anhydrous, degassed THF (0.3 mL) were placed in a 10 mL glass tube containing a magnetic stirring bar. A solution of [Ir(OMe)(cod)]$_2$ (1.3 mg, 0.0020 mmol, 1 mol%) in THF (0.7 mL) and 2-ethylbenzo[*d*]thiazole (**1a**) (97.9 mg, 0.60 mmol) were added successively. The tube was sealed with a screw cap and removed from the glove box. The reaction mixture was stirred at 60 °C for 15 h, and filtered through a glass pipette equipped with a cotton filter. The solvent was removed under reduced pressure. An internal standard (1,1,2,2-tetrachloroethane) was added to the residue. The yields of the products **3a** and **4a** were determined by ^{1}H NMR spectroscopy (82% and 32% yields, respectively). The crude material was then purified by Kugelrohr distillation (1 mmHg, 145 °C), to give the corresponding product **3a** (43.1 mg, 0.15 mmol, 75% yield) contaminated with the diborylation product **4a** (<1%) and traces of impurities, as estimated by ^{1}H NMR spectroscopy. Total yield over 100% based on **2** indicates that HBpin formed during catalytic turnover also served as a borylating reagent (theoretical maximum yield is 200%). ^{1}H NMR ($CDCl_3$): δ 1.24 (s, 12H), 1.38 (t, *J* = 7.6 Hz, 2H), 3.24 (t, *J* = 7.6 Hz, 2H), 7.32 (td, *J* = 8.4, 1.2 Hz, 1H), 7.42 (td, *J* = 7.6, 0.8 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 11.10 (br), 24.75 (4C), 28.85, 83.36 (2C), 121.42, 122.41, 124.42, 125.67, 135.19, 153.19, 173.81. ^{11}B NMR ($CDCl_3$): δ 32.6. IR (ATR): 2976, 2931, 1519, 1436, 1370, 1313, 1142, 1082, 967, 845, 758 cm^{-1}. HRMS–ESI (*m/z*): [M+H]$^+$ Calcd for $C_{15}H_{21}O_2N^{10}BS$, 289.14169; found, 289.14170.

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(14) The C(sp^2)–H borylation of heteroarenes including 1,3-benzazoles catalyzed by the Ir-Me$_4$Phen system: Larsen, M. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4287–4299.

(15) In some cases, the formation of C=N reduction products of starting materials (**1**) was indicative by ^{1}H NMR analyses of the crude products. Similar C=N reduction was observed in the C(sp^3)–H boylation of small-ring carbocycles bearing 1,3-azoles with the Silica-SMAP-Ir catalyst system (ref. 7b). The desired products **3** or **5** could be isolated by bulb-to-bulb distillation or silica gel column chromatography.

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