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A highly chemoselective Boc protection of amines using sulfonic-acid-functionalized silica as an efficient heterogeneous recyclable catalyst☆

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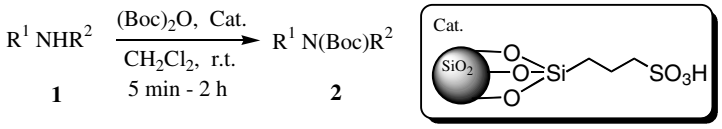
Abstract—A facile and versatile method for the chemoselective Boc protection of amines has been developed by a treatment with $(Boc)_2O$ in the presence of sulfonic-acid-functionalized silica as a catalyst. The method is general for the preparation of *N*-Boc derivatives of aliphatic (acyclic and cyclic), aromatic, and heteroaromatic amines; primary and secondary amines; aminols, amino-esters; and sulfonamides. The catalyst works under heterogeneous conditions and can be recycled.

The *tert*-butoxycarbonyl (Boc) group is one of the most useful functionalities for the protection of amines and amine derivatives.[1] The commercially available $(Boc)_2O$ is widely used for the introduction of the Boc group.[2] Different base-mediated reactions for Boc protection of amines have been developed.[3] Recently, some Lewis acids have also been applied as catalysts for this purpose.[4] However, long reaction times, unsatisfactory yields, and limited applicabilities are drawbacks in several methods. The recovery of the catalysts is also a problem. Moreover, though various catalysts have been employed, the utility of a catalyst having Brønsted acid character for the preparation of *N*-Boc derivatives has not yet been properly explored.

In continuation of our work[5] on the application of heterogeneous catalysts for the development of useful synthetic methodologies, we recently discovered that sulfonic-acid-functionalized silica is an efficient and versatile catalyst for the Boc protection of amines (Scheme 1).

A variety of amines were treated with $(Boc)_2O$ in the presence of sulfonic-acid-functionalized silica in CH_2Cl_2 at room temperature to afford the corresponding *N*-Boc protected amines (Table 1). The yields of the products were generally excellent and the times required for derivatization were short. The most suitable solvent for this conversion was CH_2Cl_2 considering the reaction times and yields of the products (Table 2). However, some of the amines were insoluble in CH_2Cl_2 and in such cases, a mixture of CH_2Cl_2–MeCN or MeOH–MeCN was used (Table 1).

Aliphatic (open chain and cyclic), aromatic, and heteroaromatic amines underwent the conversion efficiently. Aniline (Table 1, entry i) required 45 min to form the corresponding *N*-Boc product (83%) which



Scheme 1.

Keywords: Amine; Boc protection; $(Boc)_2O$; Sulfonic-acid-functionalized silica; Heterogeneous recyclable catalyst.
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Table 1. Boc protection of amines using sulfonic-acid-functionalized silica[a]

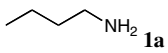
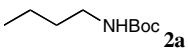
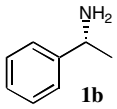
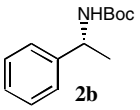
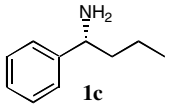
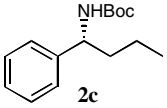
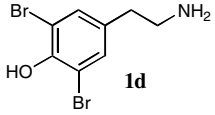
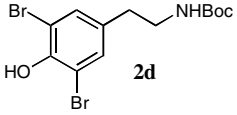
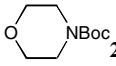
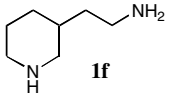
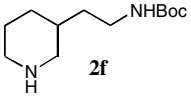
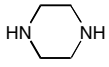
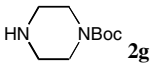
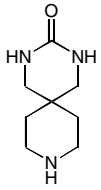
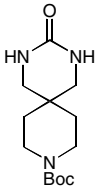
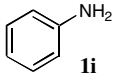
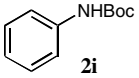
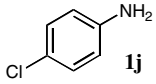
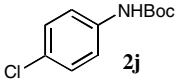
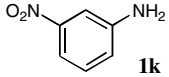
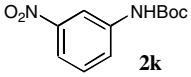
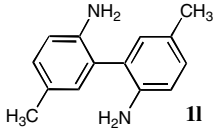
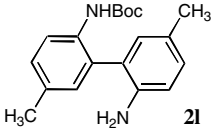
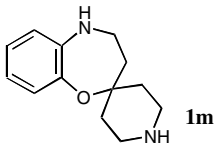
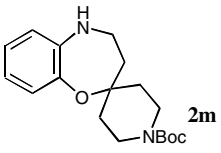
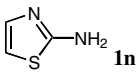
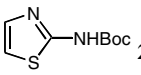
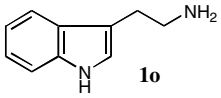
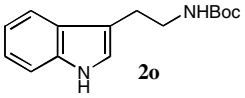
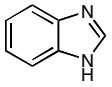
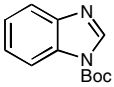
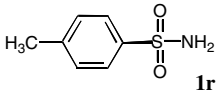
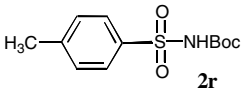
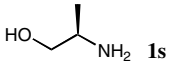
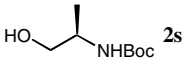
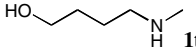
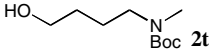
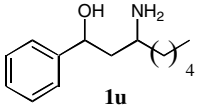
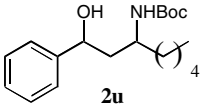
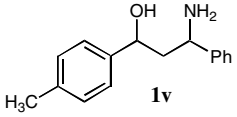
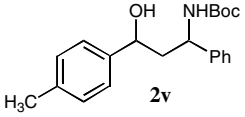
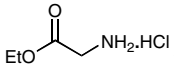
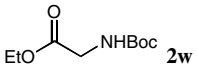
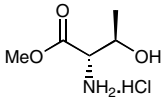
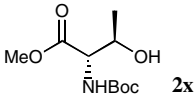
Entry	Amine	Time (min)	Product	Isolated yield (%)
a	 **1a**	5	 **2a**	99
b	 **1b**	5	 **2b**	99
c	 **1c**	5	 **2c**	99
d	 **1d**	5	 **2d**	98
e	 **1e**	10	 **2e**	96
f	 **1f**	5	 **2f**	93
g	 **1g**	10	 **2g**	94
h	 **1h**	10[b]	 **2h**	91
i	 **1i**	45	 **2i**	83
j	 **1j**	90	 **2j**	87
k	 **1k**	120[b]	 **2k**	71
l	 **1l**	65[b]	 **2l**	90
m	 **1m**	15[b]	 **2m**	91

Table 1 (*continued*)

Entry	Amine	Time (min)	Product	Isolated yield (%)
n	 **1n**	90[c]	 **2n**	86
o	 **1o**	5	 **2o**	94
p	 **1p**	90[b]	 **2p**	98
q	 **1q**	40	 **2q**	89
r	 **1r**	120[b]	 **2r**	77
s	 **1s**	10	 **2s**	95
t	 **1t**	15	 **2t**	79
u	 **1u**	5	 **2u**	98
v	 **1v**	5	 **2v**	97
w	 **1w**	30[b]	 **2w**	75
x	 **1x**	30[b]	 **2x**	73

[a] The structures of the products were determined from the spectral (IR, ^{1}H and ^{13}C NMR, and MS) and elemental analysis data.
[b] CH_3CN–CH_2Cl_2 (1:3) was used as a solvent.
[c] CH_3OH–CH_3CN (1:3) was used as a solvent.

Table 2. Solvent screen[a]

Entry	Solvent	Time (min)	Yield (%)
a	CH_2Cl_2	5	99
b	$Cl(CH_2)_2Cl$	5	98
c	CH_3CN	5	93
d	CH_3OH	60	73
e	$CHCl_3$	10	97
f	EtOAc	60	87
g	THF	60	89
h	$CH_3CN + CH_2Cl_2$ (1:3)	5	97

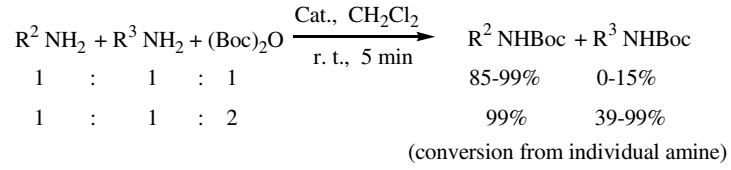
[a] All reactions were performed using 1-phenethylamine **1b** (1.0 mmol) and $(Boc)_2O$ (1.1 mmol) in 5 mL of different solvents at room temperature.

can be compared with the 14 h required for the same conversion using yttria–zirconia base catalyst.[4b] The present reaction was somewhat sluggish with an aromatic amine containing an electron-withdrawing group (Table 1, entry k), but the yield was high. Previously it was found to be difficult to prepare *N*-Boc derivatives from such amines.[4c] In the present case both primary and secondary amines worked well. In each case only the mono *N*-Boc protected product was formed. Benzimidazole and pyrazole (Table 1, entries p and q) also afforded the corresponding *N*-Boc products smoothly. Even with a sulfonamide (Table 1, entry r), the yield of the *N*-Boc derivative was impressive.

The present protocol was also utilized for the protection of the amine group of aminols (Table 1, entries d and s–v) and amino acid esters (entries w and x). In the case of aminols, only the amine group was protected leaving intact the hydroxyl group indicating the high chemoselectivity of the protocol. The protection of the amine group in amino acid esters could be useful in peptide synthesis. Chiral aminols and amino acid esters were not racemized under the present experimental conditions. This is evident from the fact that the chiral protected aminol (Table 1, entry s) and amino acid esters (entry x) when deprotected by TFA afforded the parent compounds with their original optical rotations. TFA is known to deprotect the chiral *N*-Boc amines without effecting their chirality.[6] The ester groups were also not hydrolyzed.

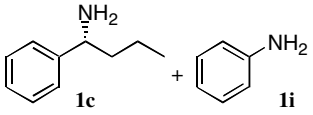
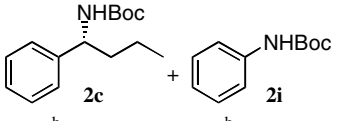
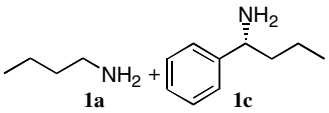
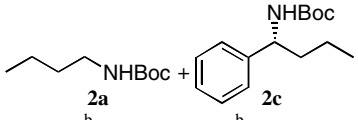
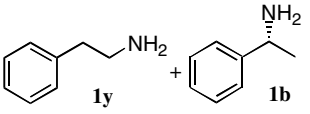
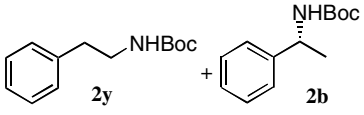
The chemoselectivity of the reaction was also demonstrated by the amine groups of different chemical nature. Thus, in 8,9-benzo-7-oxo-3,10-diaza-spiro[5.6]dodecane (Table 1, entry m) the benzylic secondary amine group remained intact while the other non-benzylic one was easily derivatized. Similarly, in 2-(1H-indol-3-yl)-ethylamine (Table 1, entry o) only the aliphatic amine group was mono Boc protected. When a mixture of aliphatic and aromatic amines (1 mmol each) was treated with $(Boc)_2O$ (1 mmol) in the presence of sulfonic-acid-functionalized silica, only the former amine was derivatized, but if $(Boc)_2O$ (2 mmol) was used, the aromatic amine was also partly converted (Scheme 2, Table 3, entry a). In the case of aliphatic amines, a primary amine was found to undergo rapid Boc protection in the presence of a secondary amine (Table 1, entry f). Even between an amine attached to a primary carbon and a secondary carbon, mainly the former could be protected using $(Boc)_2O$ (1 mmol), but if the reagent was used in excess, both groups could be protected quantitatively (Table 3, entries b and c). If in a molecule two identical amine groups were present, only one amine group was found to be protected (Table 1, entries g and l).

Sulfonic-acid-functionalized silica behaves as an organic–inorganic hybrid (interphase) catalyst wherein a Brønsted acid site has been selectively created.[7] It works under heterogeneous conditions and can easily be handled and removed from the reaction mixture. In recent years heterogeneous catalysts are finding increasing applications in the field of catalysis as they offer simpler, more reactive and more benign alternatives than their homogeneous counterparts.[8] In the present catalyst the reactive centers are highly mobile, as in a homogeneous catalyst. The catalyst was prepared[7] by the immobilization of propyl thiol on silica using 3-mercaptopropyltrimethoxysilane followed by the selective oxidation of the thiol groups by aqueous H_2O_2 to the sulfonic-acid

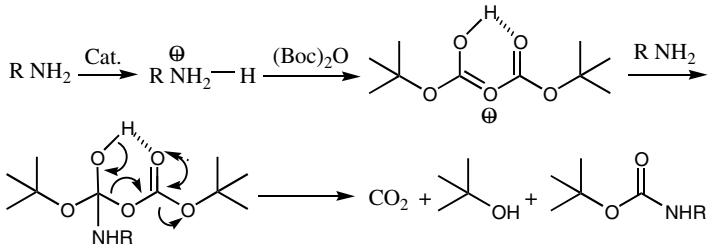


Scheme 2.

Table 3. Selective Boc protection using a mixture of amines

Entry	Mixture of amines	Products (% of isolated yield)[a]
a		 (99)[b] (99)[c] (0)[b] (39)[c]
b		 (96)[b] (99)[c] (3)[b] (98)[c]
c		 (85)[b] (99)[c] (15)[b] (99)[c]

[a] Yield with respect to the individual starting amine after 5 min of the reaction.
[b] % of the yield of product using 1 mmol of $(Boc)_2O$.
[c] % of the yield of product using 2 mmol of $(Boc)_2O$.



Scheme 3.

groups. Silica gel is less expensive than several organic polymers and readily available and it possesses the capacity to anchor an organic chain easily. The experimental procedure is simple and the structures of all the products were determined from their spectroscopic (IR, ^{1}H, ^{13}C NMR, and MS) and elemental analysis data.[9] The catalyst could be consecutively recycled three times without the loss of its activity. It can be mentioned here that the acidic ion-exchange resin, Amberlyst-15 was used earlier for the deprotection of Boc-amines.[10] We attempted to utilize the catalyst for the Boc protection of amines but the yields were not satisfactory.

The mechanism of the conversion is possibly similar to that which operates for the Lewis-acid induced Boc protection of amines.[11] The sulfonic-acid-functionalized silica catalyzes the reaction by the electrophilic activation of $(Boc)_2O$. A plausible mechanism is shown in Scheme 3.

In conclusion, we have described how sulfonic-acid-functionalized silica is a remarkably efficient heterogeneous catalyst used here for the first time for the mono Boc protection of a wide range of amines using $(Boc)_2O$. Aromatic amines containing electron-withdrawing groups also afforded the desired derivatives in good yields. Chiral substrates were resistant to racemization and labile functionalities such as esters were compatible in the conversion. The protocol is a highly chemoselective offering potential in different applications. The method also has several other advantages such as simple experimental procedures, mild reaction conditions, excellent yields of mono Boc protected amines and reusability of the catalyst.

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References and notes

1. Greene, T. W.; Wuts, P. G. M. In *Protective Group in Organic Synthesis*, 2nd ed.; Wiley: New York, 1999; pp 503–550, and references cited therein.
2. Pope, B. M.; Yamamoto, X.; Tarbell, D. S. *Org. Synth. Coll.* **1988**, *VI*, 418.
3. (a) Bailey, S. W.; Chandrasekaran, R. Y.; Ayling, J. E. *J. Org. Chem.* **1992**, *57*, 4470–4477; (b) Knölker, H. J.; Braxmeier, T. *Tetrahedron Lett.* **1996**, *37*, 5861–5864; (c) Lutz, C.; Lutz, V.; Knochel, P. *Tetrahedron* **1998**, *54*, 6385–6402.
4. (a) Porta, F.; Cenini, S.; Pizzotti, M.; Crotti, C. *Gazz. Chim. Ital.* **1985**, *115*, 275–277; (b) Pandey, P. K.; Dagade, S. P.; Upadhyay, R. K.; Dongare, M. K.; Kumar, P. *ARKIVOK* **2000**, *vii*, 28–33; (c) Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Massaccesi, M.; Melchiorre, P.; Sambri, L. *Synlett* **2004**, 1794–1798; (d) Heydari, A.; Hosseini, S. E. *Adv. Synth. Catal.* **2005**, *347*, 1929–1932.
5. (a) Das, B.; Ramu, R.; Reddy, M. R.; Mahender, G. *Synthesis* **2005**, 250–254; (b) Das, B.; Venkateswarlu, K.; Mahender, G.; Mahender, I. *Tetrahedron Lett.* **2005**, *46*, 3041–3044; (c) Das, B.; Ramu, R.; Ravikanth, B.; Reddy, K. R. *Tetrahedron Lett.* **2006**, *47*, 779–782; (d) Das, B.; Thirupathi, P.; Mahender, I.; Reddy, V. S.; Rao, Y. K. *J. Mol. Catal. A: Chem.* **2006**, *247*, 233–239.
6. Hajela, S. P.; Johnson, A. R.; Xu, J.; Sunderland, C. J.; Cohen, S. M.; Caulder, D. L.; Raymond, K. N. *Inorg. Chem.* **2001**, *40*, 3208–3216.
7. (a) Shylesh, A.; Sharma, S.; Mirajkar, S. P.; Sing, A. P. *J. Mol. Catal. A: Chem.* **2004**, *212*, 219–228; (b) Karimi, B.; Khalkhali, M. *J. Mol. Catal. A: Chem.* **2005**, *232*, 113–117.
8. (a) Corma, A. *Chem. Rev.* **1995**, *95*, 559–614; (b) Corma, A.; García, H. *Catal. Today* **1997**, *38*, 257–308.
9. General experimental procedure: To a mixture of an amine (1.1 mmol) and $(Boc)_2O$ (1.0 mmol) in CH_2Cl_2 (5 mL) sulfonic-acid-functionalized silica [prepared[7b] from silica (10 g) and 3-marcaptopropyltrimethoxysilane (5 mmol)] (20 mg) were added. The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion the mixture was filtered. The catalyst was washed with $CHCl_3$ (2×5 mL), EtOH (2×5 mL) and diethyl ether (2×5 mL) and subsequently dried for recyclization purpose. The filtrate was concentrated and the residue was subjected to column chromatography over silica gel using hexane–EtOAc as eluent to obtain a pure Boc protected amine.
The recovered catalyst was utilized consecutively three times for the Boc protection of amine group of 1-phenylethylamine (Table 1, entry b) following the above procedure for 5 min in each case to afford the corresponding *N*-Boc derivative with the yields of 97%, 96%, and 94%.
The spectral (IR, ^{1}H and ^{13}C NMR and MS) and elemental analysis data of some representative products are given below.
Compound **2f**: IR (neat): 3414, 1690, 1364, 1306 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.91 (1H, br s), 3.56 (1H, br s), 3.03 (1H, dd, $J = 12.0$, 4.0 Hz), 2.88–2.74 (2H, m), 2.72–2.60 (2H, m), 2.52 (1H, dd, $J = 12.0$, 4.0 Hz), 1.89–1.62 (5H, m), 1.59–1.41 (11H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.4, 79.2, 51.7, 46.8, 46.0, 31.1, 28.4, 23.9; FABMS: m/z 229 $[M+H]^+$; Anal. Calcd for $C_{12}H_{24}N_2O_2$: C, 63.15; H, 10.52; N, 12.28. Found: C, 62.98; H, 10.45; N, 12.20.

Compound **2h**: IR (neat): 3420, 1684, 1420, 1282 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.46–8.31 (2H, br s), 3.43 (4H, t, $J = 6.0$ Hz), 2.51 (4H, s), 1.52 (4H, t, $J = 6.0$ Hz), 1.42 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.5, 154.4, 79.8, 41.9, 39.0, 34.9, 31.6, 28.1; FABMS: *m/z* 270 $[M+H]^+$; Anal. Calcd for $C_{13}H_{23}N_3O_3$: C, 57.99; H, 8.55; N, 15.61. Found: C, 57.83; H, 8.43; N, 15.69.

Compound **2l**: IR (neat): 3413, 1686, 1412, 1247 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.72 (1H, br s), 7.38–7.15 (5H, m), 6.61 (1H, d, $J = 8.0$ Hz), 4.79 (2H, br s), 2.29 (3H, s), 2.20 (3H, s), 1.51 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.3, 143.6, 136.8, 134.7, 131.5, 129.0, 128.3, 125.3, 124.7, 122.7, 121.4, 115.3, 80.4, 28.3, 17.9, 17.5; FABMS: *m/z* 313 $[M+H]^+$; Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.07; H, 7.69; N, 8.97. Found: C, 73.13; H, 7.52; N, 9.08.

Compound **2m**: IR (neat): 3406, 1688, 1482, 1246 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.92–6.75 (2H, m), 6.63 (1H, t, $J = 8.0$ Hz), 6.57 (1H, d, $J = 8.0$ Hz), 3.92–3.73 (2H, m), 3.59 (1H, br s), 3.31–3.10 (4H, m), 2.02–1.81 (4H, m), 1.53–1.34 (2H, m), 1.42 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.6, 143.5, 142.3, 123.9, 123.7, 119.6, 118.4, 79.0, 76.4, 41.4, 40.6, 39.5, 34.6, 28.2; FABMS: *m/z* 319 $[M+H]^+$; Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.92; H, 8.17; N, 8.80. Found: C, 67.95; H, 8.06; N, 8.64.

Compound **2u**: IR (neat): 3413, 1678, 1500, 1368 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–7.18 (5H, m), 4.71 (1H, t, $J = 7.0$ Hz), 4.48 (1H, m), 3.87 (1H, br s), 3.58 (1H, br s), 1.83–1.72 (2H, m), 1.41 (9H, s), 1.36–1.14 (8H, m), 0.85 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.0, 128.4, 127.4, 125.8, 125.6, 72.7, 49.3, 45.4, 36.0, 31.6, 28.4, 25.4, 22.6, 13.9; FABMS: *m/z* 322 $[M+H]^+$. Anal. Calcd for $C_{19}H_{31}NO_3$: C, 71.03; H, 9.65; N, 4.36. Found: C, 70.93; H, 9.63; N, 4.24.

Compound **2x**: IR (neat): 3432, 1690, 1519, 1364 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.40 (1H, d, $J = 6.0$ Hz), 4.34–4.18 (2H, m), 3.80 (3H, s), 3.01 (1H, br s), 1.49 (9H, s), 1.26 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.0, 156.2, 80.2, 68.0, 58.5, 52.5, 28.2, 19.8; FABMS: *m/z* 234 $[M+H]^+$. Anal. Calcd for $C_{10}H_{19}NO_5$: C, 51.50; H, 8.15; N, 6.01. Found: C, 51.61; H, 8.06; N, 6.12.

10. Liu, Y.-S.; Zhao, C.; Bergbreiter, D. E.; Romo, D. *J. Org. Chem.* **1998**, *63*, 3471–3473.
11. Chankeshwara, S. V.; Chakraborti, A. K. *Tetrahedron Lett.* **2006**, *47*, 1087–1091.