Iodine-Catalyzed Allylic Alkylation of Thiols with Allylic Alcohols

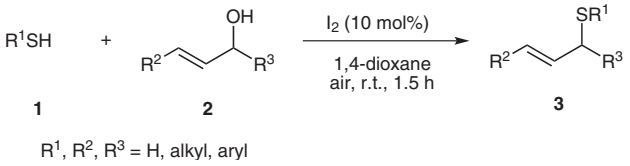
Xiaoxiang Zhang, Weidong Rao, Philip Wai Hong Chan*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore
Fax +65 63166984; E-mail: waihong@ntu.edu.sg

Received 2 July 2008

Abstract: An efficient iodine-catalyzed allylic alkylation of a wide variety of aryl and alkyl thiols with allylic alcohols is reported herein. The reaction is operationally straightforward, tolerant to air and moisture, and proceeds under very mild conditions at room temperature in good to excellent yields (50–92%).

Key words, allylic alcohols, allylic thioethers, alkyl and aryl thiols, carbon–sulfur bond formation, molecular-iodine catalysis



Scheme 1 Iodine-catalyzed allylic alkylation of thiols with allylic alcohols

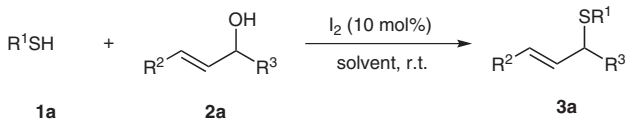
There has been a recent resurgence of interest in Lewis acid catalyzed allylic alkylation reactions that make use of allylic alcohols as the allylating reagent.[1–5] The reactions were reported to be highly atom economical,[6] forming H_2O as the only byproduct, and versatile due to the wide availability of the alcohol substrate or carbonyl precursor. However, in contrast to the increasing number of studies on C–X (X = C, N, O) bond formations using allylic alcohols as the pre-electrophile, a similar approach for the preparation of allylic thioethers has remained sparse.[7] To our knowledge, there are currently only two known examples on C–S bond formation that make use of such starting materials. The first was by Firouzabadi and co-workers who showed the allylic alkylation of thiols with allylic alcohols could be accomplished employing silica-supported $ZrCl_4$ as the catalyst.[2] At about the same time, Sanz and co-workers also described the installing of the allylic thiol moiety through the use of polymer-supported PTSA.[3] We envisaged a different strategy that also relies on the use of allylic alcohols but in combination with molecular iodine catalysis as the basis for developing a metal-catalyst-free and operationally simple version of this useful carbon–sulfur bond-forming reaction that can be accomplished under mild conditions. An inexpensive, commercially available reagent that has a high tolerance to air and moisture, molecular iodine has been shown to be versatile in mediating a wide variety of organic transformations in excellent yields and with high selectivity.[5,8] We recently also demonstrated molecular iodine to be an efficient catalyst for the allylic alkylations of 1,3-dicarbonyl compounds, sulfonamides, and carbamates with allylic alcohols.[5] As part of an ongoing program on carbon–heteroatom bond formations in our group,[5a,9] we report herein the allylic alkylation of a wide variety of aryl and alkyl thiols with allylic alcohols catalyzed by molecular iodine (Scheme 1). The reactions proceed in good to excellent yields (up to 92%), at room temperature, and without the need for inert and moisture-free reaction conditions.

At the outset of this study, we chose the substrates 4-methylbenzenethiol (**1a**) and (*E*)-1,3-di-*p*-tolylprop-2-en-1-ol (**2a**) as the model compounds to establish the reaction conditions (Table 1). This revealed that treatment of a solution of 1,4-dioxane containing four equivalents of **1a** and one equivalent of **2a** in an open round-bottom flask with 10 mol% of iodine at room temperature for 1.5 hours gave the best result, furnishing (*E*)-(1,3-di-*p*-tolylallyl)(*p*-tolyl)sulfane (**3a**) in 84% yield (Table 1, entry 1). The retention of *trans* stereochemistry in the allylated product was confirmed by comparison with ^{1}H NMR literature data of closely related compounds.[10] In addition, no byproducts that could be attributed to oxidation of **1a** could be detected by TLC or ^{1}H NMR analysis of the crude mixtures.

Under similar conditions, an examination of solvent effects revealed slightly lower product yields of 71–80% were obtained for reactions in CH_2Cl_2, toluene, THF, and H_2O (Table 1, entries 4 and 6–8). The only instance when a markedly lower product yield was afforded was with $MeNO_2$ as solvent (Table 1, entry 9). Further inspection of entries 3–5 in Table 1 reveals reaction time and loading of the thiol nucleophile to also have an effect on the outcome of reactions in CH_2Cl_2 as solvent. As previously noted, a product yield of 79% was obtained under these latter conditions (Table 1, entry 3). A product yield of 86% that was comparable to that afforded for the analogous reaction conducted in 1,4-dioxane was only achieved by increasing the reaction time from 1.5 to 14 h (Table 1, entry 4). In contrast, when the reaction was repeated but with a decrease in the loading of **1a** from four to two equivalents, a mixture of side products was afforded that could not be determined by ^{1}H NMR analysis (Table 1, entry 5). As anticipated, no reaction was observed in the absence of the iodine catalyst and both starting materials were recovered in quantitative yields (Table 1, entry 2).

SYNLETT 2008, No. 14, pp 2204–2208
Advanced online publication: 13.08.2008
DOI: 10.1055/s-2008-1078254; Art ID: D24708ST

Table 1 Optimization of the Reaction Conditions[a]



1a **2a** **3a**

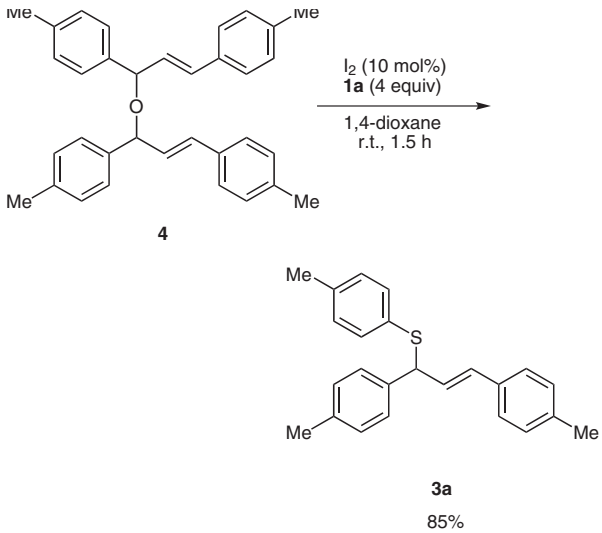
R^1, R^2, R^3 = Tol

Entry	Solvent	Yield (%)[b]
1	1,4-dioxane	84
2[c]	1,4-dioxane	–[d]
3	CH_2Cl_2	79
4[e]	CH_2Cl_2	86
5[f]	CH_2Cl_2	–[g]
6	toluene	80
7	THF	73
8	H_2O	71
9	$MeNO_2$	48

[a] All reactions were performed at r.t. for 1.5 h with an I_2/**1a**/**2a** ratio of 1:40:10.
[b] Isolated yield.
[c] Reaction conducted in the absence of the iodine catalyst.
[d] No reaction after 18 h based on TLC analysis.
[e] Reaction conducted for 14 h.
[f] Reaction conducted with 2 equiv of **1a**.
[g] Unknown mixture of byproducts obtained based on TLC and ^{1}H NMR analysis.

To define the scope of the iodine-catalyzed allylic alkylation reactions, we applied this process to a series of substituted aryl and alkyl thiols **1a–i** and allylic alcohols **2a–j**. As shown in Figure 1 and Table 2, allylic alkylation of a variety of substituted aryl thiols with allylic alcohols bearing electron-withdrawing and electron-donating groups proceeded in good-to-excellent yields. Notably, this included the allylic alkylations of sterically encumbered aryl thiols **1f** and **1g** with **2a**, which gave the corresponding allylic thioethers **3f** and **3g** in good yields (Table 2, entries 5 and 6). The present procedure was also shown to work well for the allylic alkylations of alkyl thiols with **2a** and **2c**, which gave the corresponding adducts **3h–j** in good yields (Table 2, entries 7–9). However, an inspection of entries 12–14 (Table 2) reveals the allylic alkylations of **1a** with either **2d**, **2e**, or **2f**, which contain two slightly different substituted aryl groups, to proceed with poor regioselectivity. In these reactions, the corresponding allylated adducts **3m**, **3n**, and **3o** were furnished as a 1:1 mixture of inseparable regioisomers. On the other hand, under the slightly modified conditions of CH_2Cl_2 instead of 1,4-dioxane as solvent, reaction of **1a** with the conformationally restricted allylic alcohol **2g** was found to be regioselective, giving **3p** as the sole product in good yield (Table 2, entry 15). Applying these latter conditions to the reactions of **1a** with **2h**, which bears both an aryl and alkyl group, also gave **3q** as a single regioisomer (Table 2, entry 16). Similarly, reactions of **1a** with the 2° and 3° terminal allylic alcohols **2i** and **2j** afforded **3s** as a single regioisomer and **3r** as an inseparable mixture of regioisomers in a 10:1 ratio (Table 2, entries 17 and 18). Interestingly, while the reason for the differences in reactivity is currently not clear, the analogous reactions of these latter allylic alcohols in 1,4-dioxane were found to afford a wide variety of side products that could not be separated by flash column chromatography or identified by ^{1}H NMR analysis of the respective crude mixtures.

We tentatively propose that the mechanism of the present procedure proceeds in a manner similar to that for the allylic alkylation of 1,3-dicarbonyl compounds, sulfonamides, and carbamates with allylic alcohols.[5] This involves formation of a putative allylic carbocation species from reaction of the allylic alcohol **2** with HI generated in situ. The regioselectivities obtained in these reactions could be due to subsequent attack at the sterically less hindered carbon of this presumed allylic carbocation intermediate by **1** to give the allylated product **3**. Alternatively, the allylic carbocation species could be attacked by another molecule of **2** to produce a reactive dimer **4** of the type shown in Scheme 2, which reacts further in the presence of **1** to give **3**. To support the possible involvement of such intermediates, we undertook the following experiments. The dimer **4**, obtained following the literature procedure,[5] could be converted into **3a** in 85% yield on treatment with four equivalents of **1a** and 10 mol% of iodine catalyst in 1,4-dioxane for 1.5 hours at room temperature (Scheme 2). In addition, **3a** was furnished in a slightly lower yield of 76% for the analogous reaction of **1a** with **2a** under the same conditions as those described in Table 1 (entry 1) but with NaI (10 mol%) and trifluoroacetic acid (10 mol%) in place of iodine as catalyst.



4 **3a**
85%

Scheme 2 Iodine-catalyzed conversion of the dimer **4** into the allylated aryl thiol **3a**

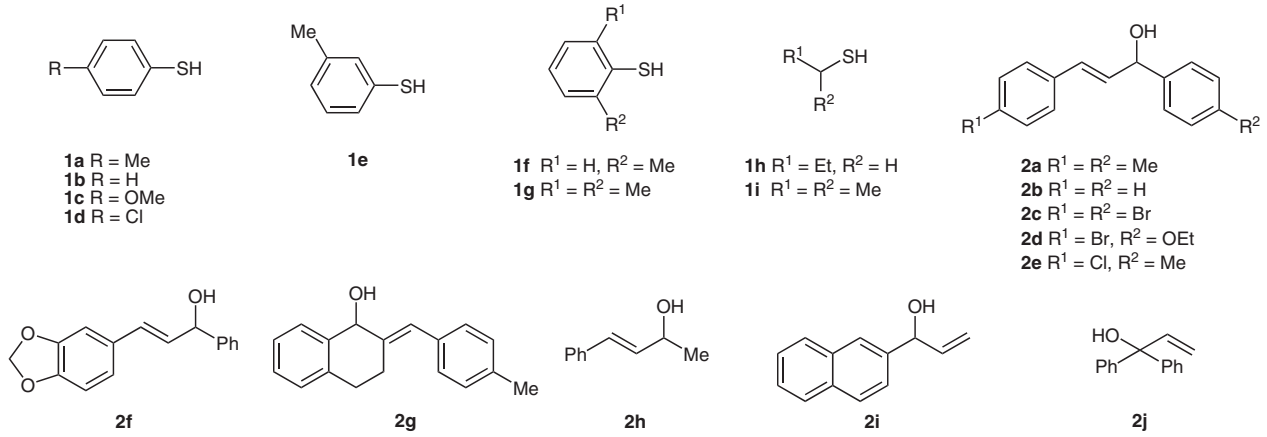
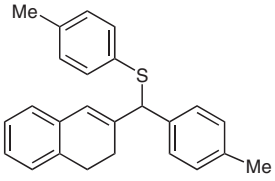
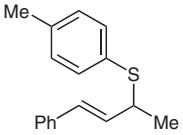
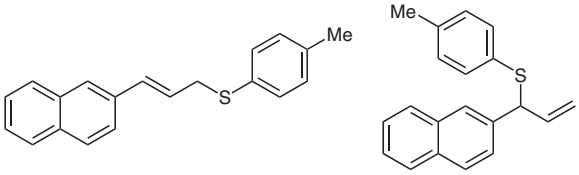
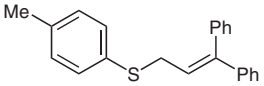


Figure 1

Table 2 Iodine-Catalyzed Allylic Alkylation of Thiols **1a–i** with Allylic Alcohols **2a–j**[a]

Entry	Substrates	Product	Yield (%)[b]
1	**1b** + **2a**	**3b**, R = H	78
2	**1c** + **2a**	**3c**, R = OMe	80[c]
3	**1d** + **2a**	**3d**, R = Cl	66
4	**1e** + **2a**	**3e**	82
5	**1f** + **2a**	**3f**, R^1 = H, R^2 = Me	80
6	**1g** + **2a**	**3g**, R^1 = R^2 = Me	70
7	**1h** + **2a**	**3h**, R^1 = Me, R^2 = H, R^3 = Et	64
8	**1i** + **2a**	**3i**, R^1 = R^2 = R^3 = Me	68
9	**1i** + **2c**	**3j**, R^1 = Br, R^2 = R^3 = Me	66
10	**1a** + **2b**	**3k**, R^1 = R^2 = H	77
11	**1a** + **2c**	**3l**, R^1 = R^2 = Br	90
12	**1a** + **2d**	**3m**, R^1 = Br, R^2 = OEt **3m′**, R^1 = OEt, R^2 = Br	85[d]
13	**1a** + **2e**	**3n**, R^1 = Cl, R^2 = Me **3n′**, R^1 = Me, R^2 = Cl	86[d]
14	**1a** + **2f**	**3o**	65[d]

Table 2 Iodine-Catalyzed Allylic Alkylation of Thiols **1a–i** with Allylic Alcohols **2a–j**[a] (continued)

Entry	Substrates	Product		Yield (%)[b]
15	**1a** + **2g**		**3p**	51
16[e]	**1a** + **2h**		**3q**	92
17[e]	**1a** + **2i**		**3r**	50[f]
18[e]	**1a** + **2j**		**3s**	56

[a] All reactions were performed at r.t. for 1.5 h with an I_2/**1a**/**2a** ratio of 1:40:10.
[b] Isolated yield.
[c] ^{1}H NMR yield.
[d] Isolated as an inseparable mixture of regioisomers in the ratio of 1:1.
[e] Reaction conducted with CH_2Cl_2 as solvent.
[f] Isolated as an inseparable mixture of regioisomers in the ratio of 10:1.

In summary, we have demonstrated a practical and operationally simplistic method for the allylic alkylation of aryl and alkyl thiols with allylic alcohols under atmospheric conditions at room temperature that proceeds in good to excellent yields. The present protocol is applicable to a variety of aryl and alkyl thiols, and allylic alcohols containing electron-withdrawing, electron-donating, and sterically encumbered substrate combinations. Efforts are currently under way to examine the scope and mechanism of this carbon–sulfur bond-formation strategy and will be reported in due course.

General Procedure

To a solution of 1,4-dioxane (2 mL) containing **1** (4 equiv) and **2** (1 equiv) in a round-bottom flask at r.t. was added molecular iodine (10 mol%). The reaction was stirred for 1.5 h, quenched with aq $Na_2S_2O_3$ and extracted with EtOAc (10 mL). The organic layer was washed with brine, dried over anhyd $MgSO_4$, concentrated, and purified by silica gel column chromatography (*n*-hexane–EtOAc, 400:1) to give the product **3**.

Representative Data for 3a

Yellow solid; mp 90–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02–7.30 (m, 12 H), 6.39 (dd, 1 H, *J* = 15.6, 8.5 Hz), 6.21 (d, 1 H, *J* = 15.6 Hz), 4.82 (d, 1 H, *J* = 8.4 Hz), 2.32 (s, 3 H), 2.30 (s, 3 H), 2.28 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6, 137.5, 137.3, 137.1, 134.1, 133.6, 131.4, 131.1, 129.5, 129.3, 129.2, 128.6, 127.8, 126.4, 56.9, 21.2, 21.2. IR (neat): ν = 3020, 2920, 1643, 1510, 1491, 1018, 961, 800 cm^{-1}. GC-MS (EI): *m/z* = 344 [M$^+$]. HRMS (EI): *m/z* calcd for $C_{24}H_{24}S$: 344.1593; found: 344.1453.

Acknowledgment

This work was supported by a College of Science Start-Up Grant from Nanyang Technological University.

References

(1) Recent reviews: (a) Muzart, J. *Tetrahedron* **2005**, *61*, 4179. (b) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, 2647. Selected examples: (c) Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* **2008**, *49*, 858. (d) Aponick, A.; Li, C.-Y.; Biannic, B. *Org. Lett.* **2008**, *10*, 669. (e) Qin, H.; Yamagiwa, F.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 409. (f) Shu, X.-Z.; Liu, X.-Y.; Xiao, H.-Q.; Ji, K.-G.; Guo, L.-N.; Liang, Y.-M. *Adv. Synth. Catal.* **2008**, *350*, 243. (g) Huang, W.; Wang, J. L.; Zhou, X. G. *Tetrahedron Lett.* **2007**, *48*, 3969. (h) Guo, S. H.; Song, F. J.; Liu, Y. H. *Synlett* **2007**, 964. (i) Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 793. (j) Mertins, K.; Lovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2006**, *348*, 691. (k) Liu, J.; Muth, E.; Florke, U.; Henkel, G.; Merz, K.; Sauvageau, J.; Schwake, E.; Dyker, G. *Adv. Synth. Catal.* **2006**, *348*, 456. (l) Ohri, R. V.; Radosevich, A. T.; Toste, F. D. *Org. Lett.* **2005**, *7*, 2501. (m) Shue, Y.-J.; Yang, S.-C.; Lai, H.-C. *Tetrahedron Lett.* **2003**, *44*, 1481. (n) Kimura, M.; Futamata, M.; Shibata, K.; Tamaru, Y. *Chem. Commun.* **2003**, 234. (o) Kimura, M.; Horino, Y.; Mukai, R.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10401. (p) Kimura, M.; Tomizawa, T.; Horino, Y.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 3627. (q) Yang, S.-C.; Hung, C.-W. *J. Org. Chem.* **1999**, *64*, 5000.

(2) Firouzabadi, H.; Iranpoor, N.; Jafarpour, M. *Tetrahedron Lett.* **2006**, *47*, 93.

(3) Sanz, R.; Martínez, A.; Miguel, D. *Adv. Synth. Catal.* **2006**, *348*, 1841.
(4) Rao, W.; Chan, P. W. H. *Org. Biomol. Chem.* **2008**, *6*, 2426.
(5) (a) Wu, W.; Rao, W.; Er, Y. Q.; Loh, K. J.; Poh, C. Y.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 2620; corrigendum: *Tetrahedron Lett*. **2008**, *49*, 4981. (b) Rao, W.; Tay, A. H. L.; Goh, P. J.; Choy, J. M. L.; Ke, J. K.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 122; corrigendum: *Tetrahedron Lett.* **2008**, *49*, 5115.
(6) (a) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (b) Trost, B. M. *Science* **1991**, *254*, 1471.
(7) For a review on allylic alkylations of thiols with allylating reagents other than allylic alcohols, see: (a) Selected examples: Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205. (b) Yatsumonji, Y.; Ishida, Y.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2007**, *9*, 4603. (c) Cao, H.; Xiao, W.-J.; Alper, H. *Adv. Synth. Catal.* **2006**, *348*, 1807. (d) Salvatore, R. N.; Smith, R. A.; Nischwitz, A. K.; Gavin, T. *Tetrahedron Lett.* **2005**, *46*, 8931. (e) Ranu, B. C.; Jana, R. *Adv. Synth. Catal.* **2005**, *347*, 1811. (f) Gais, H.-J.; Jagusch, T.; Spalthoff, N.; Gerhards, F.; Frank, M.; Raabe, G. *Chem. Eur. J.* **2003**, *9*, 4202. (g) Kondo, T.; Morisaki, Y.; Uenoyama, S.-y.; Wada, K.; Mitsudo, T.-a. *J. Am. Chem. Soc.* **1999**, *121*, 8657. (h) Zhan, Z.; Lu, G.; Zhang, Y. *J. Chem. Res., Synop.* **1999**, 280. (i) Bremberg, U.; Lutsenko, S.; Kaiser, N.-F.; Larhed, M.; Hallberg, A.; Moberg, C. *Synthesis* **2000**, 1004.
(8) Recent review: (a) Selected examples: Togo, H.; Iida, S. *Synlett* **2006**, 2159. (b) Downer-Riley, N. K.; Jackson, Y. A. *Tetrahedron* **2007**, *63*, 10276. (c) Srihari, P.; Bhunia, D. C.; Yadav, J. S. *Tetrahedron Lett.* **2007**, *48*, 8120. (d) Yadav, J. S.; Reddy, B. V. S.; Reddy, U. V. S. *Tetrahedron Lett.* **2007**, *48*, 5243. (e) Liu, Z.; Liu, L.; Shafiq, Z.; Wu, Y.-C.; Wang, D.; Chen, Y.-J. *Tetrahedron Lett.* **2007**, *48*, 3963. (f) Das, B.; Chowdhury, N.; Damodar, K. *Tetrahedron Lett.* **2007**, *48*, 2867. (g) Varala, R.; Nuvula, S.; Adapa, S. R. *J. Org. Chem.* **2006**, *71*, 8283. (h) Lin, C.; Fang, H.; Tu, Z.; Liu, J. *J. Org. Chem.* **2006**, *71*, 6588. (i) Gao, S.; Tzeng, T.; Sastry, M. N. V. *Tetrahedron Lett.* **2006**, *47*, 1889. (j) Yadav, J. S.; Reddy, B. V. S.; Shubashree, S.; Sadashiv, K. *Tetrahedron Lett.* **2004**, *45*, 2951. (k) Wang, S.-Y.; Ji, S.-J.; Loh, T.-P. *Synlett* **2003**, 2377. (l) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S. *Synlett* **2003**, 1722. (m) Yadav, J. S.; Reddy, B. V. S.; Rao, C. V. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1401. (n) Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Tetrahedron Lett.* **2002**, *43*, 3653. (o) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* **2001**, *66*, 7527. (p) Yadav, J. S.; Reddy, B. V. S.; Rao, C. V. *Synthesis* **2000**, 1532.
(9) (a) Buranaprasertsuk, P.; Chang, J. W. W.; Chavasiri, W.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 2023. (b) Chang, J. W. W.; Chee, S.; Mak, S.; Buranaprasertsuk, P.; Chavasiri, W.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 2018. (c) Chang, J. W. W.; Chan, P. W. H. *Angew. Chem. Int. Ed.* **2008**, *47*, 1138. (d) Rao, W.; Chan, P. W. H. *Tetrahedron Lett.* **2007**, *48*, 3789. (e) Chang, J. W. W.; Xu, X.; Chan, P. W. H. *Tetrahedron Lett.* **2007**, *48*, 245.
(10) Marr, F.; Fröhlich, R.; Hoppe, D. *Tetrahedron: Asymmetry* **2002**, *13*, 2587.