Synthetic and Mechanistic Aspects on the Competition between C–H Insertion and Hydride Transfer in Copper-Mediated Transformations of α-Diazo-β-Keto Sulfones

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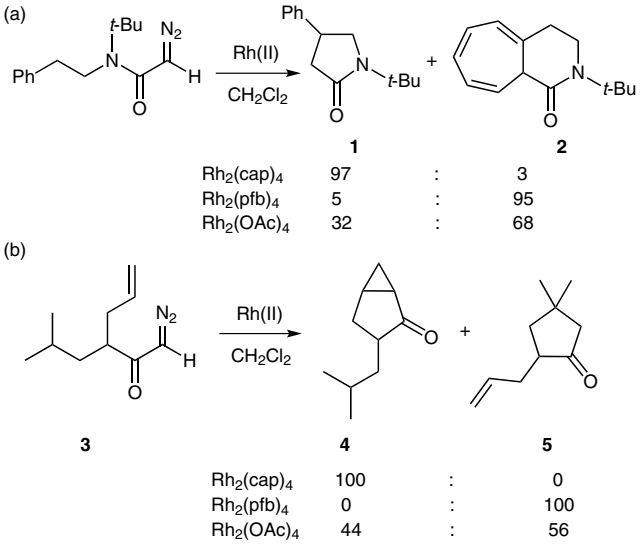
Abstract: Competition between C–H insertion and hydride transfer is reported for the copper-catalysed reactions of a range of phenyl-substituted α-diazo-β-keto sulfones. Control of chemoselectivity is possible by alteration of the electronic properties of the diazo substrate. The production of enantioenriched cyclopentanones (up to 89% ee), formed via C–H insertion, and alkylidene tetrahydrofurans (up to 43% ee), produced via hydride transfer, is described. The isolation of products derived from hydride transfer provides mechanistic insight into the copper-mediated C–H insertion of α-diazocarbonyl compounds.

Key words: diazocarbonyl, copper catalysis, bis(oxazoline), C–H insertion, hydride transfer

Metal carbenes derived from α-diazocarbonyl compounds are highly reactive species and may undergo a broad spectrum of chemical transformations including X–H insertion, cyclopropanation, ylide formation, dimerisation, aromatic addition, and Wolff rearrangement.[1] Of these processes, intramolecular C–H insertion reactions of α-diazocarbonyls have been particularly well-studied, offering excellent regioselectivity in the formation of carbocyclic products, typically cyclopentanones.[2] Control of chemoselectivity is also possible for such transformations by careful choice of catalyst and diazo substrate.[3–5] Padwa and coworkers reported that choice of rhodium(II) ligand has a profound influence on product distribution for reactions in which competition between C–H insertion and aromatic addition or cyclopropanation can occur.[6,7] C–H insertion to provide γ-lactam **1** was found to be dominant for reactions catalysed by $Rh_2(cap)_4$, while near exclusive formation of the competing aromatic addition product **2** was observed for reactions employing $Rh_2(pfb)_4$ (Scheme 1, a). Similar ligand effects were recorded for decomposition of diazo **3** in which C–H insertion and cyclopropanation are competitive. Thus, catalysis by $Rh_2(cap)_4$ provided cyclopropane **4** as the sole product while exclusive formation of **5** via C–H insertion was observed for reaction in the presence of $Rh_2(pfb)_4$ (Scheme 1, b). In both cases, use of $Rh_2(OAc)_4$ resulted in the formation of a mixture of C–H insertion and aromatic addition or cyclopropanation products.



Scheme 1 (a) C–H insertion vs. aromatic addition; (b) C–H insertion vs. cyclopropanation.[6,7]

In diazo systems where competing aromatic addition or cyclopropanation is not possible, the efficiency of C–H insertion reactions may still be affected by the potential formation of side products arising from O–H insertion, dimerisation, diazo reduction, or hydride transfer. Limited literature reports exist documenting hydride transfer as a competitive transformation to C–H insertion.[8–13] In these earlier studies, transfer of the hydride was promoted by the presence of an adjacent heteroatom (O, N), forming an intermediate oxonium or iminium ion which undergoes nucleophilic attack by the oxygen of the rhodium enolate to provide the hydride transfer product (see Scheme 2 for a representative example).[9] The hydride transfer products are typically obtained as minor reaction products, however, in certain instances this pathway has been found to dominate over C–H insertion.[8,10] The alternative hydride transfer reaction known as the 1,2-hydride shift (or β-hydride elimination) has been more commonly reported in the literature and is often observed as a competitive side

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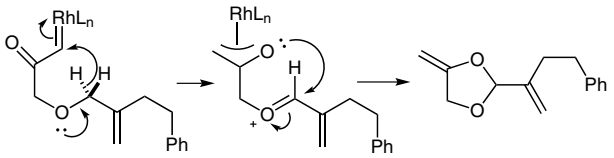
reaction in transformations of α-diazocarbonyls possessing β-hydrogen atoms.[1,14–16]



Scheme 2 Oxygen-promoted hydride transfer

We have previously reported that asymmetric copper-catalysed reactions of α-diazo-β-keto phenylsulfones lead to highly enantioenriched cyclopentanone products via intramolecular C–H insertion.[17,18] We report herein that competing hydride transfer may also occur, resulting in the formation of 2-alkylidene tetrahydrofuran products. The influence of substrate modification adjacent to the target C–H insertion site on both chemoselectivity and enantioselectivity is also explored.

Reactions of α-diazo-β-keto sulfones examined in this study were conducted in refluxing dichloromethane in the presence of a copper catalyst generated in situ from 5 mol% $CuCl_2$, 6 mol% bis(oxazoline) ligand **6**–**10** (Figure 1), and 6 mol% NaBARF {BARF = tetrakis[3,5-bis-(trifluoromethyl)phenyl]borate}. The diazo compounds **11a**–**c** were synthesised from the corresponding 4-substituted phenyl(butanoates) using standard procedures.[19–21]

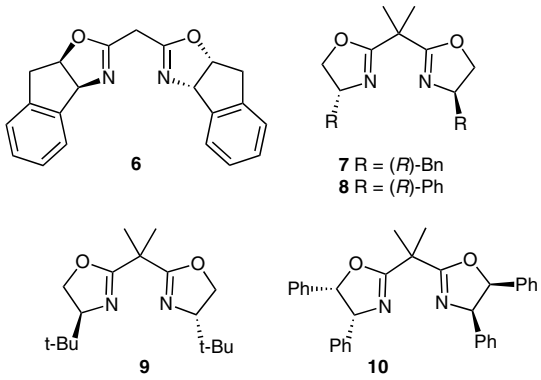
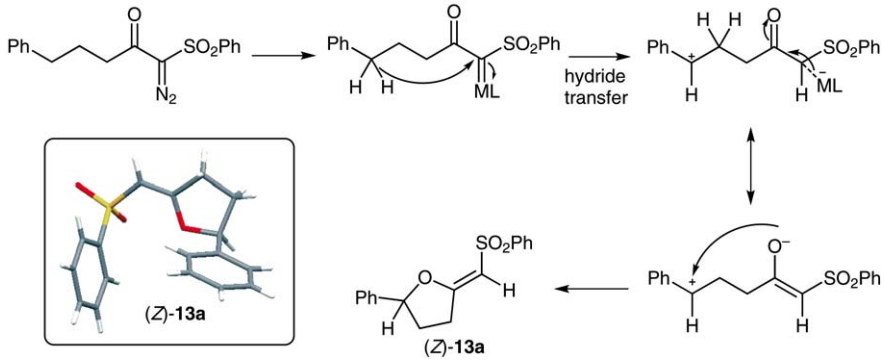


Figure 1 Bis(oxazoline) ligands **6**–**10**

The copper-catalysed reactions of α-diazo-β-keto sulfone **11a** were initially explored (Table 1, entries 1–5). Intramolecular C–H insertion was found to be the dominant reaction pathway for this substrate, providing cyclopentanone **12a** in high enantioselectivity (up to 89% ee) and good yield following chromatographic purification.[17] Interestingly, in addition to the C–H insertion product **12a**, a minor amount of the alkylidene tetrahydrofuran **13a** was also recovered from this reaction. Tetrahydrofuran **13a** was observed in varying amounts (up to 21% relative to cyclopentanone formation) in the ^{1}H NMR spectra of the crude reaction mixtures for the reactions of **11a** (Table 1, entries 1–5), and was isolated as the *Z*-isomer exclusively following column chromatography, as confirmed by X-ray crystallography[22] (Scheme 3).

The formation of **13a** was rationalised to be due to competing hydride transfer to generate an intermediate possessing a copper enolate and benzylic carbocation. This intermediate then undergoes cyclisation via enolate trapping to provide the substituted tetrahydrofuran **13a** (Scheme 3). Evidently, stabilisation of the carbocation at the benzylic position is sufficient to enable hydride transfer, which is more commonly seen when activated by oxygen or nitrogen.[8–10] Supporting this is the observation that hydride transfer to the carbenoid carbon was not observed for reactions with other α-diazo-β-keto sulfones in which the C–H insertion site is adjacent to an alkyl or benzyl substituent, examined as part of an earlier study,[17] presumably because the carbocationic intermediate formed via the hydride transfer pathway is sufficiently stable to form only when it is benzylic but not with the other diazo substrates. Significantly, formation of **13a** was only observed for copper-catalysed reactions of diazo **11a** and not for reactions employing $Rh_2(OAc)_4$.

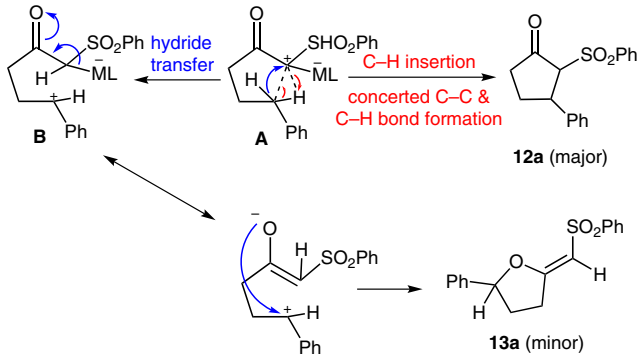
Literature research revealed the description of the synthesis of **13a** and a number of related tetrahydrofuran products via base-mediated cyclisation of hydroxyl propargylic sulfones.[23] Using this methodology, (*E*)-*exo*-alkylidene tetrahydrofurans were isolated as the sole product in high yield (80–85%).[23] Similar (*Z*)-2-alkylidene tetrahydrofuran products have also been obtained from mercury(II)- and palladium(II)-mediated cyclisation of acetylenic alcohols and used as the key intermediates in



Scheme 3 Proposed hydride-transfer mechanism

prostacyclin PGI_2 synthesis.[24,25] To the best of our knowledge, this is the first reported example of the synthesis of alkylidene tetrahydrofurans from diazocarbonyl precursors and as such offers an additional route to substituted tetrahydrofurans with high *Z* selectivity. The production of 2,3,5-trisubstituted tetrahydrofurans by rhodium-mediated cyclisation of α-diazo esters has been previously described by Taber,[26,27] however, this earlier work involved insertion at electronically activated sites adjacent to oxygen rather than a hydride-transfer mechanism as described in this work.

The formation of products derived from hydrogen transfer in competition with the C–H insertion pathway provides interesting mechanistic insight into the nature of the C–H insertion process. Thus, in intermediate **A** (Scheme 4) concerted C–C and C–H bond formation with concomitant cleavage of the γ-C–H bond is envisaged to lead to insertion product **12a**, in line with mechanistic proposals by Taber[28] and Doyle.[29] Davies has described the alternative formation of C–H insertion products through asynchronous bond formation and breaking in the same transition state.[30] The observation of hydride transfer product **13a** in the copper-mediated reaction of **11a** is consistent with the asynchronous insertion pathway, leading at the extreme to hydride transfer, in a process which is competitive with C–H insertion. It is possible therefore, for the C–H insertion process to 'tip over' to hydride transfer for copper-catalysed reactions in which the intermediate carbocation **B** is sufficiently stable.



Scheme 4 C–H insertion vs. hydride transfer

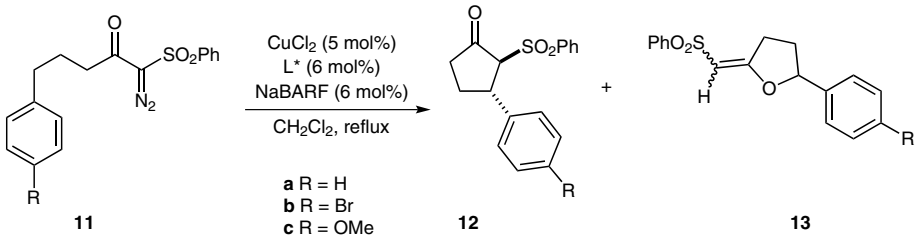
In order to investigate the effects on chemo- and enantioselectivity of modification of electronic properties at the benzylic position of **11a**, two novel α-diazo-β-keto sulfone substrates were prepared: 1-diazo-5-(4-bromophenyl)-1-phenylsulfonylpentan-2-one (**11b**) and 1-diazo-5-(4-methoxyphenyl)-1-phenylsulfonylpentan-2-one (**11c**), featuring electron-withdrawing and electron-donating groups, respectively, at the *para* position of the phenyl ring. In terms of asymmetric induction, with only one exception noted (Table 1, entry 5 vs. 15), a slight decrease in enantioselectivity was recorded for reactions of the bromo- and methoxy-substituted α-diazo-β-keto sulfones **11b** and **11c** (Table 1, entries 6–14), respectively, relative to cyclisations with the corresponding unsubstituted diazo compound **11a** (Table 1, entries 1–4). This outcome is in agreement with previous reports by Hashimoto and coworkers who also observed reduced levels of asymmetric induction for rhodium(II)-catalysed C–H insertion reactions of α-diazo-β-keto esters featuring electron-withdrawing (Br, 70% ee) and electron-donating (OMe, 57% ee) groups on the *para* position of the phenyl ring, relative to reactions with the unsubstituted diazo substrate (76% ee).[32]

While the introduction of an electron-withdrawing halide substituent (R = Br) onto the phenyl ring of the diazo framework was found to result in a largely similar product distribution relative to reactions with **11a** (Table 1, entries 1–5 vs. 6–10), a dramatic shift in chemoselectivity towards intramolecular tetrahydrofuran formation was observed for reactions of the *p*-methoxyphenyl-substituted diazo sulfone **11c**. Thus, for each of the copper-catalysed reactions of **11c** examined (Table 1, entries 11–15) hydride transfer to provide **13c** was observed to dominate over C–H insertion forming cyclopentanone **12c**. This outcome is in agreement with the mechanism earlier proposed for the formation of **13a** (Scheme 3); the increase in electron density contributed by the *p*-methoxy substituent favours carbocation formation through complete hydride transfer relative to the more concerted C–H insertion pathway. Subsequent intramolecular attack of the carbocationic centre by the enolic oxygen leads to the formation of the novel tetrahydrofuran **13c**.

In contrast to reactions of **11a** and **11b** in which tetrahydrofurans **13a** and **13b**, respectively, were obtained exclusively as the *Z*-isomer, a mixture of (*Z*)-**13c** and (*E*)-**13c** was observed to form for reactions of the *p*-methoxy-substituted diazo **11c** (Table 2, entries 1–5). Interestingly, a modest level of asymmetric induction was recorded by HPLC analysis for the formation of (*Z*)-**13c** and (*E*)-**13c** in each of the copper-catalysed reactions of **11c** examined, with the benzyl-substituted bis(oxazoline) **7** affording the highest enantioselectivity for both isomers (Table 2, entry 2). Importantly, this observation provides direct evidence of involvement of the copper–bis(oxazoline) complex in the C–O bond formation leading to the tetrahydrofuran products produced via the hydride-transfer pathway. Given the synthetic value of the substituted tetrahydrofuran framework, work is currently under way to explore a broader range of substrates and catalysts for the production of novel enantioenriched alkylidene tetrahydrofuran products. In addition, the investigation of additional competing side reactions, believed to originate from O–H insertion, is also ongoing.

In conclusion, isolation of alkylidene tetrahydrofuran products **13a–c** in the copper-catalysed reactions of α-diazo-β-keto sulfones **11a–c** provides evidence of asynchronous bond forming/breaking in the copper-mediated C–H insertion process. In systems such as **11** where a relatively stable carbocation can be formed, the asynchronous C–H insertion 'tips over' into hydride transfer as a competitive pathway. The observed increase in the hydride transfer product upon introduction of the *p*-methoxy

Table 1 Copper–Bis(oxazoline)-Catalysed Reactions of α-Diazo-β-Keto Sulfones **11a–c**



11 **12** **13**

Entry	Diazo	R	L*	Time (h)	**12**/**13**[a]	Yield (%) **12**[b]	ee (%) of **12**[c,d]
1	**11a**	H	**6**	2	1:0.17	87	89 (2*R*,3*R*)
2	**11a**	H	**7**	2	1:0.06	58	81 (2*S*,3*S*)
3	**11a**	H	**8**	2	1:0.15	69	57 (2*S*,3*S*)
4	**11a**	H	**9**[e]	19	1:0.27	55	64 (2*R*,3*R*)
5	**11a**	H	**10**	2	1:0.04	54	52 (2*S*,3*S*)
6	**11b**	Br	**6**	6	1:0.04	60	87 (2*R*,3*R*)
7	**11b**	Br	**7**	5	1:0.09	86	67 (2*S*,3*S*)
8	**11b**	Br	**8**	3	1:0.01	69	39 (2*S*,3*S*)
9	**11b**	Br	**9**	4	1:0.18	73	59 (2*R*,3*R*)
10	**11b**	Br	**10**	2	1:0.02	65	49 (2*S*,3*S*)
11	**11c**	OMe	**6**	2	1:8.80[f]	19[g]	88 (2*R*,3*R*)
12	**11c**	OMe	**7**	2	1:8.69[f]	20[g]	71 (2*S*,3*S*)
13	**11c**	OMe	**8**	2	1:3.71[f]	25[g]	49 (2*S*,3*S*)
14	**11c**	OMe	**9**	2	1:8.11[f]	10[g]	58 (2*R*,3*R*)
15	**11c**	OMe	**10**	2	1:4.98[f]	26[g]	59 (2*S*,3*S*)

[a] Ratio of C–H insertion (**12**)/THF formation (**13**) based on integration of the C(2)H doublet of **12** and the δ_H = 5.59–5.64 ppm singlet of **13**, respectively, in the ^{1}H NMR spectra of the crude reaction mixtures.
[b] Yield of *trans*-cyclopentanone **12** after column chromatography.
[c] Enantiopurity of **12** as determined by chiral stationary-phase HPLC (see Supporting Information for details).
[d] Absolute stereochemistry of **12a** determined by comparison to previously reported data.31 Absolute stereochemistry of **12b** and **12c** assigned by analogy to **12a**.
[e] Reaction catalysed by CuCl.
[f] Mixture of (*Z*)-**13c** and (*E*)-**13c** observed in the ^{1}H NMR spectrum of the crude reaction mixture.
[g] Isolated product contains minor amount (<10%) of (*E*)-**13c**.

Table 2 Copper–Bis(oxazoline)-Catalysed Reactions of **11c**

Entry	L*	(*Z*)-**13c**/(*E*)-**13c**[a]	ee of (*Z*)-**13c** (%)[b]	ee of (*E*)-**13c** (%)[b]
1	**6**	1:0.01	8	25
2	**7**	1:0.02	32	43
3	**8**	1:0.45	3	6
4	**9**	1:0.01	9	8
5	**10**	1:0.02	2	30

[a] As determined from the ^{1}H NMR spectrum of the crude reaction mixture of **11c**.
[b] As determined by chiral stationary-phase HPLC analysis (see Supporting Information for details).

substituent supports this mechanistic interpretation. The observation of enantioselectivity in the formation of tetrahydrofuran **13c** is particularly interesting as it indicates that the copper–bis(oxazoline) complex remains involved during the final cyclisation step.

General Procedure for Reactions of α-Diazo-β-Keto Sulfones 11a–c

The $CuCl_2$–L*–(NaBARF) catalyst was generated in situ from a mixture of $CuCl_2$ (5 mol%), bis(oxazoline) ligand (6 mol%), and NaBARF (6 mol%) in CH_2Cl_2 (15 mL). This catalytic mixture was stirred under nitrogen at 40 °C for 1.5 h. α-Diazo-β-keto sulfone **11a–c** (150 mg, 1 equiv) was then added dropwise in CH_2Cl_2 (15 mL) over 0.5 h to the refluxing solution. The progress of the reaction was monitored by IR spectroscopy, where reaction completion was indicated by the disappearance of the characteristic diazo peak at 2112–2122 cm^{-1}. Upon reaction completion, evaporation of the

reaction solvent at reduced pressure gave the crude product mixture. Purification by flash chromatography on silica gel, employing EtOAc–hexane as eluent, gave the cyclopentanone (**12a**–**c**, less polar fraction) and tetrahydrofuran (**13a**–**c**, more polar fraction) products.

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Primary Data for this article are available online at http://www.thieme-connect.com/ejournals/toc/synlett and can be cited using the following DOI: 10.4125/pd0054th.

References and Notes

(1) Doyle, M.; McKervey, M.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, **1998**.
(2) Slattery, C. N.; Ford, A.; Maguire, A. R. *Tetrahedron* **2010**, *66*, 6681.
(3) Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1797.
(4) Doyle, M. P.; Zhang, Y. *ARKIVOC* **2010**, *(viii)*, 10.
(5) Doyle, M. P.; Ene, D. G.; Forbes, D. C.; Pillow, T. H. *Chem.Commun.* **1999**, 1691.
(6) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874.
(7) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669.
(8) Wardrop, D. J.; Forslund, R. E. *Tetrahedron Lett.* **2002**, *43*, 737.
(9) Clark, J. S.; Dossetter, A. G.; Wong, Y.-S.; Townsend, R. J.; Whittingham, W. G.; Russell, C. A. *J. Org. Chem.* **2004**, *69*, 3886.
(10) Chelucci, G.; Culeddu, N.; Saba, A.; Valenti, R. *Tetrahedron Lett.* **1999**, *40*, 8269.
(11) Mander, L. N.; Owen, D. J. *Tetrahedron Lett.* **1996**, *37*, 723.
(12) White, J. D.; Hrnciar, P. *J. Org. Chem.* **1999**, *64*, 7271.
(13) Doyle, M. P.; Dyatkin, A. B.; Autry, C. L. *J. Chem. Soc, Perkin Trans. 1* **1995**, 619.
(14) Taber, D. F.; Hoerrner, R. S. *J. Org. Chem.* **1992**, *57*, 441.
(15) Taber, D. F.; Hennessy, M. J.; Louey, J. P. *J. Org. Chem.* **1992**, *57*, 436.
(16) Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. *J. Org. Chem.* **1996**, *61*, 2908.
(17) Slattery, C. N.; Maguire, A. R. *Org. Biomol. Chem.* **2011**, *9*, 667.
(18) Slattery, C. N.; Clarke, L.-A.; O'Neill, S.; Ring, A.; Ford, A.; Maguire, A. R. *Synlett* **2012**, 765.
(19) Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 2860.
(20) Koskinen, A. M. P.; Munoz, L. *J. Chem. Soc., Chem. Commun.* **1990**, 652.
(21) Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Roos, G. H. P. *J. Chem. Soc., Chem. Commun.* **1990**, 361.
(22) (Z)-13a: CCDC number 969646.
(23) Dai, W.-M.; Lee, M. Y. H. *Tetrahedron* **1998**, *54*, 12497.
(24) Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 5842.
(25) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718.
(26) Taber, D. F.; Song, Y. *Tetrahedron Lett.* **1995**, *36*, 2587.
(27) Taber, D. F.; Song, Y. *J. Org. Chem.* **1996**, *61*, 6706.
(28) Taber, D. F.; Ruckle, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 7686.
(29) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.
(30) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063.
(31) Maguire, A. R.; Kelleher, L. L.; Ferguson, G. *J. Mol. Catal. B: Enzym.* **1996**, *1*, 115.
(32) Hashimoto, S.-i.; Wantanabe, N.; Ikegami, S. *Synlett* **1994**, 353.

