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Me_2Zn-Mediated Addition of Acetylenes to Aldehydes and Ketones

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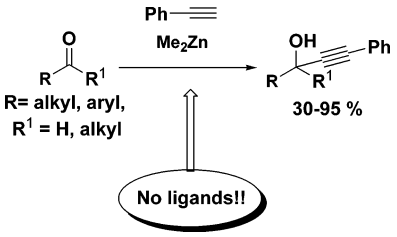


Contrary to expectations, commercially available 2 M Me_2Zn in toluene is able to promote the addition of phenylacetylene to aldehydes and ketones. This reactivity is determined by a new, unprecedented mechanism, which involves activation of the zinc reagent via coordination with carbonyl substrates that behave "ligand like". Broad scope, high tolerance to functional groups, and a simple procedure make this new method highly interesting for the synthetic chemist.

The addition of acetylides to carbonyl substrates gives access to propargylic alcohols, which are valuable building blocks and useful intermediates for the synthesis of complex natural products.[1] Moreover, the addition of alkynes to ketones is a practical strategy to create tertiary alcohols with a new stereogenic center under mild conditions (Figure 1).[2]

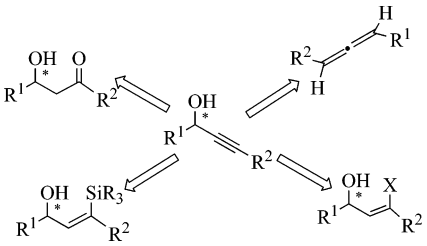
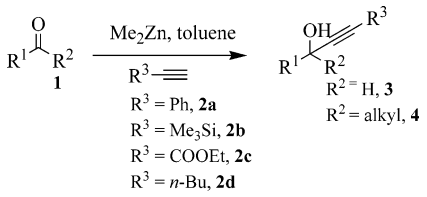


FIGURE 1. Acetylenic alcohols as precursors of valuable compounds.

SCHEME 1. Addition of Acetylenes 2a−d to Carbonyl Compounds Promoted by Me_2Zn



Traditionally, propargylic alcohols are synthesized by addition of a metal acetylide to aldehydes or ketones with a stoichiometric or catalytic amount of a base.[3] However, the reported methods possess some drawbacks and hence a general, highly tolerable and simple procedure for the selective alkynylation of enolizable aldehydes and ketones, is desirable. We found that mixtures of Me_2Zn and acetylenes add to aldehydes and ketones affording the desired products in good to excellent yields (Scheme 1).

Thus, when the commercially available 2 M solution of Me_2Zn in toluene was mixed with of phenylacetylene (1.5 equiv each) at room temperature and reacted with benzaldehyde (1 equiv) at 0 °C, the addition product **3a** was isolated in 45% yield after 24 h (entry 1, Table 1). Performing the reaction at room temperature gave **3a** in 89% yield (entry 2, Table 1). Consequently, this protocol was used for all further reactions.

A substrate screening revealed that other acetylenes were also applicable although they proved to be less reactive than phenylacetylene (Table 1, entries 3−5). Various aldehydes reacted smoothly giving the corresponding propargylic alcohols in good to high yields at room temperature. Table 2 shows that aromatic and aliphatic ketones reacted as well.

When a Me_2Zn/phenylacetylene mixture was used (1.5 equiv each with respect to the carbonyl compound), only aliphatic ketones furnished addition products in high yields, while aromatic ketones were rather unreactive substrates. The introduction of an electron-withdrawing group enhanced the reactivity of the latter substrates. The use of 3 equiv of the Me_2Zn/phenylacetylene mixture increased the yield in the addition to acetophenone and chloroacetophenone (Table 2, entries 2 and 3), but the

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(1) (a) Marshall, J. A.; Bourbeau, M. P. *Org. Lett.* **2003**, *5*, 3197. (b) Cuzzupe, A. N.; Hutton, C., A.; Lilly, M. J.; Mann, R. K.; McRae, K. J.; Zammit, S. C.; Rizzacasa, M. A. *J. Org. Chem.* **2001**, *66*, 2382. (c) Pilli, R. A.; Victor, M. M.; de Meijere, A. *J. Org. Chem.* **2000**, *65*, 5910. (d) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.

(2) For reviews, see: (a) Pu, L. *Tetrahedron* **2003**, *59*, 9873. (b) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N, *Eur. J. Org. Chem.* **2004**, 4095. For recent papers about allkynylation, see: (a) Liu, L.; Wang, R.; Kang, Y.-F.; Chen, C.; Xu, Z.-Q.; Zhou, Y.-F.; Ni, M.; Cai, H.-Q.; Gong, M.-Z. *J. Org. Chem.* **2005**, *70*, 1084, and ref. therein. (b): Xu, Z.; Wang, R.; Xu, Y.; Da, C.-s.; Yan, W.-j.; Chen, C. *Angew. Chem., Int. Ed*. **2003**, *42*, 5747. (c) Zhou, Y.-f.; Wang, R.; Xu, Z.-q; Yan, W.-j.; Liu, L.; Gao, Y.-f.; Da, C.-s. *Tetrahedron*: *Asymmetry* **2004**, *15*, 589. (d) Li, M.; Zhu, X.-Z.; Yuan, K.; Cao, B.-X.; Hou, X.-L. *Tetrahedron*: *Asymmetry* **2004**, *15*, 219.

(3) (a) Anad, N. K.; Carreira, E. M. *J. Am. Chem.* Soc. **2001**, *123*, 9687. (b) Li, X.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636. (c) Cozzi, P. G. *Angew. Chem., Int. Ed*. **2003**, *42*, 2895. (d) Lu, G.; Li, X.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Angew. Chem.*, *Int. Ed*. **2003**, *42*, 5057. (e) Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* **2003**, *44*, 6767.(f) Liu, L.; Kang, Y.-f.; Wang, R.; Zhou, Y.-f.; Chen, C.; Ni, M.; Gong, M.-z *Tetrahedron*: *Asymmetry* **2004**, *15*, 3757.

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TABLE 1. Alkynylation of Aldehydes Using Me_2Zn as Promoter

entry[a]	aldehyde	R^3	product	yield[b] (%)
1	benzaldehyde	Ph	**3a**	45[c]
2	benzaldehyde	Ph	**3a**	30[d]
3	benzaldehyde	Ph	**3a**	78
4	benzaldehyde	TMS	**3b**	48
5	benzaldehyde	*n*Bu	**3c**	80
6	benzaldehyde	CO_2Et	**3d**	30
7	4′-chlorobenzaldehyde	Ph	**3e**	83
8	4′-bromobenzaldehyde	Ph	**3f**	70
9	3′-fluorobenzaldehyde	Ph	**3g**	92
10	3′-bromobenzaldehyde	Ph	**3h**	86
11	4′-trifluoromethylbenzaldehyde	Ph	**3i**	90
12	4′-nitrobenzaldehyde	Ph	**3j**	79
13	4′-methylbenzaldehyde	Ph	**3k**	68
14	1-naphthylaldehyde	Ph	**3l**	86
15	*trans*-cinnamaldehyde	Ph	**3m**	70
16	octanal	Ph	**3n**	91
17	cyclohexylaldehyde	Ph	**3o**	89

[a] All reactions were carried out in anhydrous toluene at room temperature, employing 1.5 equiv of a Me_2Zn/phenylacetylene mixture. [b] Yield after flash chromatography. [c] The reaction was performed at 0 °C. [d] The reaction was performed using a 1.1 M toluene solution of Et_2Zn.

TABLE 2. Alkynylation of Ketones with Phenyl Acetylene Using Me_2Zn as Promoter

entry[a]	ketone	product	yield[b] (%)
1	acetophenone	**4a**	14
2	acetophenone	**4a**	36[c]
3	4′-chloroacetophenone	**4b**	40[c]
4	4′-fluoroacetophenone	**4c**	31
5	4′-bromoacetophenone	**4d**	44
6	3′-trifuoromethylacetophenone	**4e**	94
7	3′-cyanoacetophenone	**4f**	41
8	4-phenylbut-3-en-2-one	**4g**	66
9	oxo-phenylacetic acid methylester	**4h**	80
10	2-pentanone	**4i**	85
11	1-hexen-5-one	**4j**	86
12	4-methyl-2-pentanone	**4k**	59
13	3-methyl-2-butanone	**4l**	77
14	4-phenyl-2-butanone	**4m**	75
15	methylcyclopropyl ketone	**4n**	40
16	2,2-dimethyl-1-cyclopentanone	**4o**	55
17	cyclohexanone	**4p**	80

[a] All reactions were carried out in anhydrous toluene at room temperature, employing 1.5 equiv of Me_2Zn/phenylacetylene mixture. [b] Yield after flash chromatography. [c] The reactions were performed using 3 equiv of Me_2Zn/phenylacetylene mixture.

results were still not satisfactory. As demonstrated with various substrates, the procedure is highly tolerant to a broad range of functional groups.

These results are intriguing also from a theoretical point of view, because they open the reaction mechanism to questions. It was previously reported that the addition of Me_2Zn to a solution of phenylacetylene did not show any change in the ^1H and ^{13}C spectra, indicating that no reaction took place between the two compounds.[4] More recent studies revealed that the formation of MeZnCCPh is promoted by the adventitious presence of moisture, although the reaction is incomplete.[5] Apparently, in both studies it was necessary to activate the Me_2Zn in order to make it a more reactive base toward acetylenes. It is well-known that amino alcohols activate alkyl-,[6] aryl-,[7] and alkynylzinc[3] derivatives toward the attack of carbonyl substrates. This activation is crucial to make reaction with the carbonyl compound possible.[8] Our results indicate that the carbonyl oxygen might behave in a "ligand like" fashion promoting the reaction of Me_2Zn with an alkyne by coordination of its lone pairs to the Me_2Zn. To elucidate the nature of the deprotonation and of the subsequent addition step, we have undertaken a DFT study of a small model system, consisting of Me_2Zn, acetone, and acetylene.

All calculations were performed at the B3LYP/LACVP* level (Hay−Wadt double-ζ valence + ECP for Zn,[9] 6-31G* for other atoms) in Jaguar 4.2 from Schrödinger, Inc.[10] Stationary points were verified by analytic normal-mode analysis. All reaction barriers were calculated from the lowest preceding point on the potential energy surface, always a precomplex of all reactants. Initially, we investigated the deprotonation of acetylene by Me_2Zn (Figure 1).

In the absence of activation, the barrier is calculated to be 155 kJ/mol, too high to be expected to show significant reactivity at room temperature. Coordinating a molecule of acetone to the Zn atom lowers the barrier to 138 kJ/mol, a value more in line with the observed reactivity. Adding harmonic corrections to these figures (ZPE or $\Delta\Delta G$) changes the absolute numbers, but does not affect the trend. Looking at the structures, we can see that acetone coordination induces a bending in the linear and nonpolar Me_2Zn molecule, increasing the basicity of the methyl group.

We also investigated the subsequent addition of MeZnCCH to a ketone. In the simplest possible mechanism, starting from the favored adduct in the preceding deprotonation step, the acetylene is simply transferred to the carbonyl carbon in a four-membered monocyclic TS (Figure 2).

This reaction has an activation barrier of only 83 kJ/mol, indicating that in the presence of ketone, the alkynylzinc species is reacted as soon as it is formed.

In consideration of the accepted mechanism for ligand-assisted addition of Et_2Zn to aldehydes,[6b] we also investigated the possibility that a zinc ketone complex acts as a bifunctional catalyst, bringing together an additional 1 equiv of ketone and zinc reagent in a bicyclic TS (Figure 3). This reaction has an even lower barrier, only 66 kJ/mol, but at the cost of a higher molecularity and thus an unknown entropic cost. The relative importance of the two pathways will be determined by the propensity of the zinc species to form higher order complexes, which in turn will be strongly affected by the solvent. However,

(4) Li reported that a mixture of phenylacetylene and Me_2Zn was rather unreactive towards aldehydes: Li, Z.; Upadhyay, V.; DeCamp, A. E.; DiMichele L.; Reider, P. J. *Synthesis* **1999**, 1453.

(5) Pinet, S.; Pandya, S. U.; Chavant, P. Y.; Ayling, A.; Vallee, Y. *Org. Lett.* **2002**, *4*, 1463.

(6) (a) Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc*. **2003**, *125*, 5130, and references therein. (b) Yamakawa, M.; Noyori, R. J. *J. Am. Chem. Soc.* **1995**, *117*, 6327. For reviews, see: (c) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (d) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.

(7) (a) Rudolph, J.; Rasmussen, T.; Bolm C.; Norrby, P.-O. *Angew. Chem., Int. Ed*. **2003**, *42*, 3002. (b) Rudolph, J.; Bolm C.; Norrby, P.-O. *J. Am. Chem. Soc*. **2005**, *127*, 1548 and refs therein.

(8) (a) Frantz D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (b) Dahmen, S. *Org. Lett.* **2004**, *6*, 2113.

(9) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82,* 270.

(10) http://www.schrodinger.com.

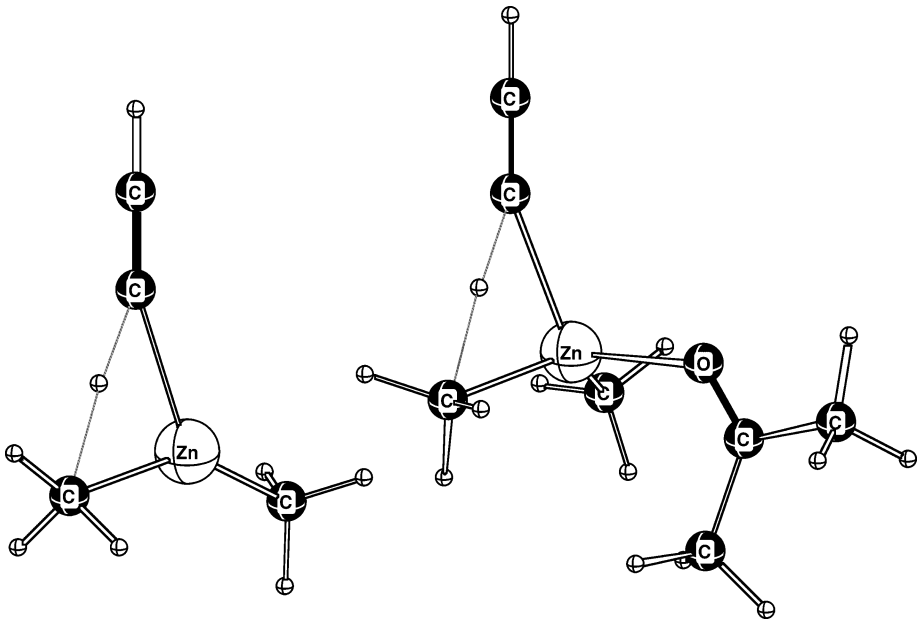

FIGURE 2. TSs for the deprotonation of acetylene.

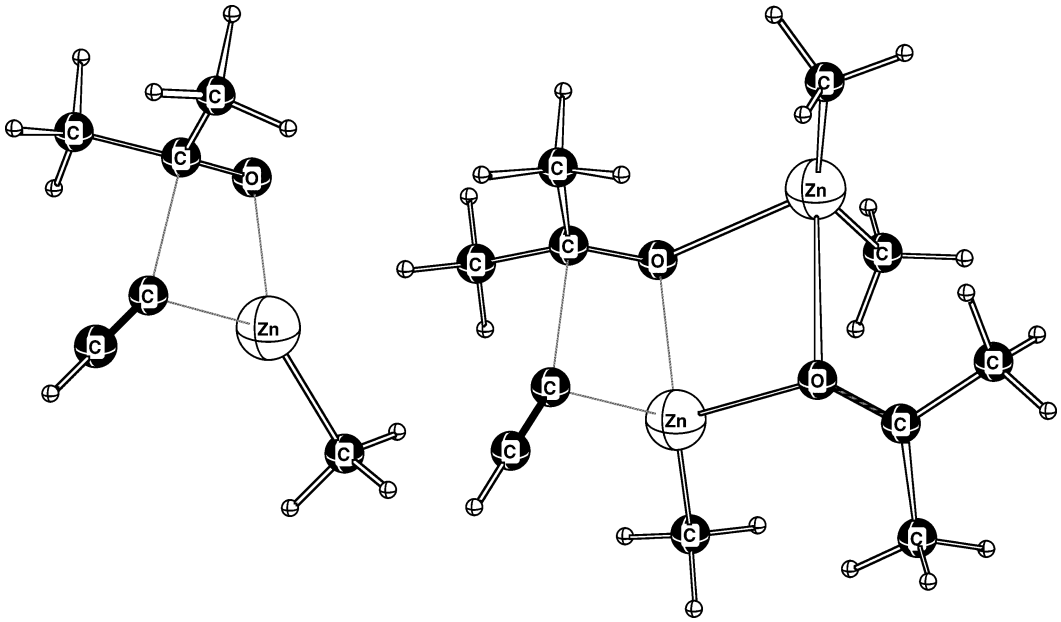

FIGURE 3. Transition states found for the addition of acetylene to acetone.

the relatively low barrier to reaction indicates that the alkynyl zinc, already complexed to the ketone, may react through the monocyclic TS before encountering other activating species.

In conclusion, we have described the unexpected and facile addition of phenylacetylene to aldehydes and ketones promoted by Me_2Zn without the employment of specific ligands. This reaction has an interesting potential for the direct synthesis of tertiary propargylic alcohols. Furthermore, our study demonstrates that the substrate itself can become a ligand and catalyze a background reaction, which might result in lowering the enantioselectivity in a desired asymmetric transformation.

Experimental Section

1,3-Diphenylprop-2-yn-1-ol (**3a**),[11] 1-phenyl-3-trimethylsilylprop-2-yn-1-ol (**3b**),[12] 1-phenylhept-2-yn-1-ol (**3c**),[13] 4-hydroxy-4-phenylethyl-2-butynoate (**3d**),[14] 1-(4-chlorophenyl)-3-phenylprop-2-yn-1-ol (**3e**),[11] 1-(4-bromophenyl)-3-phenylpropyn-1-ol (**3f**),[15] 1-(3-fluorophenyl)-3-phenylprop-2-yn-1-ol (**3g**),[16] 1-(3-bromophenyl)-3-phenylprop-2-yn-1-ol (**3h**),[17] 3-phenyl-1-(4-trifluoromethylphenyl)prop-2-yn-1-ol (**3i**),[18] 1-(4-nitrophenyl)-3-phenylprop-2-yn-1-ol (**3j**),[3b] 3-phenyl-1-*p*-tolylprop-2-yn-1-o (**3k**),[19] 1-naphthyl-3-phenylprop-2-yn-1-ol (**3l**),[19] 1,5-diphenylpent-1-en-4-yn-3-ol (**3m**),[20] 1-phenyldec-1-yn-3-ol (**3n**),[21] 1-cyclohexyl-3-phenylprop-2-yn-1-ol (**3o**),[21] 2,4-diphenylbut-3-yn-2-ol (**4a**),[3d] 2-(4-chlorophe-

(11) Li, Z.-B.; Pu, L. *Org. Lett.* **2004**, *6*, 1065.
(12) Nakamura, S.; Kusuda, S.; Kawamura, K.; Toru, T. *J. Org. Chem.* **2002**, *67*, 640.
(13) Braga, A. L.; Appelt, H. R.; Silveira, C. C.; Wessjohann, L. A.; Schneider, P. H. *Tetrahedron* **2002**, *58*, 10413.
(14) Krause, N.; Seebach, D. *Chem. Ber.* **1987**, *120*, 1845.
(15) Liu, L.; Pu, L. *Tetrahedron* **2004**, *60*, 7427.
(16) Kamble, R. M.; Singh, V. K. *Tetrahedron Lett.* **2003**, *44*, 5347.
(17) Xu, Z.; Chen, C.; Xu, J.; Miao, M.; Yan, W.; Wang, R. *Org. Lett.* **2004**, *6*, 1193.

nyl)-4-phenylbut-3-yn-2-ol (**4b**),[22] 2-(4-fluorophenyl)-4-phenylbut-3-yn-2-ol (**4c**),[3c] 2-(4-bromophenyl)-4-phenylbut-3-yn-2-ol (**4d**),[3c] 2-(3-trifluoromethylphenyl)-4-phenylbut-3-yn-1-ol (**4e**),[3c] 3-methyl-1,5-diphenylpent-1-en-4-yn-3-ol (**4g**),[23] 2-hydroxy-2,4-diphenylethyl-but-3-ynoate (**4h**),[24] 3methyl-1-phenylhex-1-yn-3-ol (**4i**),[25] 3,5-dimethyl-1-phenylhex-1-yn-3-ol (**4k**),[26] 3,4-dimethyl-1-phenylpent-1-yn-3-ol (**4l**),[27] 3-methyl-1,5-diphenylpent-1-yn-3-ol (**4m**),[3c] 2-cyclopropyl-4-phenylbut-3-yn-2-ol (**4n**),[3c] 2,2-dimethyl-1-phenylethynylcyclopentanol (**4o**),[3c] and 1-phenylethynyl-1-cyclohexanol (**4p**)[27] are known compounds.

Typical Procedure for the Alkynylation of Carbonyl Compounds. In an oven-dried flask connected to a nitrogen/vacuum line was placed phenylacetylene (1.6 mmol) followed by the slow addition of Me_2Zn 2 M solution in toluene (1.5 mmol, 0.75 mL). The resulting solution was stirred at room temperature for 30 min. Then, the aldehyde or ketone (1 mmol) was added dropwise to the reaction mixture. The resulting solution was stirred at room temperature for 24 h, and then the reaction mixture was diluted with diethyl ether (5 mL) and quenched with water (10 mL). The mixture was stirred for 10 min and then filtered over Celite. The aqueous phase was separated and extracted with diethyl ether (2 × 5 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure to give a crude oil which was purified by flash chromatography (cyclohexane/diethyl ether 8:2−9:1 or cyclohexane/acetone 8:1−9:1 as eluant).

4-(1-Hydroxy-1-methyl-3-phenylprop-2-yl-benzonitrile) (4f). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.87 (s, 3H); 7.37−7.34 (m, 3H); 7.53−7.47 (m, 3H); 7.64 (m, 1H); 7.98 (m, 1H); 8.04 (t, 1H, J = 1.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 33.6; 69.7; 85.7; 91.1; 112.4; 118.8; 121.9; 128.4; 128.9; 129.2; 129.6; 131.3; 131.7; 147.2; 176.4. Anal. Calcd: C, 88.13; H, 8.05; N, 5.71. Found: C, 88,06; H, 8.18; N, 5.75.

3-Methyl-1-phenylhept-6-en-1-yn-3-ol (4j). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.64 (s, 3H); 1.88−1.97 (m, 3H); 2.35−2.47 (m, 2H); 5.03−5.18 (m, 2H); 5.89−6.00 (m, 1H); 7.22−7.30 (m, 3H); 7.36−7.39 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 29.3; 30.0; 42.7; 68.5; 83.7; 92.5; 114.9; 122.7; 128.2; 131.6; 138.4; 140.6. Analysis calcd: C, 83.96; H, 8.05. Found: C, 84,00; H, 8.01.

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Supporting Information Available: Copies of ^{1}H NMR for compounds **3a**−**o** and **4a**−**e**,**g**−**i**,**k**−**o** and energies and Cartesian coordinates, TS energies (Hartree), zero potential energy (kJ/mol), and lowest frequencies (cm^{-1}) for reactants and complexes determined at the B3LYP/LACVP* level of theory. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Praveen Rao, P. N.; Uddin, J. Md.; Knaus, E. E. *J. Med. Chem.* **2004**, *47*, 3972.
(19) Liu, Q.-Z.; Xie, N.-S.; Luo, Z.-B.; Cui, X.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *J. Org. Chem*. **2003**, *68*, 7921.
(20) Kang, Y.-F.; Liu, L.; Wang, R.; Yan, W.-J.; Zhou, Y.-F. *Tetrahedron: Asymmetry* **2004**, *15*, 3155.
(21) Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143.
(22) Saito, B.; Katsuki, T. *Synlett* **2004**, 1557.
(23) Zhou, Y.; Wang, R.; Xu, Z.; Yan, W.; Liu, L.; Kang, Y.; Han, Z. *Org. Lett.* **2004**, *6*, 4147.
(24) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451.
(25) Miyamoto, H.; Yasaka, S.; Tanaka, K. *Bull. Chem. Soc. Jpn*. **2001**, *74*, 185.
(26) Riddell, F. G.; Bremner, M.; Strange, J. H. *Magn. Reson. Chem.* **1994**, *32*, 118.
(27) Ishikawa, T.; Mizuta, T.; Hagiwara, K.; Aikawa, T.; Kudo, T.; Saito, S. *J. Org. Chem.* **2003**, *68*, 3702.