ORGANIC LETTERS

2008
Vol. 10, No. 14
2939−2942

Diastereoselective Cobalt-Catalyzed Alkylative Aldol Cyclizations Using Trialkylaluminum Reagents

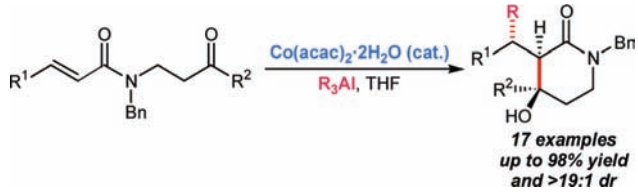
Mairi E. Rudkin,[†] Pekka M. Joensuu,[†] William S. MacLachlan,[‡] and Hon Wai Lam*,[†]

School of Chemistry, University of Edinburgh, The King's Buildings, West Mains Road, Edinburgh EH9 3JJ, U.K., and Neurosciences CEDD, GlaxoSmithKline Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, U.K.

h.lam@ed.ac.uk

Received April 17, 2008

ABSTRACT



Co(acac)$_2$·2H$_2$O serves as an effective precatalyst for alkylative aldol cyclizations of α,β-unsaturated amides with ketones using trialkylaluminum reagents. These reactions provide β-hydroxylactams containing three contiguous stereocenters with high levels of diastereoselection.

Transition-metal-catalyzed domino reactions initiated by conjugate additions are a powerful set of transformations in organic synthesis.[1] These reactions potentially allow rapid increases in complexity in a single step with high levels of stereocontrol. A well-known subset of these transformations are alkylative aldol reactions, involving the catalytic conjugate addition of an organometallic reagent to an α,β-unsaturated carbonyl compound, followed by trapping of the resultant metalloenolate with an aldehyde or ketone. Although there are numerous examples of intermolecular catalytic alkylative aldol reactions,[2] these have until recently been largely restricted to conjugate additions to enones, with subsequent aldol reaction to an aldehyde.[2a–h] The use of non-enone substrates[2i–k,3] and/or ketone electrophiles[2k,3] has now been reported by a number of research groups.

Intramolecular variants of these reactions represent efficient methods to access highly functionalized cyclic products, and the groups of Krische[4] and Miyaura[5] have described important developments in this area. These studies

[†] University of Edinburgh.
[‡] GlaxoSmithKline.

(1) For recent reviews encompassing this topic, see: (a) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217–224. (b) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354–366.

(2) For representative examples, see: (a) Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Tetrahedron Lett.* **1996**, *37*, 5141–5144. (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620–2623. (c) Keller, E.; Maurer, J.; Naasz, R.; Schader, T.; Meetsma, A.; Feringa, B. L. *Tetrahedron: Asymmetry* **1998**, *9*, 2409–2413. (d) Mandoli, A.; Arnold, L. A.; de Vries, A. H. M.; Salvadori, P.; Feringa, B. L. *Tetrahedron: Asymmetry* **2001**, *12*, 1929–1937. (e) Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841–5842. (f) Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2002**, *67*, 7244–7254. (g) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 10984–10985. (h) Nicolaou, K. C.; Tang, W.; Dagneau, P.; Faraoni, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 3874–3879. (i) Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5306–5310. (j) Howell, G. P.; Fletcher, S. P.; Geurts, K.; ter Horst, B.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 14977–14985. (k) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 7439–7443.

(3) For a novel conjugate addition−aldol strategy that obviates the requirement for preformed organometallics, see: Subbaraj, K.; Montgomery, J. *J. Am. Chem. Soc.* **2003**, *125*, 11210–11211.

(4) (a) Cauble, D. F.; Gipson, J. D.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 1110–1111. (b) Bocknack, B. M.; Wang, L.-C.; Krische, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5421–5424. (c) Agapiou, K.; Cauble, D. F.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4528–4529.

(5) Nishikata, T.; Kobayashi, Y.; Kobayshi, K.; Yamamoto, Y.; Miyaura, N. *Synlett* **2007**, 3055–3057.

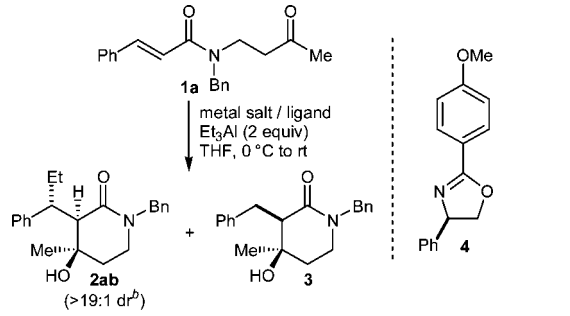
10.1021/ol800883b CCC: $40.75
Published on Web 06/13/2008

again utilize enones as substrates and either dialkylzinc or organoboron reagents as the organometallic, resulting in carbocyclic products.[4,5] Expansion of the scope of these reactions to encompass other conjugate acceptors and organometallic reagents to result in a correspondingly broader range of products, including valuable heterocyclic structures, is a desirable objective. Herein, we report highly diastereoselective cobalt-catalyzed alkylative aldol cyclizations that result in the formation of β-hydroxylactams containing three contiguous stereogenic centers, using trialkylaluminums as the organometallic reagents.

During our recent studies of cobalt-catalyzed reductive aldol cyclizations, it was found that certain substrates containing a β-unsubstituted α,β-unsaturated amide as the conjugate acceptor furnished small quantities of alkylative aldol products when triethylaluminum was used in place of diethylzinc as the stoichiometric reductant.[6a] In addition, during further studies of our nickel-catalyzed reductive aldol cyclizations,[7] we observed that with substrate **1a**, the use of Et_3Al provided small quantities of the alkylative aldol product **2ab** as a single diastereoisomer,[8] in addition to the reductive aldol product **3** (Table 1, entry 1).[9] Collectively, these results were of interest not only because of the highly diastereoselective formation of **2ab** but also because, to our knowledge, *there have been no prior reports of conjugate addition of trialkylaluminum reagents to* α,β*-unsaturated amides*.[10,11] Intrigued by these observations, we embarked upon a study to identify conditions that would favor the formation of **2ab** over **3**. The presence of bidentate (entry 2) or monodentate (entry 3) phosphine ligands still provided **3** as the major product, along with traces of unidentified side-products. The use of nitrogen ligand **4**[12] (entry 4) offered no improvement, and our attention then returned to cobalt-based precatalysts. Although the combination of $CoCl_2$ and Cy_2PPh[6] was found to increase the proportion of the desired product **2ab** (entry 5), we were gratified to observe that $Co(acac)_2{\cdot}2H_2O$ along with oxazoline **4** provided **2ab** as the sole product (entry 6). The same result was obtained in the absence of ligand **4** (entry 7), and therefore, these optimized conditions were adopted for a study of the scope and limitation of the process (Table 2).

Using Et_3Al, substrates containing a range of aromatic (Table 2, entries 2, 6, 9−10, 13, and 15−17) and heteroaromatic (entries 11 and 12) substituents at the β-carbon of the α,β-unsaturated amide were found to undergo alkylative aldol cyclization. A study of different substituents at the *para*-position of the aromatic ring revealed that electron-donating groups favored the reaction (entries 6 and 9) compared with an electron-withdrawing chlorine atom (entry 10). However, substrate **1g** containing an *o*-methoxyphenyl substituent provided the desired product **2g** in 21% yield, along with the reductive aldol product (28% yield) and recovered starting material (16% yield) (entry 13). The higher trialkylaluminum reagents *n*-Pr_3Al and *n*-Hex_3Al were accommodated (entries 3, 4 and 7, 8), but yields were lower using Me_3Al (entries 1 and 5). Replacement of the methyl ketone with an ethyl ketone was also tolerated (entries 15 and 16). In most of the

Table 1. Survey of Reaction Conditions for Cyclization of **1a**[a]



entry	metal salt (10 mol %)	ligand (10 mol %)	**2a/3**[c]
1	$Ni(acac)_2$		10:90
2	$Ni(acac)_2$	*rac*-BINAP	8:92[d]
3	$(PPh_3)_2NiBr_2$		<5:95[d]
4	$Ni(acac)_2$	**4**	5:95[e]
5	$CoCl_2$	Cy_2PPh	25:75
6	$Co(acac)_2{\cdot}2H_2O$	**4**	>95:5[e]
7	$Co(acac)_2{\cdot}2H_2O$	−	>95:5

[a] All reactions proceeded to >95% conversion. [b] dr = (major isomer): Σ(other isomers). [c] Determined by ^1H NMR analysis of the unpurified reaction mixture. [d] Small quantities of unidentified side-products were observed. [e] No enantioselectivity was observed in the reaction. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, acac = acetonylacetonate.

(6) (a) Lam, H. W.; Joensuu, P. M.; Murray, G. J.; Fordyce, E. A. F.; Prieto, O.; Luebbers, T. *Org. Lett.* **2006**, *8*, 3729–3732. For an intermoelcular variant, see: (b) Lumby, R. J.; Joensuu, P. M.; Lam, H. W. *Org. Lett.* **2007**, *9*, 4367–4370.

(7) Joensuu, P. M.; Murray, G. J.; Fordyce, E. A. F.; Luebbers, T.; Lam, H. W. *J. Am. Chem. Soc.* **2008**, *130*, 7328–7338.

(8) The relative stereochemistries of **2ab** and **2i** (see Table 2) were determined by X-ray crystallography. The stereochemistries of the remaining products obtained in Table 2 were assigned by analogy. See the Supporting Information for further details.

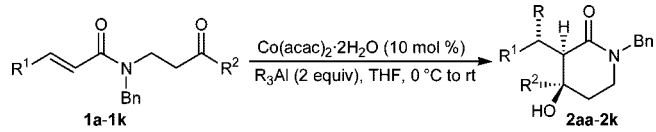
(9) Certain substrates also provided varying degrees of alkylative aldol cyclization using $Ni(acac)_2/Et_2Zn$; see ref 7.

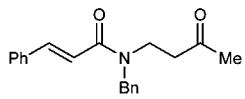
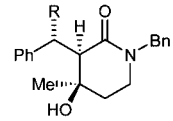
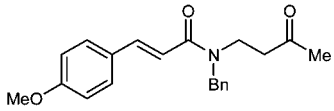
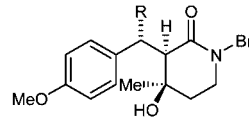
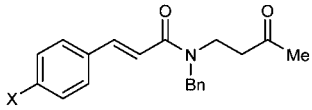
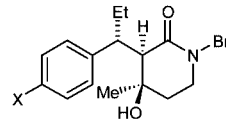
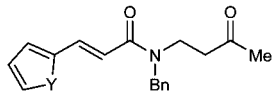
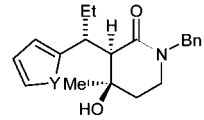
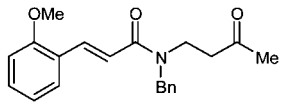
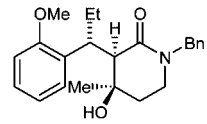
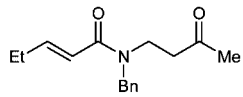
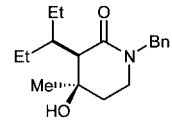
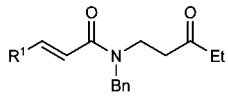
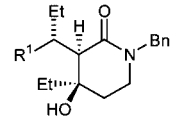
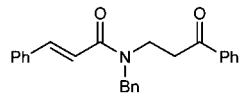
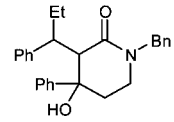
(10) For nickel-catalyzed conjugate addition of trialkylaluminum reagents to enones, see: (a) Jeffery, E. A.; Meisters, A.; Mole, T. *J. Organomet. Chem.* **1974**, *74*, 365–371. (b) Bagnell, L.; Jeffery, E. A.; Meisters, A.; Mole, T. *Aust. J. Chem.* **1975**, *28*, 801–815. (c) Ashby, E. C.; Heinsohn, G. *J. Org. Chem.* **1974**, *39*, 3297–3299.

(11) For copper-catalyzed conjugate addition of trialkylaluminum reagents to enones or enals, see: (a) Westermann, J.; Nickisch, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1368–1370. (b) Kabbara, J.; Flemming, S.; Nickisch, K.; Neh, H.; Westermann, J. *Tetrahedron* **1995**, *51*, 743–754. For selected examples of asymmetric variants, see: (c) Takemoto, Y.; Kuraoka, S.; Hamaue, N.; Iwata, C. *Tetrahedron: Asymmetry* **1996**, *7*, 993–996. (d) Bennett, S. M. W.; Brown, S. M.; Cunningham, A.; Dennis, M. R.; Muxworthy, J. P.; Oakley, M. A.; Woodward, S. *Tetrahedron* **2000**, *56*, 2847–2855. (e) Liang, L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2002**, *13*, 1393–1396. (f) Su, L.; Li, X.; Chan, W. L.; Jia, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 1865–1869. (g) Alexakis, A.; Albrow, V.; Biswas, V.; d'Augustin, M.; Prieto, O.; Woodward, S. *Chem. Commun.* **2005**, 2843–2845. (h) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376–1378. (i) Fuchs, N.; d'Augustin, M.; Humam, M.; Alexakis, A.; Taras, R.; Gladiali, S. *Tetrahedron: Asymmetry* **2005**, *16*, 3143–3146. (j) Li, K.; Alexakis, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7600–7603. (k) Vuagnoux-d'Augustin, M.; Alexakis, A. *Tetrahedron Lett.* **2007**, *48*, 7408–7412. For copper-catalyzed conjugate addition of Me_3Al to nitroalkenes, see: (l) Polet, D.; Alexakis, A. *Tetrahedron Lett.* **2005**, *46*, 1529–1532.

(12) Oxazoline ligands similar to **4** have been successfully applied in enantioselective [2 + 2 + 2] cycloadditions using $Ni(acac)_2$ as a precatalyst in the presence of Me_3Al. See: Ikeda, S.; Kondo, H.; Arii, T.; Odashima, K. *Chem. Commun.* **2002**, 2422–2423.

Table 2. Cobalt-Catalyzed Alkylative Aldol Cyclizations



entry	substrate		R	product		dr[a,b]	yield (%)[c]
1		**1a**	Me		**2aa**	>19:1	43
2			Et		**2ab**	>19:1	98
3			*n*-Pr		**2ac**	>19:1	58
4			*n*-Hex		**2ad**	>19:1	75
5		**1b**	Me		**2ba**	>19:1	48
6			Et		**2bb**	>19:1	91
7			*n*-Pr		**2bc**	>19:1	62
8			*n*-Hex		**2bd**	>19:1	61
9		X = Me **1c**	Et		**2c**	>19:1	71
10		X = Cl **1d**	Et		**2d**	>19:1	48
11		Y = O **1e**	Et		**2e**	>19:1	76
12		Y= S **1f**	Et		**2f**	>19:1	85
13		**1g**	Et		**2g**	>19:1	21[d,e]
14		**1h**	Et		**2h**	>19:1	35[f]
15		R^1 = Ph **1i**	Et		**2i**	>19:1	60
16		R^1 = PMP **1j**	Et		**2j**	>19:1	70
17		**1k**	Et		**2ka** **2kb**	1:1	52[g,h]

[a] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [b] dr = (major isomer):Σ(other isomers). [c] Isolated yield. [d] The reductive aldol product **5** (see the Supporting Information for structure) was obtained in 28% yield. [e] Unreacted starting material (16%) was recovered. [f] Unreacted starting material (35%) was recovered. [g] Combined yield of both isolated diastereomers **2ka** (27%) and **2kb** (25%). The relative stereochemistries of **2ka** and **2kb** could not be established. [h] The reductive aldol product **6** (see the Supporting Information for structure) was obtained in 26% yield.

aforementioned examples, the reactions proceeded with uniformly high diastereoselectivities.[8] However, a pendant phenyl ketone was found to have a deleterious effect on this selectivity, providing **2k** as a 1:1 diastereomeric mixture, in addition to the reductive aldol product (entry 17). Precursor **1h**, containing a β-alkyl substituent at the α,β-unsaturated amide, proved to be a less reactive substrate (entry 14).

We suggest that these reactions most likely proceed via the intervention of π-allylcobalt species. The generation of π-allylmetal complexes by Lewis acid promoted oxidative addition of low-valent transition metals to α,β-unsaturated carbonyl compounds is well documented.[13,14] Significantly, during a study of Pd-catalyzed conjugate addition reactions,

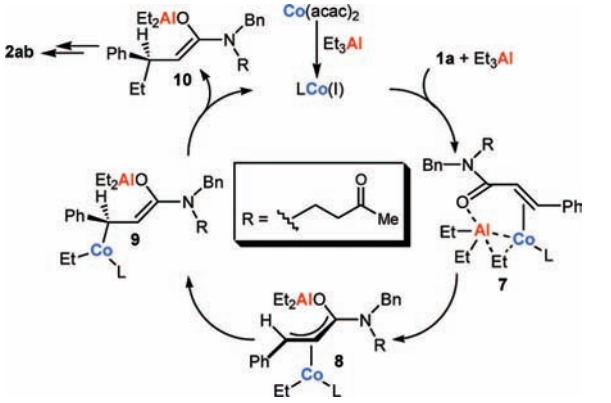
(13) (a) Johnson, J. R.; Tully, P. S.; MacKenzie, P. B.; Sabat, M. *J. Am. Chem. Soc.* **1991**, *113*, 6172–6177. (b) Grisso, B. A.; Johnson, J. R.; MacKenzie, P. B. *J. Am. Chem. Soc.* **1992**, *114*, 5160–5165.

(14) (a) Ogoshi, S.; Yoshida, T.; Nishida, T.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 1944–1950. (b) Ogoshi, S.; Tomiyasu, S.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2002**, *124*, 11598–11599.

Ogoshi, Kurosawa, and co-workers observed the oxidative addition of Pd(0) to enones in the presence of a range of Lewis acids, including Me_3Al.[14a]

Accordingly, a possible catalytic cycle for these reactions, using substrate **1a** and Et_3Al for illustrative purposes, is presented in Scheme 1. It is likely that treatment of $Co(acac)_2$ with Et_3Al generates a cobalt(I) species. In the presence of further Et_3Al, Co(I) can coordinate to **1a** to provide **7**, containing a three-center, two-electron bridging interaction between cobalt, aluminum, and an ethyl ligand.[15] Oxidative addition of Co(I) into the α,β-unsaturated amide, accompanied by transmetalation, would provide π-allylcobalt(III) species **8**. A hapticity change from η^3 to η^1 would give **9**, which can then undergo reductive elimination to generate *Z*-aluminum enolate **10**, which in turn can undergo aldol cyclization to give the product **2ab** after workup.

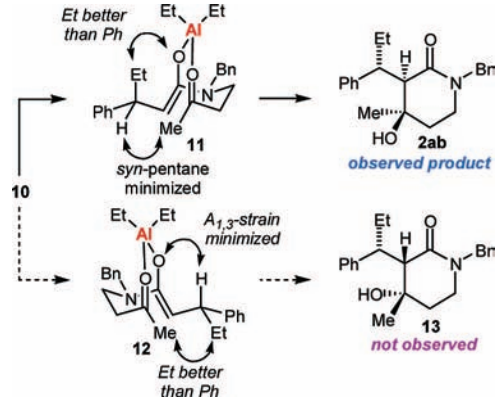
Scheme 1. Plausible Catalytic Cycle



A comparison of the results in entries 2 and 17 of Table 2 suggests that the situation may actually be more complex. Whereas highly efficient conjugate addition of an ethyl group is observed with substrate **1a** (entry 2), simply switching the pendant electrophile from a methyl ketone to a phenyl ketone in **1k** leads to a significant degree of competitive conjugate reduction (entry 17). This observation suggests that the pendant ketone is able to influence the course of the reaction through coordination to cobalt and/or the alkylaluminum functionality in one or more of the intermediates analogous to **7**−**9**. The reasons for reductive rather than alkylative aldol cyclization being favored when $Ni(acac)_2$ rather $Co(acac)_2{\cdot}2H_2O$ is employed (Table 1) or when Et_2Zn is used in place of trialkylaluminum reagents,[6a,7] are unclear at this time.

Finally, the stereochemical outcome of these reactions deserves comment. The high diastereoselectivity observed in the majority of examples in Table 2 was initially surprising, since the stereogenic center created upon conjugate addition does not reside within the ring formed during cyclization, in contrast to previous reports.[4] Assuming that aldol cyclization of **10** occurs through a chelated Zimmerman−Traxler-type transition state,[16] two conformations **11** and **12** seem reasonable (Scheme 2).

Scheme 2. Possible Explanation for Stereochemical Outcome



Cyclization through **11** minimizes unfavorable *syn*-pentane interactions,[17] whereas cyclization through **12** minimizes $A_{1,3}$-strain[18] in the enolate. The exclusive formation of **2ab** suggests that if this model is valid, minimization of *syn*-pentane interactions is the dominant stereocontrol element.[19] Once again however, the situation could be more complex if coordination of the pendant ketone to the cobalt and/or aluminum centers occurs in any of the intermediates **7**−**9**, since this coordination necessarily places the ketone on one particular diastereotopic face of the aluminum enolate, which may have important stereochemical consequences.

In summary, we have described highly diastereoselective cobalt-catalyzed alkylative aldol cyclizations that provide β-hydroxylactams containing three contiguous stereocenters. Further studies in this area will be reported in due course.

Acknowledgment. This work was supported by the University of Edinburgh and GlaxoSmithKline. We thank the EPSRC National Mass Spectrometry Service at the University of Wales, Swansea, for providing high-resolution mass spectra. We thank Professor Simon Parsons and Russell D. L. Johnstone at the School of Chemistry, University of Edinburgh, for assistance with X-ray crystallography.

Supporting Information Available: Experimental procedures, full spectroscopic data for new compounds, and crystallographic data (CIF). This material available free of charge via the Internet at http://pubs.acs.org.

OL800883B

(15) For examples of three-center, two-electron bridging interaction of Ni(0) with main-group organometallic reagents, see: (a) Hratchian, H. P.; Chowdhury, S. K.; Gutiérrez-García, V. M.; Amarasinghe, K. K. D.; Heeg, M. J.; Schlegel, H. B.; Montgomery, J. *Organometallics* **2004**, *23*, 4636–4646. (b) Ogoshi, S.; Ueta, M.; Arai, T.; Kurosawa, H. *J. Am. Chem. Soc.* **2005**, *127*, 12810–12811.

(16) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

(17) (a) Evans, D. A.; Nelson, J. V.; Taber, T. *Top. Stereochem.* **1982**, *13*, 1–115. (b) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151–4157.

(18) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.

(19) For a similar discussion in intermolecular alkylative aldol reactions, see ref 2j.