ORGANIC LETTERS

2000
Vol. 2, No. 26
4209−4212

Improved Ester Interchange Catalysts

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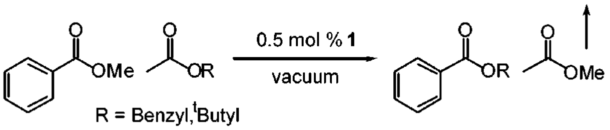
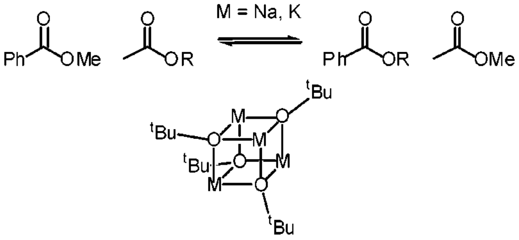
Received October 20, 2000

ABSTRACT



Mixed alkoxide/aryloxide clusters are long-lived and milder than previously reported ester interchange catalysts. They completely transform difficult substrates in a single synthetic operation with lower catalyst and reagent ester loadings. In addition to superior activities, these mixed clusters are kinetically less basic toward enolizable esters.

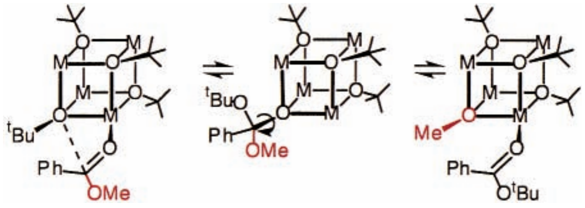
In 1997 we reported the high ester interchange activity (up to 10^7 TO/h) of alkali metal alkoxides in aprotic solvents (eq 1).[1] Under these conditions alkali metal alkoxide catalysts exist as tetrameric clusters[2] and react at rates far in excess of those normally observed in protic solvents (e.g., NaOEt in ethanol).[3]



(1)

Mechanistically, the interchange is thought to proceed by ester precoordination and intramolecular delivery of alkoxide, geometrically facilitated by the cluster framework. Productive breakdown of the cluster-bound tetrahedral intermediate gives a product ester and a newly substituted cluster (Scheme 1).[4]

Scheme 1



This mechanism provides a multistep pathway for equilibrating ester -OR groups. Since interchange rates are rapid and volatile product esters can be removed, this reaction can be utilized to synthesize new esters,[5] and in particular the synthetically useful *tert*-butyl esters.

Optimization of this chemistry to the synthesis of *tert*-butyl esters from methyl esters resulted in a protocol that involved *multiple additions* of 1 mol % of KO^{t}Bu and *tert*-butyl acetate, followed by the evacuative removal of the

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[1] Stanton, M. G.; Gagné, M. R. *J. Am. Chem. Soc.* **1997**, *119*, 5075−5076.

[2] (a) Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 7288−7293. (b) Jackman, L. M.; Smith, B. D. *J. Am. Chem. Soc.* **1988**, *110*, 3829−3835, and references therein. (c) Schmidt, P.; Lochmann, L.; Scneider, B. *J. Mol. Struct.* **1971**, *9*, 403−411. (d) Bauer, W.; Lochmann, L. *J. Am. Chem. Soc.* **1992**, *114*, 7482−7489. (e) Chisholm, M. H.; Drake, S. R.; Naiini, A. A.; Streib, W. E. *Polyhedron* **1991**, *10*, 337−335. (f) Chisholm, M. H.; Drake, S. R.; Naiini, A. A.; Streib, W. E. *Polyhedron* **1991**, *10*, 805−810. (g) Kahn, J. D.; Haag, A.; von Ragué Schleyer, P. *J. Phys. Chem.* **1988**, *92*, 212−220. (h) Halaska, W.; Lochmann, L.; Lim, D. *Collect. Czech. Chem. Commun.* **1968**, *33*, 3245−3253.

[3] Pregel, M. J.; Dunn, E. J.; Nagelkerke, R.; Thatcher, G. R. J.; Buncel, E. *Chem. Soc. Rev.* **1995**, 449−455.

[4] Stanton, M. G.; Allen, C. B.; Kissling, R. M.; Lincoln, A. L.; Gagné, M. R. *J. Am. Chem. Soc.* **1998**, *120*, 5981−5989.

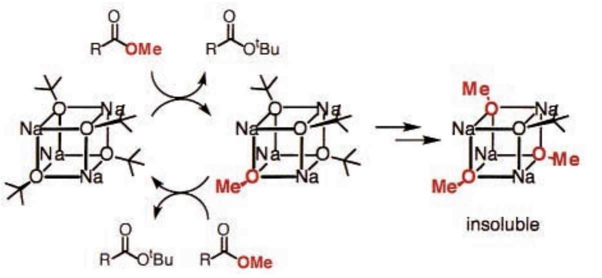
[5] For a related transesterification protocol that equilibrates alcohols and esters using KOMe/18-c-6, see: Rowan, S. J.; Hamilton, D. G.; Brady, P. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1997**, *119*, 2578−2579.

10.1021/ol0067585 CCC: $19.00

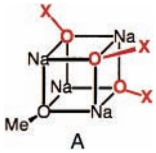
volatile methyl acetate byproduct.[6] This procedure gave high conversion to *tert*-butyl ester products, typically using 5−10 mol % of catalyst and 5−8 equiv of reagent ester and was also applicable to the synthesis of phosphonates.[7]

Although reaction rates are high, catalyst precipitation limited the number of achievable turnovers, a problem that was partially overcome by the multiple addition protocol. Isolation of a precipitate with a 3:1 NaOMe:NaO^{t}Bu stoichiometry pointed to the replacement of solubilizing cluster *tert*-butyl groups as the cause of catalyst loss (Scheme 2), as NaOMe and KOMe are insoluble sheetlike materials.[8]

Scheme 2



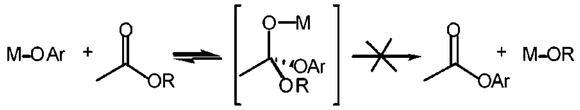
Since extending the lifetime of these catalysts required a strategy that prevented the formation of insoluble polymethoxide (or similar) clusters or arrays, we chose to incorporate several nonreacting but solubilizing components into the cluster. The first substituents investigated were aryloxides (**A**, X = Ar), since the steric and electronic



A

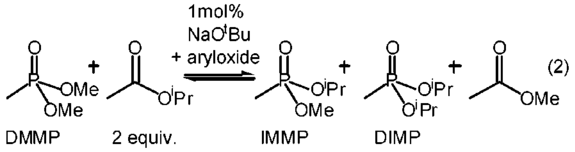
properties of this group can be readily modified. We reasoned that because aryloxides are better leaving groups, they would stay in the cluster since breakdown of any putative tetrahedral intermediate would always redeposit -OAr into the cube (Scheme 3). This notion is consistent with the observation

Scheme 3



that alkyl and aryl esters do not undergo productive interchange.[4] Thus, mixtures of alkoxide and aryloxide salts should form mixed clusters[9] wherein the alkoxide participates in alkyl ester interchange, while the aryloxides, being insulated from interchange, are able to provide long-term solubility and cluster integrity. This strategy additionally provides a handle for systematically varying the steric and electronic properties of the cluster substituents.

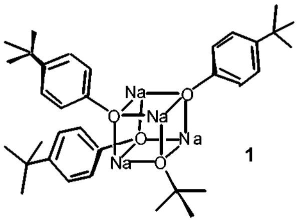
The efficacy of new catalyst mixtures was gauged by monitoring the approach to equilibrium of the transformation in eq 2 using 1 mol % of NaO^{t}Bu and varying amounts of



an aryloxide additive. Establishing global equilibrium in this reaction is challenging, as DIMP formation is slow, although equilibrium between DMMP and IMMP is established quickly.[7,10]

Catalyst performance, as judged by the final [DIMP], improved as the ratio of NaOC$_6$H$_4$-4-^{t}Bu[11] to *tert*-butoxide increased from 0 to 1 to 2, and peaked at 3, 4, and 5. Under conditions where equilibrium was not achieved, increasing the ratio from 3 to 4 to 5 did not change the product ratios. Varying the para substituent of the aryloxide additive revealed a nonlinear Hammett-type relationship with the 4-*tert*-butyl- and 4-chloro-derived catalysts being superior (4-CF$_3$ $\ll$ 4-H $\approx$ 4-OMe < 4-^{t}Bu $\leq$ 4-Cl). *Sodium* salts were also superior to *potassium* salts.

A combination of 1 mol % of NaO^{t}Bu and 3 mol % of NaOC$_6$H$_4$-4-^{t}Bu establishes equilibrium in 20 min (eq 2) while 5 mol % of NaO^{t}Bu could not. The coordination chemistry of Na-alkoxides and aryloxides suggests that the active catalyst is the mixed cluster **1**.[12]



1

The optimum catalyst mixture for phosphonates proved to also be an excellent catalyst for carbonyl ester interchange and provided a mild straightforward methodology for ester synthesis.

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(6) Stanton, M. G.; Gagné, M. R. *J. Org. Chem.* **1997**, *62*, 8240−8242.

(7) Kissling, R. M.; Gagné, M. R. *J. Org. Chem.* **1999**, *64*, 1585−1590.

(8) Weiss, E. *Z. Anorg. Allg. Chem.* **1964**, *332*, 197−203.

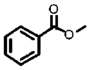
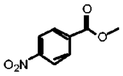
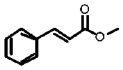
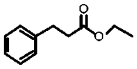
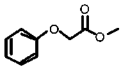
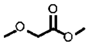
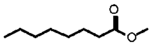
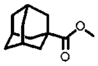
(9) For relevant examples of characterized mixed alkali metal alkoxide, aryloxide, or acetylide clusters, see: (a) Jackman, L. M.; Rakiewicz, E. F. *J. Am. Chem. Soc.* **1991**, *113*, 1202−1210. (b) Jackman, L. M.; Rakiewicz, E. F.; Benesi, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 4101−4109. (c) Thompson, A.; Corley, E. G.; Huntington, M.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028−2038.

(10) Equilibrium values for eq 2: using 2 equiv of ^{i}PrOAc dimethyl methylphosphonate (DMMP) 11%, isopropyl methyl methylphosphonate (IMMP) 51%; diisopropyl methylphosphonate (DIMP) 38%.

(11) Control experiments showed that NaOAr is not a competent catalyst.

(12) NMR experiments indicate that at this ratio some 2:2 and 0:4 also exist in solution, the former of which undoubtedly contributes to catalysis as well.

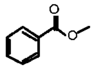
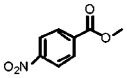
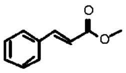
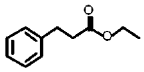
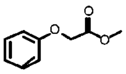
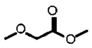
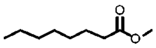
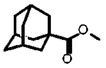
Table 1. Conversion of Methyl to Benzyl Esters with Benzyl Acetate and **1**

entry	substrate	acetate equiv.	mol% **1**	% product[a]
1		1.2	0.5	(Q[b])/97
2		1.5	0.5	(99)/93
3		2	2	(Q)/92
4		3	2	(Q)/94
5		2	2	(99)/93
6		2	2	(97)/92
7		1.2	1	(99)/92
8		2	2	(99)/97

[a] (% conversion)/% yield >98% purity. [b] Q = quantitative conversion by GC.

Tables 1 and 2 illustrate the effectiveness of catalyst **1** under optimized conditions. Sterically undemanding reagent esters such as benzyl acetate interchange quickly and generally lead to quantitative conversions to desired product in less than 1 h with as little as 0.5 mol % of **1** and 1.2 equiv of reagent ester. Bulky reagent esters such as *tert*-butyl acetate interchange more slowly and require higher catalyst loadings and more equivalents of reagent ester to achieve high (>98%) conversion. Compared to our first generation catalyst,[6] this methodology provides high product yields with lower catalyst loadings and operationally requires only a single catalyst addition. Moreover, several substrates were found to react more smoothly using **1** as catalyst. For example, acidic substrates such as those in entries 5 and 6 and the nitro-substituted substrate of Tables 1 and 2 are now satisfactorily converted to the desired product. In the case of the bulky adamantyl esters in entries 8, benzyl ester formation proceeded smoothly but formation of the *tert*-butyl ester did not, effectively establishing an upper limit on the steric encumbrance tolerated by the catalyst. The reaction is also scalable as methyl benzoate was readily converted to benzyl (>99%) and *tert*-butyl (96%) benzoate on a 100 mmol scale.

Table 2. Conversion of Methyl to *tert*-butyl Esters with *tert*-Butyl Acetate and **1**

entry	Substrate	Acetate equiv.	mol% **1**	% product[a]
1		3	2	(99)/93
2		3	3	(95)/92
3		5	2	(Q)/99
4		5	3	(94)/87
5		7	5	(99)/97
6		7	5	(99)/55
7		5	3	(Q)/96
8		3	3	3/-

[a] (% conversion)/% yield >98% purity. [b]Quantitative conversion by GC.

Typically the esters were distilled from CaH$_2$ or sublimed and stirred together neat in a Schlenk flask under inert an atmosphere. A 0.5 M THF solution of **1**, prepared by mixing freshly sublimed NaO^{t}Bu and NaOAr in the proper ratio, was added to the stirring esters and the flask opened to vacuum (0.15 mmHg, 25 °C). Reactions with high boiling esters were left open to the vacuum and were typically complete in 10 min−2 h. Reactions with a volatile reactant were treated with catalyst as above and the methyl acetate distilled into a cooled receptor under static pressure (40−55 mmHg). These conditions typically required 2−6 h for complete conversion (>98%) to product.

The successful utility of **1** at lower catalyst loadings prompted a reexamination of α-amino acid methyl esters which were racemized by [KO^{t}Bu]$_4$ catalysts.[6] The integrity of the α-chiral center was most conveniently monitored by using an enantiopure reagent ester and determining the ratio

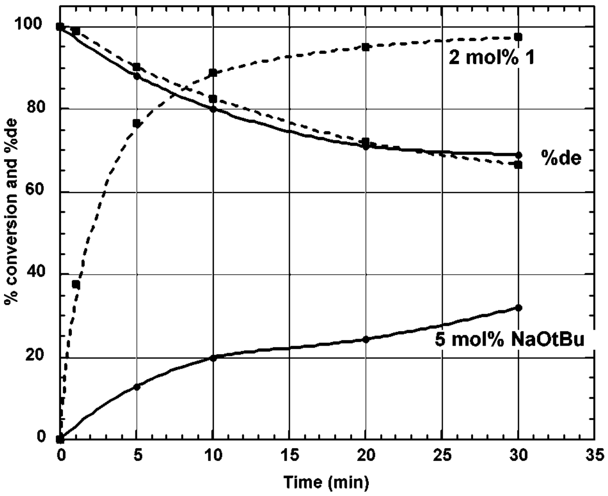
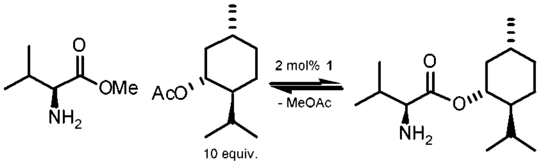


Figure 1. % conversion and % de versus time for eq 3 as catalyzed by 2 mol % of **1** (dash) and 5 mol % of NaO^{t}Bu (solid).

of diastereomers in the product esters by gas chromatography (eq 3). Unlike [KO^{t}Bu]$_4$ catalysis, the α-stereocenter was appreciably more stable to racemization using **1**. Figure 1 shows the conversion to product superimposed on the diastereomeric excess (% de) for 2 mol % of **1** (dash) and 5 mol % of NaO^{t}Bu (solid).[13] Inspection of the curves indicates that catalyst **1** provides superior conversion versus racemization rates, even at reduced loadings. Future experiments will optimize this interchange vs racemization activity by further variations in the aryloxide additive.



(3)

In summary, we have developed a new family of ester interchange catalysts that are milder and more robust than the simple alkali metal alkoxide catalysts previously reported. Application of these catalysts to ester interchange allows the *one-step* synthesis of protected esters from simple methyl or ethyl esters.

Acknowledgment. We thank the United States Army Research Office (DAAG55-95-1-0257), 3M, DuPont, Union Carbide, and the UNC University Research Council for funding of this research. M.R.G. is a Camille Dreyfus Teacher Scholar (2000).

Supporting Information Available: Experimental procedures for all syntheses, characterization of new compounds, and ^{1}H and ^{13}C NMR for all synthesized compounds in Tables 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Under identical conditions, 5 mol % of KO^{t}Bu gave a rate of conversion similar to 2 mol % of **1**; however, the % de drops to 15% and 5% after 1 and 5 min, respectively. Thus **1** is not only less basic but more active than [KO^{t}Bu]$_4$.