A New Route to Enolate Anion Chemistry

Gavin L. Edwards, William B. Motherwell,* Deirdre M. Powell and David A. Sandham

Department of Chemistry, Imperial College of Science, Technology and Medicine, South Kensington, London SW7 2AY, UK

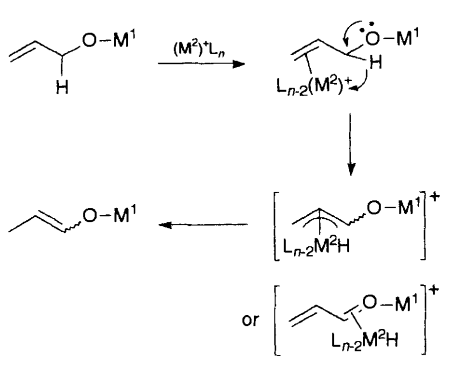
The direct conversion of an allylic alcohol to an α-alkylated carbonyl derivative may be achieved in a one-pot sequence *via* rhodium promoted isomerization of the derived lithium alkoxide or potassium triethylboronate complex.

The formation and reactivity of enolate anions has unquestionably served as a pre-eminent cornerstone for carbon–carbon bond formation in the armoury of the synthetic chemist. Traditionally, such intermediates have been generated from the corresponding carbonyl compound, either by base-induced deprotonation, or *via* conjugate addition or reduction sequences using an appropriate α,β-unsaturated derivative.[1] We reasoned, however, that an alternative stategy should exist, whereby, the selection of an allylic alcohol as a substrate would permit prior formation of the derived alkoxide anion to be followed by relocation of the carbon–carbon double bond using a controlled transition metal-mediated isomerization. Although the formation of enolic derivatives from a wide variety of allylic ethers (*e.g.* alkyl, aryl, silyl) by such isomerizations has been extensively studied[2] and is now a standard synthetic operation, as, for example in hydroxy group deprotection,[3] the direct generation of reactive metal enolates in such a fashion for further *in situ* reaction has not, to the best of our knowledge, been previously considered.

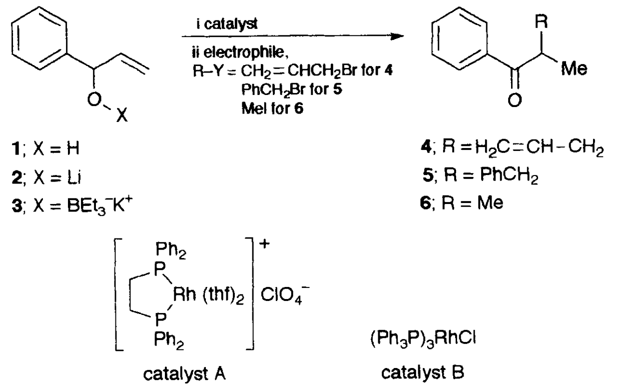
The foregoing concept is summarized in more detail in Scheme 1, which also indicates two further factors of considerable importance in the overall design. In the first instance, our choice of metal M^1 was determined by the desire to avoid the use of an ionic metal alkoxide which could function directly as an irreversible ligand for the transition metal M^2 and also to obtain covalent enolates of a known and well-behaved type. Of equal importance was the selection of a cationic transition metal catalyst M^2 accommodating three vacant coordination sites, and which, by operating either *via* the π-allyl hydride mechanism or an 'oxonium ion' ion equivalent as shown, would be expected to benefit (in energetic terms) from oxygen lone-pair participation. Although the catalytic isomerization of allylic alcohols to carbonyl compounds is well known,[2] the remarkable demonstration of the persistence of simple enols under rhodium catalysis, which was reported recently by Bosnich[4] during the course of our studies, has confirmed this mechanistic approach and shown that both hydride abstraction and delivery occur in an irreversible fashion. The present work was, however, undertaken with the fundamentally different objective of generating a synthetically useful enolate; and thereby avoiding the phenomenon of facile tautomerism, which destroys the inherent potential of enols for directly controlled carbon–carbon bond formation.

We now report our preliminary efforts to validate this approach using lithium alkoxides or potassium triethylboronate complexes for M^1 in conjunction with the cationic rhodium complex $[Rh(dppe)(thf)_2]^+(ClO_4)^-$,[4] conveniently prepared by controlled hydrogenation of the corresponding 1,5-cyclooctadiene (cod) derivative $[Rh(dppe)(cod)]^+(ClO_4)$ [dppe = ethylenebis(diphenylphosphine)].

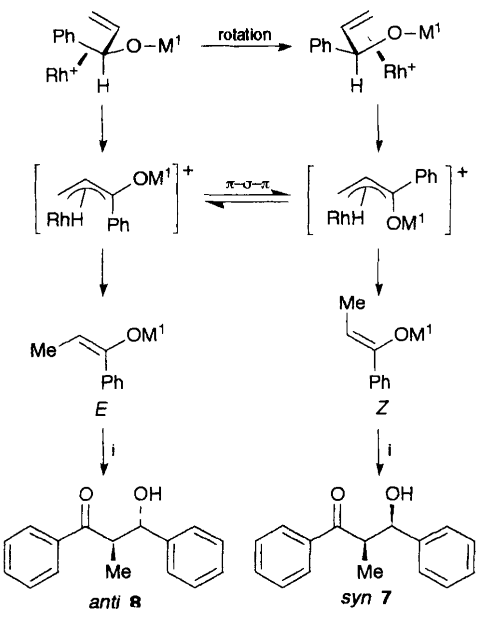
1-Phenylprop-2-en-1-ol **1** was selected as a suitable substrate for initial study of the one-pot isomerization–alkylation



Scheme 1



Scheme 2

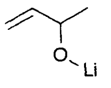


Scheme 3 *Reagents*: i, PhCHO, M^1 = Li

sequence outlined in Scheme 2. In a typical experiment, prior formation of the alkoxide 'anion' in tetrahydrofuran (thf) is followed by addition of the rhodium catalyst (2–5 mol%) to the reaction *via* cannula and thermal isomerization is allowed to proceed until all of the starting allylic alcohol has been consumed, as evidenced by TLC aliquot monitoring. The reaction mixture is then cooled in an ice–salt bath, followed by addition of the electrophile and allowed to stir overnight. The lithium alkoxide **2** was prepared by addition of one equivalent of butyllithium to the alcohol, while potassium triethylboronate complex **3** was generated either by the reaction of **1** with potassium hydride and then triethylborane or, at a later stage even more simply, by reaction with potassium triethylborohydride in the presence of triethylborane as catalyst.

Table 1

Alkoxide	Catalyst	Product	Yield (%)
2	A	**4**	82
2	A	**5**	75
2	A	**6**	62
2	B	**4**	68
3	A	**4**	69



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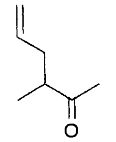

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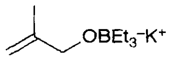

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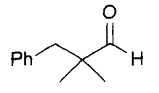

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The results for a series of α-alkylated products are given in Table 1 and confirm that both the covalent lithium alkoxide **2** and the boron 'ate' complex **3** can undergo this type of reaction. Interestingly, we have also shown that Wilkinson's catalyst is highly effective in promoting isomerization of lithium alkoxide **2**, although its function may be as the precursor of an even more reactive species in the catalytic cycle.

The lithium alkoxide **2** was also an appropriate model to examine the present sequence in terms of generating a particular enolate geometry. As outlined in Scheme 3, inherent possibilities exist for control either in the initial requirements for stereoselective hydride abstraction, or by interconversion of the two π-allyl intermediates by the π–σ–π mechanism.[5] In the event, isomerization of **2** with $[Rh(dppe)(thf)_2]^+$ followed by reaction with benzaldehyde under kinetically controlled conditions[6] gave the aldol products **7** and **8** in good overall yield (84%) with a distinct preference (**7**:**8**, 8.6:1) for the formation of the thermodynamically less stable *syn* diastereoisomer. This result therefore indicates that at least 86% of the product was derived *via* the *Z*-enolate.[7]

We have also briefly studied the application of this method to energetically more demanding substrates. Thus, isomerization of the lithium alkoxide **9** of but-3-en-2-ol with the catalyst $[Rh(dppe)(thf)_2]^+$ followed by alkylation of the resultant enolate with allyl bromide gave ketone **10** (36%, isolated and further characterized as its 2,4-dinitrophenylhydrazone derivative) as the sole ketonic regioisomer derived from the first-formed thermodynamic enolate. In similar fashion, alkylation of the aldehyde enolate produced from the boron 'ate' complex **11** of the corresponding primary allylic alcohol gave, after quenching with benzyl bromide the labile aldehyde[8] **12** (30%, isolated and characterized as the derived primary alcohol from lithium aluminium hydride reduction), thereby avoiding the necessities of purifying and manipulating isobutyraldehyde *via* the multistep metalloimine sequences.[9]

The foregoing results have hopefully indicated that an allylic alcohol can serve not merely as a latent but as a direct synthon for entry into enolate anion chemistry and, when taken in conjunction with established chemistry involving chiral enolates[10] and the isomerization of allylic alcohols[2,11] and amines [12] using chiral transition metal catalysis indicates potential for the development of stereocontrolled carbon–carbon bond formation.

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References

1 A. J. Waring, *Comprehensive Organic Chemistry*, eds. D. H. R. Barton and W. D. Ollis, vol. 1 ed. J. F. Stoddart, Pergamon Press, Oxford, New York, Toronto, Sydney, Paris, Frankfurt, 1978, 5.2, p. 1017 and references cited therein; *Comprehensive Carbanion Chemistry*, eds. E. Buncel and T. Durst, Elsevier, New York, 1984.

2 K. Tani, *Pure Appl. Chem.*, 1985, **57**, 1845 and references cited therein.

3 E. J. Corey and J. W. Suggs, *J. Org. Chem.*, 1973, **38**, 3224.

4 S. H. Bergens and B. Bosnich, *J. Am. Chem. Soc.*, 1991, **113**, 958.

5 J. W. Faller, M. E. Thomsen and M. J. Mattina, *J. Am. Chem. Soc.*, 1971, **93**, 2642.

6 C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn and J. Lampe, *J. Org. Chem.*, 1980, **45**, 1066.

7 C. H. Heathcock, *Science*, 1981, **214**, 395.

8 G. Stork and S. R. Dowd, *Org. Synth.*, 1974, **54**, 46.

9 J. K. Whitesell and M. A. Whitesell, *Synthesis*, 1983, 517.

10 N. S. Simpkins, *Chem. Soc. Rev.*, 1990, **19**, 335; I. Paterson, *Chem. Ind.*, 1988, 373.

11 S. Otsuka and K. Tani, in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, Orlando, 1985, vol. 5.

12 K. Tani, T. Yamagata, S. Akutgawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori and S. Otsuka, *J. Am. Chem. Soc.*, 1984, **106**, 5208.