DOI: 10.1002/adsc.200505212

Cobalt-Catalysed Addition of Allylidene Dipivalate to Aldehydes. A Formal Homoaldol Condensation

Marco Lombardo,* Sebastiano Licciulli, Filippo Pasi, Gaetano Angelici, Claudio Trombini*

Dipartimento di Chimica "G. Ciamician", Università degli Studi di Bologna, via Selmi 2, 40126, Bologna, Italy
Fax: (+39)-(0)51-209-9456; e-mail: marco.lombardo@unibo.it, claudio.trombini@unibo.it

Received: May 23, 2005; Accepted: September 9, 2005

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

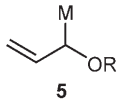
Abstract: A Co(I)-catalysed condensation of allylidene dipivalate with aldehydes to give (*Z*)-4-hydroxybut-1-enyl pivalates in 62 to 87% isolated yields, is reported. Reactions are run in acetonitrile at 0 or 25 °C depending on the nature of the aldehyde, and exploiting the Co(II)/Zn(0) redox couple for the preparation of the catalytic Co(I) species.

Keywords: Allylidene dipivalate; catalysis; cobalt(I); homoaldol reaction; γ-hydroxy carbonyl compounds; regioselectivity

Introduction

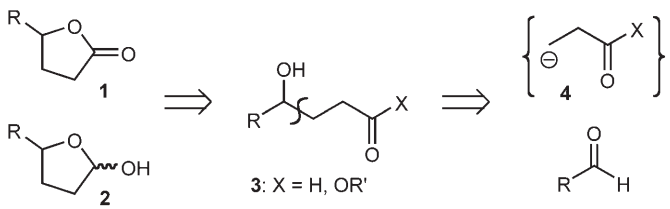
Designing novel synthons to be efficiently applied in broad scope reactions is a topic in the field of molecular engineering devoted to the development of alternative synthetic pathways. An example is offered by three-carbon homologating agents containing a nucleophilic centre on carbon 3 relative to the heteroatom[1] (d^3 synthons), among which synthetic equivalents of the homoenolate anion **4** are important building blocks in organic synthesis.[2] The reaction of **4** with aldehydes, the homoaldol reaction, opens a route to γ-substituted butanolides **1** or butyrolactols **2** *via* adducts **3**, according to the disconnective approach reported in Scheme 1.

Much effort has been devoted in the last decades to the design of organometallic d^3 synthons mimicking propanal or propionate homoenolate **4**. There are examples where the highly susceptible aldehyde function is protected as acetal,[3] but, more frequently, the homoenolate ion is masked in the form of a heterosubstituted allyl-metal complex **5**. Significant examples are based on allyl-titanium complexes carrying nitrogen[4] or oxygen[5] substituents on the metallated allyl terminus.

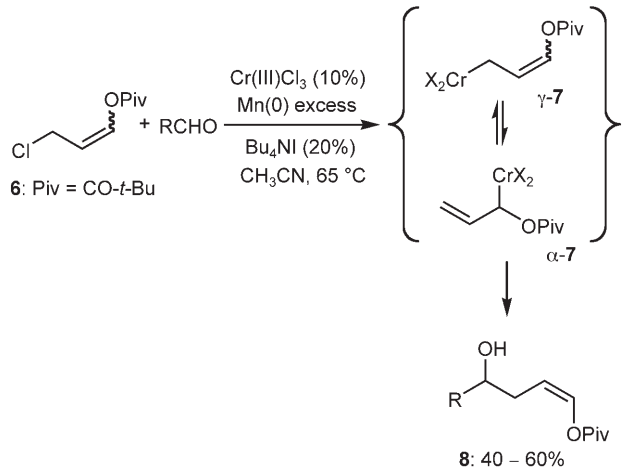


5

In the frame of a research project aimed at exploiting 3-halopropenyl esters as three-carbon homologating agents in organic synthesis,[6] we developed a catalytic route to the homoaldol reaction based on the Cr(III)-Mn(0) redox couple and on 3-chloropropenyl pivalate **6** as the precursor of the homoenolate species, that is an ester-substituted allyl-chromium(III) complex **7** (Scheme 2).[7] Under the reported conditions, a good control of regioselectivity was achieved: isolated yields



Scheme 1.



Scheme 2.

of (*Z*)-4-hydroxy-alk-1-enyl pivalates **8** varied in the 40–60% interval and regioisomer ratios in favour of **8** ranged from 72/28 to 90/10.

Here we report the development of an improved procedure for the synthesis of adducts **8**, which displayed the following features:

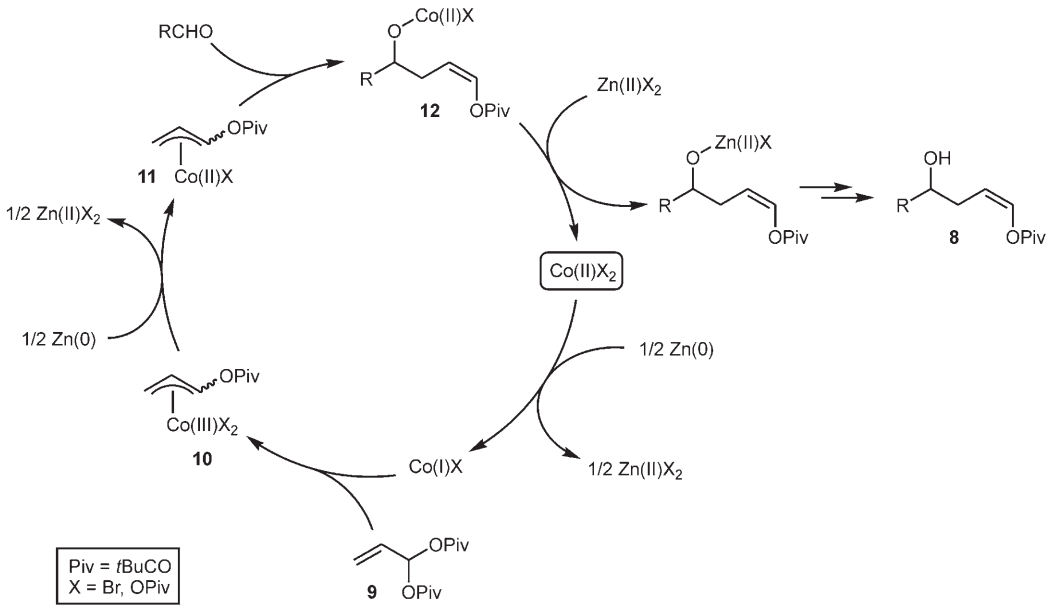
(i) it was again mechanistically based on the insertion of a low-valent metal to a suitable substituted allylic precursor, rather than on more expensive and critical protocols requiring the use of organolithium or organomagnesium derivatives,
(ii) it exploited a less environmentally toxic and dangerous metal than chromium, one of the top priority pollutants according to the US Environmental Protection Agency,[8]
(iii) it required milder reaction conditions, and
(iv) it attained better yields and virtually complete regioselectivity.

Results and Discussion

En route to new synthetic equivalents **5** of the homoenolate ion, our attention was attracted on one hand by acylals, on the other by recent studies from the groups of Périchon[9] and Gosmini[10] on the generation of Co(I) species in acetonitrile, by exploiting the Co(II)/Zn(0) redox couple. Since Co(I) proved to oxidatively add to the carbon-halogen bond of aryl halides and to the carbon-acetate bond of allyl acetate,[11] we tested the reaction of allylidene dipivalate (**9**) with aldehydes in the presence of the redox couple Co(II)/Zn(0), and eventually we succeeded in attaining a new catalytic version of the homoaldol reaction. The acylal **9** was obtained by the reaction of acrolein with pivalic anhydride, and played the role of the precursor of the new propanal homoenolate equivalent **10** or **11** (Scheme 3).

A very simple synthetic protocol was developed: **9** and an aldehyde are poured into a freshly prepared solution of anhydrous $CoBr_2$[12] (30% with respect to the limiting reactant, the aldehyde) in acetonitrile, then zinc powder is added to the solution. The addition of zinc metal immediately fosters the reaction cascade depicted in Scheme 3. Temperature is the key factor to achieve a complete control of regiochemistry. To this purpose, the overall process is run at 0 °C or at 20–25 °C, depending on the nature of the aldehyde. More reactive aliphatic aldehydes (runs 7–11) need cooling to 0 °C to undergo regioselective nucleophilic attack from the less hindered terminus of **11** (Table 1, runs 7–11), while complete regioselectivity is attained at 25 °C using the less reactive aromatic aldehydes (runs 1–6).

A transient Co(I) species, likely stabilised by acetonitrile ligands in its coordination sphere, in the presence of **9** undergoes insertion into the carbon-oxygen bond, rather than over-reduction to inactive Co metal by excess of zinc metal, or dismutation to Co(0) and Co(II). The resulting intermediate **10**, an allylic Co(III) complex, should be reduced, on pure electrochemical grounds,[13] to the allylic Co(II) complex **11**[14] by the excess of Zn(0).[15] The interaction of **11** with the aldehyde takes place at the less hindered terminus of the allylic moiety, giving the Co(II) adduct **12**. Generation of the easily reducible $CoBr_2$ may take place *via* transmetalation of **12** with $ZnBr_2$, thus completing the catalytic cycle. Configurationally pure (*Z*)-4-hydroxy-alk-1-enyl pivalates (**8**) are formed as the sole products.



Scheme 3.

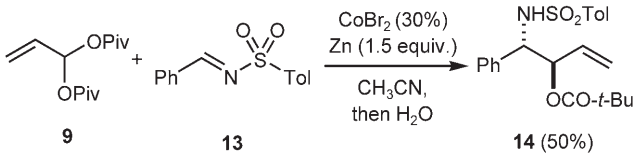
Table 1. Co(II)-catalysed synthesis of (*Z*)-4-hydroxy-alk-1-enyl pivalates **8** in CH_3CN.

Run	RCHO	*t* [h]	*T* [°C]	**8**, Yield [%]
1	Benzaldehyde	6	25	**8a**, 87
2	4-Methoxybenzaldehyde	6	25	**8b**, 80
3	4-Chlorobenzaldehyde	6	25	**8c**, 70
4	4-Methylbenzaldehyde	6	25	**8d**, 67
5	1-Naphthaldeyde	6	25	**8e**, 66
6	2-Furancarboxaldehyde	6	25	**8f**, 68
7	2-Methylpropanal	6	0	**8g**, 82
8	3-Phenylpropanal	6	0	**8h**, 70
9	Cyclohexanecarboxaldehyde	6	0	**8i**, 67
10	Octanal	6	0	**8j**, 62
11	Dodecanal	6	0	**8k**, 67

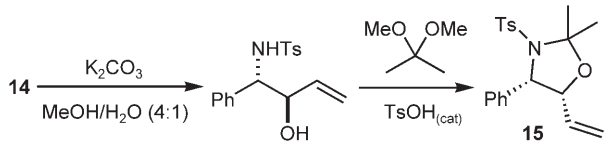
Table 1 collects a series of preliminary results, where isolated yields of **8** lie in the 62–87% range. Products **8** can be easily hydrolysed to 5-substituted butyrolactols; indeed, stirring **8a** and **8 h** with 3 equivalents of K_2CO_3 in 9:1 methanol/water for 2 h at 25 °C is sufficient to quantitatively convert the two starting materials into *cis-trans* mixtures of 5-phenyltetrahydrofuran-2-ol[16] or 5-(2-phenylethyl)-tetrahydrofuran-2-ol,[17] respectively. Moreover, the (*Z*)-configuration of the double bond of **8** looks promising, in terms of possible diastereocontrol, for subsequent epoxidation or dihydroxylation processes. Work to this purpose is in progress.

With the aim to broaden the scope of the reaction, we checked the reactivity of acylal **9** toward an imine, in the presence of Co(I). An acceptable conversion (50%) was obtained with *N*-benzylidene *p*-toluensulfonamide (**13**), but a full reversal of regioselectivity in the addition of **9** to **13** was observed, affording the adduct **14** in a virtually pure *anti* diasetreoselectivity (Scheme 4).

In order to unambiguously assign the *anti* stereorelationship between the newly formed stereocentres, **14** was converted into the cyclic oxazolidine **15** (Scheme 5). The shielding (0.8–1.0 ppm) of the internal vinylic proton of **15** caused by the spatial proximity of the phenyl ring proved the *cis* substitution in **15**, thus confirming the *anti* stereochemistry of **14**.



Scheme 4.



Scheme 5.

Conclusion

A simple and economic approach to (*Z*)-4-hydroxy-alk-1-en-1-yl pivalates **8**, interesting protected forms of homoaldols, has been developed, based on the use of acylal **9** and of the redox couple Co(II)/Zn(0). Reactions are run in acetonitrile at 0–25 °C and look attractive for scaling-up studies, provided that the exothermic reaction associated to the initial redox processes is properly managed (see Experimental Section).

Further studies are in progress in order to: (i) ascertain which factors, other than temperature, could affect regioselectivity, (ii) check the effect of modified acylal structures, for instance, by changing the ester moieties, and (iii) acquire insight about the true structure of the catalytically active species by suitable computational approaches.

Experimental Section

Allylidene Dipivalate (9)

Two drops of H_2SO_4 were added to a solution of pivalic anhydride (90 mmol, 18.3 mL) in CH_2Cl_2 (100 mL). A solution of freshly distilled acrolein (6.56 mL, 100 mmol) in CH_2Cl_2 (10 mL) was added drop by drop, at a rate slow enough to maintain the solution at room temperature. The reaction mixture was stirred at room temperature for 6 h and filtered through a short pad of K_2CO_3. The solvent was removed at reduced pressure and the residue distilled (bp 78–80 °C/6 mmHg) to afford **9** as a clear liquid; yield: 16.3 g (67.5 mmol, 75%).

Synthesis of (*Z*)-4-Hydroxyalk-1-enyl Pivalate (8); General Procedure

Commercial $CoBr_2 \cdot 2\,H_2O$ (0.076 g, 0.3 mmol) was flamed under a positive argon pressure until the colour turns from purple to bright green. Anhydrous $CoBr_2$ was dissolved in freshly distilled acetonitrile (2 mL), giving a deep blue solution. To this solution, acylal **9** (0.34 mL, 1.4 mmol) and the aldehyde (1 mmol) were added, the solution retaining the original blue colour. The temperature was set at 0 or 25 °C with an ice or oil bath, and commercial zinc powder (0.85 g, 1.3 mmol) was added. An initial exothermic reaction was observed while the heterogeneous solution turned reddish brown. The reaction mixture was vigorously stirred at the same temperature for 6 hours, quenched with saturated aqueous $NaHCO_3$ solution (1 mL) and salts were removed by filtration on a short pad of Celite®. The filtered solution was dried over Na_2SO_4, evaporated at reduced pressure and the residue was purified by flash-chromatography on silica eluting with cyclohexane/ethyl acetate mixtures.

Cobalt-Catalysed Reaction of Allylidene Dipivalate (9) with *N*-Benzylidene-*p*-toluenesulfonamide (13); Synthesis of 1-Phenyl-1-(tosylamino)but-3-en-2-yl Pivalate (14)

To a blue solution of $CoBr_2$ (0.065 g, 0.3 mmol) in acetonitrile (3 mL) prepared as previously described, were added in turn

acylal **9** (0.34 mL, 1.4 mmol) and the *N*-benzylidene-*p*-toluenesulfonamide (**13**)[18] (0.26 g, 1 mmol). The temperature was set at 25 °C with an oil bath, and commercial zinc powder (0.13 g, 2 mmol) was added with vigorous stirring. The reaction mixture was stirred at the same temperature for 12 hours, quenched with saturated aqueous NH_4Cl solution (2 mL) and salts are removed by filtration on a short pad of Celite®. The filtered solution was extracted two times with ethyl acetate, dried over Na_2SO_4 and evaporated at reduced pressure. The residue was purified by flash-chromatography on silica eluting with cyclohexane/ethyl acetate 9:1 to afford aminol **14**; yield: 0.2 g (0.5 mmol, 50%).

4,5-*cis*-2,2-Dimethyl-4-phenyl-3-tosyl-5-vinyloxazolidine (15)

Aminol **14** (0.05 g, 0.12 mmol) was dissolved in MeOH/H_2O (1 mL, 4:1 v/v), K_2CO_3 (0.50 g, 0.36 mmol) was added and the reaction mixture was stirred at room temperature overnight. MeOH was removed at reduced pressure and the aqueous layer was extracted with ether. The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The crude mixture was dissolved into freshly distilled 2,2-dimethoxypropane (1 mL) and a catalytic amount of *p*-toluenesulfonic acid was added. The reaction mixture was stirred at room temperature overnight, filtered (Celite®) and the organic layer was evaporated under reduced pressure. Purification by flash-chromatography on SiO_2 (cyclohexane/ethyl acetate, 9:1) afforded **15**; yield: 0.02 g (0.06 mmol, 50%).

Acknowledgements

This work was supported by M. I. U. R. (Rome) grants (PRIN project "Stereoselezione nella sintesi organica" and FIRB project "Progettazione, preparazione e valutazione biologica e farmacologica di nuove molecole organiche quali potenziali farmaci innovativi") and by the University of Bologna (Funds for selected research topics).

References and Notes

[1] J. C. Stowell, *Chem. Rev.* **1984**, *84*, 409–435.
[2] H. Ahlbrecht, U. Beyer, *Synthesis* **1999**, 365–390.
[3] a) F. A. Luzzio, R. W. Fitch, *J. Org. Chem*. **1999**, *64*, 5485–5493; b) M. García-Valverde, R. Pedrosa, M. Vicente, *Tetrahedron: Asymmetry* **1995**, *6*, 1787–1794; c) M. Kawashima, T. Fujisawa, *Bull. Chem. Soc. Jpn*. **1988**, *61*, 3377–3379; d) J. Barluenga, J. R. Fernandez, C. Rubiers, M. Yus, *J. Chem. Soc. Perkin Trans. 1* **1988**, 3113–3117; e) T. Mandai, T. Moriyama, K. Tsujimoto, M. Kawada, J. Otera, *Tetrahedron Lett.* **1986**, *27*, 603–606; f) H. J. J. Loozen, *J. Org. Chem*. **1975**, *40*, 520–521.
[4] a) C. Gaul, D. Seebach, *Helv. Chim. Acta* **2002**, *85*, 963–978; b) H. Roder, G. Helmchen, E.-M. Peters, K. Peters, H.-G. Schnering, *Angew. Chem. Int. Ed. Eng*. **1984**, *23*, 898–899.
[5] a) S. Okamoto, X. Teng, S. Fujii, Y. Takayama, F. Sato, *J. Am. Chem. Soc*. **2001**, *123*, 3462–3471; b) T. Hanazawa, S. Okamoto, F. Sato, *Org. Lett*. **2000**, *2*, 2369–2371; c) X. Teng, Y. Takayama, S. Okamoto, F. Sato, *J. Am. Chem. Soc*. **1999**, *121*, 11916–11917.
[6] M. Lombardo, S. Licciulli, C. Trombini, *Pure Appl. Chem.* **2004**, *76*, 657–669; M. Lombardo, K. Gianotti, S. Licciulli, C. Trombini, *Tetrahedron* **2004**, *60*, 11725–11732.
[7] M. Lombardo, S. Morganti, S. Licciulli, C. Trombini, *Synlett* **2003**, 43–46.
[8] Chromium is listed by the US EPA as one of 129 priority pollutants. Chromium is considered one of the 14 most noxious heavy metals. Chromium is also listed among the 25 hazardous substances thought to pose the most significant potential threat to human health. EPA, Office of Water, Water Quality Standards Database: http://oaspub.epa.gov/wqsdatabase/wqsi epa criteria.rep parameter.
[9] S. Seka, O. Buriez, J. Périchon, *Chem. Eur. J.* **2003**, *9*, 3597–3603.
[10] M. Amatore, C. Gosmini, J. Périchon, *Eur. J. Org. Chem*. **2005**, 989–992; C. Gosmini, J. Périchon, *Org. Biomol. Chem*. **2005**, *3*, 216–217, and references cited therein.
[11] P. Gomes, C. Gosmini, J. Périchon, *Synthesis* **2003**, 1909–1915; P. Gomes, C. Gosmini, J. Périchon, *Lett. Org. Synth*. **2004**, *1*, 105–108.
[12] Cheaper $CoCl_2$ or $Co(Ac)_2$ are not useful under these conditions in acetonitrile. While reduction of $CoCl_2$ by means of unactivated commercial Zn(0) in acetonitrile is very sluggish, the acetate does not undergo reduction at all.
[13] O. Buriez, E. Labbé, J. Périchon, *J. Electroanal. Chem.* **2003**, *543*, 143–151.
[14] The η^3 structure was arbitrarily assigned to complexes **10** and **11** not on the basis of experimental evidence but purely on analogy to what was proposed in ref.[11]
[15] An experiment planned to verify the possible interaction of zinc metal with allylidene dipivalate in acetonitrile, gave unambiguous evidence of a complete lack of reactivity.
[16] Spectroscopic data are in perfect agreement to those reported by X. Verdaguer, M. C. Hansen, S. C. Berk, S. L. Buchwald, *J. Org. Chem*. **1997**, *62*, 8522–8528.
[17] Spectroscopic data are in perfect agreement to those reported by J. Cossy, F. Bargiggia, S. BouzBouz, *Org. Lett*. **2003**, *5*, 459–462.
[18] L. C. Vishwakarma, O. D. Stringer, F. A. Davis, *Org. Synth*. **1988**, *66*, 203–210.

