ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 10957–10959

www.rsc.org/chemcomm

COMMUNICATION

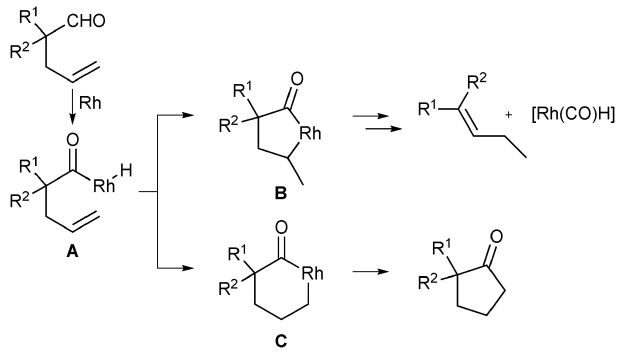
Facile and chemoselective rhodium-catalysed intramolecular hydroacylation of α,α-disubstituted 4-alkylidenecyclopropanals†

Damien Crépin, Coralie Tugny, James H. Murray and Christophe Aïssa*

Received 28th July 2011, Accepted 18th August 2011
DOI: 10.1039/c1cc14626b

Mild intramolecular hydroacylation of α,α-disubstituted 4-alkylidenecyclopropanals has been developed, avoiding decarbonylation and affording cycloheptenones in good yields. The reaction is chemoselective in favour of the alkylidenecyclopropane moiety when potential alkene or alkyne acceptors are tethered to the substrate.

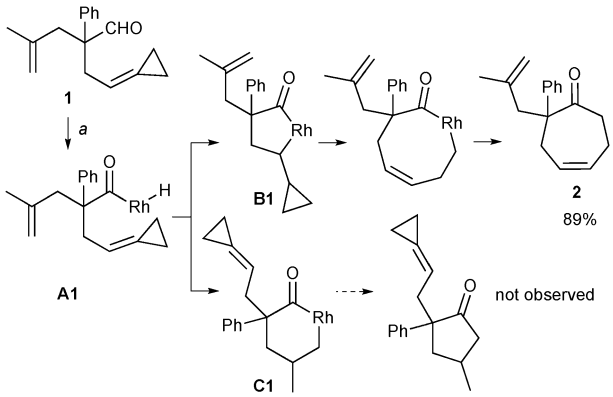
Rhodium-catalysed intramolecular hydroacylation is a remarkable example of atom-economical transformation.[1–3] Early experimental studies suggest that migratory insertion of the terminal olefin into the rhodium–hydrogen bond of acylhydridorhodium **A** leads to both pentarhodacycle **B** and hexarhodacycle **C** (Scheme 1).[4] Moreover, more recent theoretical studies conducted with non-substituted 4-pentenal suggest that pentarhodacycles **B** are the key intermediates leading to decarbonylation of the substrate whilst hexarhodacycles **C** would undergo productive carbon–carbon reductive elimination.[5] To the extent that the Thorpe–Ingold effect[6] would favour the predominant formation of rhodacycle intermediates **B** over hexarhodacycle **C** from α,α-disubstituted aldehydes (R^1, $R^2 \neq H$), these mechanistic considerations are in good accordance with the notorious reluctance of α,α-disubstituted aliphatic aldehydes to undergo intramolecular hydroacylation.[2b,c,7] Hence, relatively harsh reaction conditions are often required to promote the



Scheme 1 Formation of pentarhodacycle and hexarhodacycle intermediates from α,α-disubstituted aliphatic aldehydes.

University of Liverpool, Chemistry Department, Crown Street, L69 7ZD, Liverpool, UK. E-mail: aissa@liverpool.ac.uk; Fax: +44 151 794 3588; Tel: +44 151 795 2170

† Electronic supplementary information (ESI) available: Detailed description of experimental procedures and characterisation of new compounds. See DOI: 10.1039/c1cc14626b



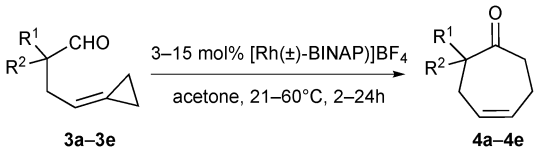
Scheme 2 Smooth formation of α,α-disubstituted cycloheptenones. *a*: [Rh((±)-BINAP)]BF_4 (10 mol%),[8] acetone, 21 °C, 12 h. Positive charge and ligand sphere on rhodium are omitted for simplicity.

usually low yielding formation of cyclopentanones,[2c,7] with rare exceptions,[7c,e] and products resulting from side reactions such as carbon–carbon double bond migration and decarbonylation have been observed.[2c,7b]

We found that treatment of α,α-disubstituted aldehyde **1** with [Rh((±)-BINAP)]BF_4 (10 mol%) (BINAP = 2,2′-bis(disphenylphosphino-1,1′-binaphthyl)) in acetone at room temperature led to the smooth formation of cycloheptenone **2** in 89% isolated yield whilst no cyclopentanone was observed (Scheme 2).[8] This result is in good accordance with the previous reasoning and suggests that migratory insertion of the alkylidenecyclopropane moiety in **A1** and formation of pentarhodacycle intermediate **B1** prevail over migratory insertion of the terminal olefin and formation of hexarhodacycle **C1**. Swift ring enlargement and reductive elimination would then divert **B1** from the decarbonylative pathway. Presumably, the release of strain energy during the migratory insertion from **A1** toward **B1** and during the subsequent ring enlargement plays an important role in favouring this productive reaction pathway.

However, it has been proposed that the turnover number of rhodium-catalysed hydroacylation of 4-pentenals can be improved by suppressing the decarbonylation pathway, either in the presence of ethylene[4a] or by coordination of another olefin.[4b] Accordingly, we wondered whether a second olefin must be tethered to α,α-disubstituted 4-alkylidenecyclopropanes in order to observe smooth conversion. Conversely, would the

Table 1 General preparation of α,α-disubstituted cycloheptenones[a]



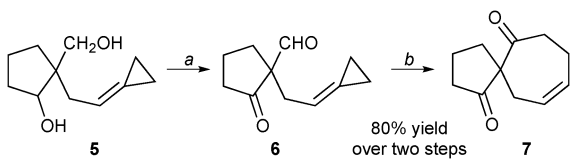
Entry	R^1	R^2	Product	Time/h	Yield[b] (%)
1	Ph	Me	**4a**	2	85[c]
2	Ph	Me	**4a**	14	86[d]
3	CH_2OTBS	Me	**4b**	2	87
4	CH_2OTBS	CH_2Ph	**4c**	3	93
5	CH_2OCH_2Ph	Me	**4d**	4	77
6	CH_2Opiv	Me	**4e**	8	54[e]

[a] All reactions were performed at 60 °C except otherwise noted. The active catalyst was prepared prior to use by hydrogenation of $[Rh(nbd)_2]BF_4$ (10 mol%) (nbd = norbornadiene) in the presence of (±)-BINAP (10 mol%) at room temperature.[8] [b] Isolated yields. [c] At 21 °C. [d] 3 mol% of catalyst was used. [e] 15 mol% of catalyst was used.TBS = *tert*-butyldimethylsilyl. Piv = pivaloate.

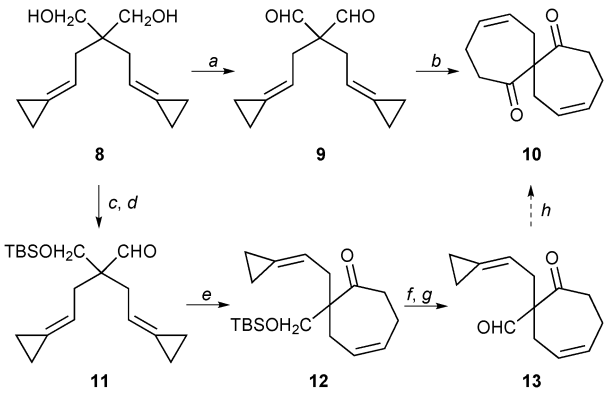
reaction be similarly chemoselective if the second tethered olefin in **1** is replaced by other alkenes or an alkyne?

We first examined the generality of the transformation depicted in Scheme 2 with substrates which did not pose an issue of chemoselectivity and found that treatment of aldehydes **3a–d** led to the formation of α,α-disubstituted cycloheptenones **4a–d** in good to excellent isolated yields (Table 1). In general, reactions were complete within few hours. As shown with **4a** (entries 1 and 2), it was possible to decrease the catalyst loading from 10 mol% to 3 mol% without observing a decrease of isolated yield, although the reaction rate was slower. Alkyl and phenyl substituents were suitable for the reaction (entries 1–5). Moreover, silyl and benzyl ethers were also tolerated (entries 3–5). Conversely, aldehyde **3e** was not stable at room temperature, even in the absence of a catalyst, which explains the lower yield obtained with this substrate (entry 6).

A similar instability was observed with 1,3-keto-aldehyde **6** and 1,3-bisaldehyde **9** derived from oxidation of diols **5** and **8**, respectively (Schemes 3 and 4). However, it was possible to treat **6** and **9** with the optimised catalyst after only minimal purification by filtration over celite and aqueous work up using a saturated solution of $CuSO_4$,[9] respectively, enabling the rapid formation of spiro-bisketones **7** and **10** in 80% and 82% isolated yields over two steps, respectively. It is noteworthy that the bidirectional intramolecular hydroacylation of **9** into **10** represents an advantageous synthetic shortcut when compared to the longer linear sequence consisting of functional group



Scheme 3 Formation of spiro-1,3-bisketone. *Reaction conditions*: *a*: Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; *b*: $[Rh(BINAP)]BF_4$ (10 mol%),[6] acetone, 60 °C.



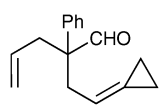
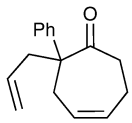
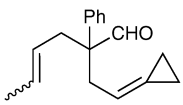
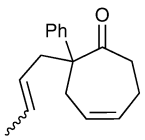
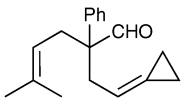
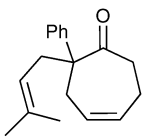
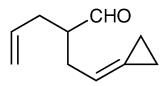
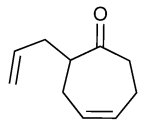
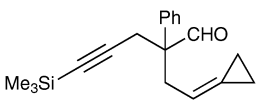
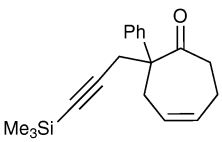
Scheme 4 Bidirectional formation of spiro-1,3-bisketone. *Reaction conditions*: *a*: $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; *b*: $[Rh((\pm)\text{-BINAP})]BF_4$ (10 mol%),[8] acetone, 21 °C, 82% over two steps; *c*: TBSCl, DMAP, Et_3N, CH_2Cl_2, 83%; *d*: $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 97%; *e*: $[Rh((\pm)\text{-BINAP})]BF_4$ (10 mol%),[8] acetone, 60 °C, 88%; *f*: TBAF, THF, 85%; *g*: $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; *h*: $[Rh((\pm)\text{-BINAP})]BF_4$ (10 mol%),[8] acetone, 60 °C, incomplete conversion.

manipulations of diol **8** into aldehyde **11**, followed by a first intramolecular hydroacylation giving ketone **12** in 88% yield, and further functional group manipulations toward **13**, which revealed itself very difficult to handle and led to irreproducible results during the second incomplete intramolecular hydroacylation toward **10**.

Having established that a tethered olefin is not required for the reaction to proceed smoothly, we then turned our attention to the study of the chemoselectivity of this reaction when several carbon–carbon multiple bonds present in the substrate are capable of undergoing intramolecular migratory insertion into the rhodium–hydrogen bond of acylhydridorhodium intermediates.

Substitution of the alkene moiety did not change the chemoselectivity initially observed with **1**. Hence, treating aldehydes **14a–c** with the rhodium catalyst at room temperature afforded cycloheptenones **15a–c** in good isolated yields (Table 2, entries 1–3). As it was the case for **9**, aldehydes **14a** and **b** obtained after Swern oxidation[10] were not purified otherwise than by $CuSO_4$ aqueous work up,[9] this procedure giving better results over two steps with those substrates. It is noteworthy that unsubstituted 4-pentenal gave the fastest turnovers in Bosnich's initial studies on intramolecular hydroacylation catalysed by cationic rhodium catalysts.[2c] Hence, the exclusive formation of cycloheptenone **15a** from **14a**, as opposed to the possible formation of a cyclopentanone, attests to the chemoselectivity of the reaction in favour of the alkylidenecyclopropane moiety. This complete chemoselectivity does not appear to depend on the substitution in the α position of the starting aldehyde, since cycloheptenone **15d** was obtained exclusively from aldehyde **14d** in much shorter time (entry 4). Finally, we examined the chemoselectivity of the reaction in the presence of an alkyne with substrate **14e**. Partial decomposition and incomplete conversion were observed after twelve hours. Nevertheless, cycloheptenone **15e** was obtained in 58% isolated yield (entry 5). Incomplete conversion and a complex mixture of products were also obtained when aldehyde **14f**, tethered to a simple methyl-substituted alkyne, was treated with $[Rh((\pm)\text{-BINAP})]BF_4$. However, using $[Rh(dppf)]BF_4$ as a catalyst restored the

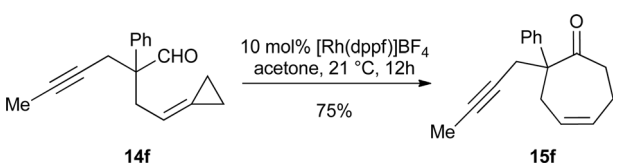
Table 2 Chemoselectivity favouring alkylidenecyclopropanes over alkenes and alkynes[a]

Entry	Substrate	Product	Yield[b] (%)
1	 **14a**	 **15a**	75[c,d]
2	 **14b** (*E*/*Z* = 5:1)	 **15b** (*E*/*Z* = 4:1)	70[c]
3	 **14c**	 **15c**	75
4	 **14d**	 **15d**	99[e]
5	 **14e**	 **15e**	58

[a] [Rh((±)-BINAP)]BF_4 (10 mol%),[8] acetone, 21 °C, 12 h. [b] Isolated yields. [c] Yield over two steps including Swern oxidation for the preparation of the aldehyde. [d] 4 h. [e] NMR yield after 1 h.

chemoselectivity and cycloheptenone **15f** was obtained in good isolated yield (Scheme 5), whilst catalysts prepared with other bisphosphines (*e.g.* dppe, dppp, dppb) were mostly inactive.[11]

In conclusion, we have demonstrated that rhodium-catalysed intramolecular hydroacylation of α,α-disubstituted 4-alkylidenecyclopropanals is a smooth process in contrast to the same reaction conducted on α,α-disubstituted 4-pentenals. In both cases, a pentarhodacycle intermediate is likely formed preferentially. This intermediate can rearrange toward productive carbon–carbon bond formation in the case of alkylidenecyclopropanals whereas decarbonylation and double bond migration are the dominant pathways in the case of 4-pentenals.[2c,7b] Moreover, the reaction is chemoselective in favour of the alkylidenecyclopropane moiety when an alkene or an alkyne are tethered to the substrate, a fact which remained to be established before the present study.



14f **15f**

Scheme 5 Alternative reaction conditions for chemoselective hydroacylation of alkylidenecyclopropanes in the presence of simple internal alkyne.

Financial support from EPSRC (DTA studentship to D.C.), City of Paris (Scholarship to C.T.), RCUK (Fellowship to C.A.), and the University of Liverpool is acknowledged. The authors are also grateful to the EPSRC National Mass Spectrometry Service Centre in Swansea for some HRMS measurements.

Notes and references

1 For reviews, see: (*a*) M. C. Willis, *Chem. Rev.*, 2010, **110**, 725; (*b*) G. C. Fu, in *Modern Rhodium-Catalyzed Organic Reactions*, ed. P. A. Evans, Wiley-VCH, New York, 2005, p. 85.

2 For selected examples, see: (*a*) K. Sakai, J. Ido, O. Oda and N. Nakamura, *Tetrahedron Lett.*, 1972, **13**, 1287; (*b*) R. C. Larock, K. Oertle and G. F. Potter, *J. Am. Chem. Soc.*, 1980, **102**, 190; (*c*) D. P. Fairlie and B. Bosnich, *Organometallics*, 1988, **7**, 936; (*d*) A. D. Aloise, M. E. Layton and M. D. Shair, *J. Am. Chem. Soc.*, 2000, **122**, 12610; (*e*) Y. Sato, Y. Oonishi and M. Mori, *Angew. Chem., Int. Ed.*, 2002, **41**, 1218; (*f*) K. Tanaka and G. C. Fu, *J. Am. Chem. Soc.*, 2001, **123**, 11492; (*g*) H. D. Bendorf, C. M. Colella, E. C. Dixon, M. Marchetti, A. N. Matunokis, J. D. Musselman and T. A. Tiley, *Tetrahedron Lett.*, 2002, **43**, 7031; (*h*) K. Takeishi, K. Sugishima, K. Sasaki and K. Tanaka, *Chem.–Eur. J.*, 2004, **10**, 5681; (*i*) M. M. Coulter, P. K. Dornan and V. M. Dong, *J. Am. Chem. Soc.*, 2009, **131**, 6932.

3 (*a*) C. Aïssa and A. Fürstner, *J. Am. Chem. Soc.*, 2007, **129**, 14836; (*b*) D. Crépin, J. Dawick and C. Aïssa, *Angew. Chem., Int. Ed.*, 2010, **49**, 620.

4 (*a*) R. Campbell Jr., C. F. Lochow, K. P. Vora and R. G. Miller, *J. Am. Chem. Soc.*, 1980, **102**, 5824–5830; (*b*) D. P. Fairlie and B. Bosnich, *Organometallics*, 1988, **7**, 946.

5 I. F. D. Hyatt, H. K. Anderson, A. T. Morehead Jr. and A. L. Sargent, *Organometallics*, 2008, **27**, 135.

6 (*a*) R. M. Beesley, C. K. Ingold and J. F. Thorpe, *J. Chem. Soc. Trans.*, 1915, **107**, 1080; (*b*) M. E. Jung and J. Gervay, *J. Am. Chem. Soc.*, 1991, **113**, 224.

7 (*a*) B. R. James and C. G. Young, *J. Chem. Soc., Chem. Commun.*, 1983, 1215; (*b*) T. Sattelkau and P. Eilbracht, *Tetrahedron Lett.*, 1998, **39**, 9647; (*c*) M. Rolandsgard, S. Baldawi, D. Sirbu, V. Bjørnstad, C. Rømming and K. Undheim, *Tetrahedron*, 2005, **61**, 4129; (*d*) S. Mukherjee and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 11336; (*e*) V. Bjørnstad and K. Undheim, *Synthesis*, 2008, 962.

8 Representative procedure: a Teflon-screw Schlenk flask equipped with a small stirring bar was charged with $[Rh(nbd)_2]BF_4$ (4.4 mg, 0.0117 mmol), (±)-BINAP (7.8 mg, 0.0117 mmol), and acetone (2.3 mL) under N_2 before bubbling H_2 (4.8 mL, 0.199 mmol) *via* a syringe before closing the flask under N_2. After stirring for 1h at room temperature, this solution was added to aldehyde **1a** (28 mg, 0.117 mmol) in another Teflon-screw Schlenk flask before closing the flask under N_2. After stirring for 12h at room temperature, the mixture was allowed to cool before evaporation. Purification by flash chromatography (petroleum ether/ethyl acetate: 250/1) gave ketone **2** (25 mg, 89%) as white solid.

9 M. L. Grachan, M. T. Tudge and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2008, **47**, 1469.

10 A. J. Mancuso, S.-L. Huang and D. Swern, *J. Org. Chem.*, 1978, **43**, 2980.

11 dppf = 1,1′- bis(diphenylphosphino)-ferrocene, dppe = 1,2-bis-(diphenylphosphino)-ethane, dppp = 1,3-bis(diphenylphosphino)-propane, dppb = 1,4-bis(diphenylphosphino)-butane. We thank one of the referees for suggesting this experiment.