JOC Article

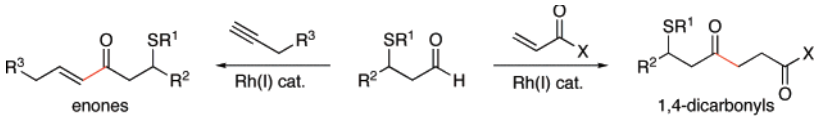
Rhodium-Catalyzed Intermolecular Chelation Controlled Alkene and Alkyne Hydroacylation: Synthetic Scope of β-*S*-Substituted Aldehyde Substrates

Michael C. Willis,*,† Helen E. Randell-Sly,† Robert L. Woodward,† Steven J. McNally,† and Gordon S. Currie‡

Department of Chemistry, University of Bath, Bath, BA2 7AY, UK and AstraZeneca, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK

m.c.willis@bath.ac.uk

Received March 16, 2006

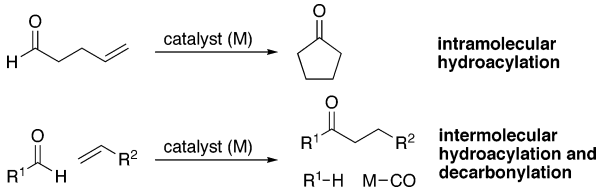


The use of β-*S*-substituted aldehydes in rhodium-catalyzed intermolecular hydroacylation reactions is reported. Aldehydes substituted with either sulfide or thioacetal groups undergo efficient hydroacylation with a variety of electron-poor alkenes, such as enoates, in Stetter-like processes and with both electron-poor and neutral alkynes. In general, the reactions with electron-poor alkenes demonstrate good selectivity for the linear regioisomer, and the reactions with alkynes provide enone products with excellent selectivity for the *E*-isomers. The scope of the process was shown to be broad, tolerating a variety of substitution patterns and functional groups on both reaction components. A novel CN-directing effect was shown to be responsible for reversing the regioselectivity in a number of alkyne hydroacylation reactions. Catalyst loadings as low as 0.1 mol % were achievable.

Introduction

Given the abundance of C−H bonds in organic molecules, the selective activation and use of these bonds in controlled synthetically useful transformations is an attractive prospect.[1] Many reactions that are based on C−H activation offer excellent opportunities for atom economy[2] and often deliver unusual reactivity that is not accessible using standard functional groups. The transition-metal-catalyzed hydroacylation (HA) of alkenes and alkynes is one such transformation.[3] Metal-catalyzed HA reactions involve the activation of the C−H bond of an aldehyde to generate an acyl-metal species and then the addition of this species across a C−C multiple bond to deliver ketone-containing products. The utility of HA reactions has been limited by the propensity of the key acyl-metal intermediates to undergo decarbonylation processes, producing reduced substrates and

SCHEME 1



carbonylated catalysts.[4] Bosnich[5] and others[6] have shown that Rh-catalyzed intramolecular HA reactions to generate cyclopentanone products are efficient processes (Scheme 1). Highly enantioselective cyclopentanone syntheses have also been developed;[7] however, the ring size of the cycloalkanone product is crucial in determining the efficiency of intramolecular reactions.[8] Simply extending the tether length between the

† University of Bath.
‡ AstraZeneca.

(1) For recent reviews on C−H activation, see: (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (c) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1699−1712. (c) *Handbook of C−H Transformations: Applications in Organic Synthesis*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005.

(2) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.

(3) Sakai, K.; Ide, J.; Oda, O.; Nakamura, N. *Tetrahedron Lett.* **1972**, 1287.

(4) (a) Lochow, C. F.; Miller, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 1281. (b) Larock, R. C.; Oertle, Potter, G. F. *J. Am. Chem. Soc.* **1980**, *102*, 190. (c) Milstein, D.; *Chem. Commun.* **1982**, 1357.

(5) (a) Fairlie, D. P.; Bosnich, B. *Organometallics* **1988**, *7*, 936. (b) Fairlie, D. P.; Bosnich, B. *Organometallics* **1988**, *7*, 946.

(6) For selected recent examples of catalytic cyclopentanone synthesis, see: (a) Gable, K. P.; Benz, G. A. *Tetrahedron Lett.* **1991**, *32*, 3473. (b) Sattelkau, T.; Eilbracht, P. *Tetrahedron Lett.* **1998**, *39*, 9647. (c) Morgan, J. P.; Kundu, K.; Doyle, M. P. *Chem. Commun.* **2005**, 3307.

10.1021/jo060582o CCC: $33.50
Published on Web 06/09/2006

aldehyde and alkene functional groups has generally been unsuccessful as a strategy to prepare larger ring systems, although the use of diene-[9] and cyclopropane-containing[10] substrates has allowed access to several enlarged ring structures. Intermolecular reactions are more challenging, with the use of high temperatures and/or pressures of CO or ethene often being needed to limit decarbonylation.[11] The synthetic utility of many systems is also limited, with aromatic aldehydes and simple unfunctionalized alkenes being the most commonly employed substrates. An exception to this is the method developed by Brookhart, who has reported the combination of a range of alkyl and aryl aldehydes with electron-rich vinyl silanes using Co(I) complexes at ambient temperatures.[12] Jun has been able to utilize alkyl and aryl aldehydes in combination with simple alkenes using catalytic Rh(I) and catalytic 2-amino-picoline at elevated temperatures (generally >100 °C).[13] The Jun methodology involves the in situ generation of aldimine intermediates, and it is proposed that chelation-stabilization of the subsequently formed iminoacyl-rhodium species is responsible for the success of these systems.

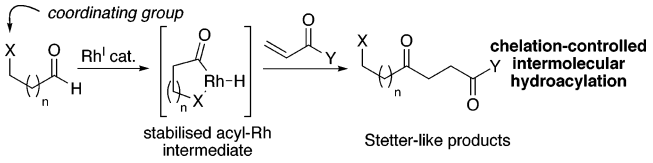
Alkyne hydroacylation has been less studied,[14] although Fu has shown that Rh-catalyzed intramolecular alkyne HA can be used to prepare cyclopentenones via the *trans*-addition of acyl-rhodium species to alkynes.[15] Desymmetrization methods have been used to allow the enantioselective synthesis of similar products.[16] More recently, Tanaka has employed 5- and 6-alkynals to access α-alklylidene-cyclopentanones and cyclohexanones.[17] Jun has also demonstrated that his aldimine methods can be used to effect intermolecular alkyne HA.[18]

The focus of the present research was the development of synthetically useful intermolecular hydroacylation methodology that could employ both alkene and alkyne substrates, tolerate a variety of functional groups, operate under mild reaction conditions, and employ low catalyst loadings.[19]

Results and Discussion

Despite the high temperatures needed in the Jun chemistry, the ability to employ a range of aldehydes in HA reactions, together with encouraging studies from Suggs,[20] Suemune,[21] and Bendorf,[22] suggested that chelation stabilization of rhodium-acyls offered the possibility of developing a more broadly applicable HA system. Our goals were to define a range of aldehydes bearing coordinating substituents that would form stable chelated intermediates and still allow the HA reaction to proceed under mild conditions (Scheme 2). Importantly, for the process to be synthetically useful, we reasoned that the coordinating group must offer the possibility of further functionalization or derivatization after the HA event. For similar reasons we wished to employ functionalized alkenes with the hope of producing more valuable products and settled on the use of enones, with synthetically useful 1,4-dicarbonyl compounds the target.[23] The transformation could then be considered as a Rh(I)-catalyzed Stetter reaction.[24]

SCHEME 2



We elected to evaluate aldehyde substrates in addition reactions with methyl acrylate (Table 1). With the possible synthetic utility in mind we first evaluated aldehydes bearing ether substituents as the coordinating group. The reaction between methyl acrylate and β-benzyloxypropanal, employing Wilkinson's complex as the catalyst, resulted in decarbonylation (entry 1).[23] Switching the catalyst to the cationic complex [Rh(dppe)]ClO_4, used extensively in intramolecular systems,[5] resulted in no reaction, attributed to catalyst deactivation due to the electron-rich aryl group of the benzyl ether (entry 2). Using a methyl ether resulted in a small amount of the desired product, but decarbonylation was by far the major pathway (entry 3). However, the use of the corresponding methyl sulfide delivered 36% of the HA adduct together with a side-product originating from Tischenko-like processes (entry 4).[25] Employing dichloroethane (DCE) as solvent and increasing the reaction temperature to 60 °C achieved a 96% conversion to product

(7) For examples of enantioselective cyclisations, see; (a) Bosnich, B. *Acc. Chem. Res.* **1998**, *31*, 667 and references therein. (b) Ducray, P.; Rousseau, B.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 3800. (c) Tanaka, M.; Imai, M.; Fujio, M.; Sakamoto, E.; Takahashi, M.; Eto-Kato, Y.; Wu, X. M.; Funakoshi, K.; Sakai, K.; Suemune, H. *J. Org. Chem.* **2000**, *65*, 5806 and references therein. (d) Kundu, K.; McCullagh, J. V.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 16042.

(8) Campbell, R. E., Jr.; Miller, R. G. *J. Organomet. Chem.* **1980**, *186*, C27. See also ref 6a.

(9) Sato, Y.; Oonishi, Y.; Mori, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1218.

(10) Aloise, A. D.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 12610.

(11) For Rh-based systems used in combination with CO or ethylene atmospheres, see: (a) Schwartz, J.; Cannon, J. B. *J. Am. Chem. Soc.* **1974**, *96*, 4721. (b) Vora, K. P.; Lochow, C. F.; Miller, R. G. *J. Organomet. Chem.* **1980**, *192*, 257. (c) Isnard, P.; Denise, B.; Sneeden, R. P. A.; Cognio, J. M.; Dural, P. *J. Organomet. Chem.* **1982**, *240*, 285. (d) Vora, K. P. *Synth. Commun.* **1983**, *13*, 99. (e) Marder, T. B.; Roe, D. C.; Milstein, D. *Organometallics* **1988**, *7*, 1451. For Ru based systems, see; (f) Kondo, T.; Tsuji, Y.; Watanabe, Y. *Tetrahedron Lett.* **1987**, *28*, 6229. (g) Kondo, T.; Akazome, M.; Tsuji, Y.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 1286. (h) Kondo, T.; Hiraishi, N.; Morisaki, Y.; Wada, K.; Watanabe, Y.; Mitsudo, T.-A. *Organometallics* **1998**, *17*, 2131.

(12) (a) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1997**, *119*, 3165. (b) Lenges, C. P.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 6965. Also see ref 11a.

(13) (a) Jun, C.-H.; Lee, D.-Y.; Lee, H.; Hong, J.-B. *Angew. Chem., Int. Ed.* **2000**, *39*, 3070. (b) Jun, C.-H.; Moon, C. W.; Lee, D.-Y. *Chem. Eur. J.* **2002**, *8*, 2423. (c) Jun, C. H.; Lee, J. H. *Pure Appl. Chem.* **2004**, *76*, 577 and references therein.

(14) (a) Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 2554. (b) Kokubo, K.; Matsumasa, K.; Nishinaka, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 303.

(15) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 11492.

(16) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10296.

(17) Takeishi, K.; Sugishima, K.; Sasaki, K.; Tanaka, K. *Chem. Eur. J.* **2004**, *10*, 5681.

(18) Jun, C.-H.; Lee, H.; Hong, J.-B.; Kwon, B.-I. *Angew. Chem., Int. Ed.* **2002**, *41*, 2146.

(19) (a) Willis, M. C.; McNally, J. S.; Beswick, P. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 340. (b) Willis, M. C.; Randell-Sly, H. E.; Woodward, R. L.; Currie, G. S. *Org. Lett.* **2005**, *7*, 2249.

(20) (a) Suggs, J. W. *J. Am. Chem. Soc.* **1978**, *100*, 640. (b) Suggs, J. W. *J. Am. Chem. Soc.* **1979**, *101*, 489.

(21) (a) Tanaka, M.; Imai, M.; Yamamoto, Y.; Tanaka, K.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *Org. Lett.* **2003**, *5*, 1365. (b) Imai, M.; Tanaka, M.; Tanaka, K.; Yamamoto, Y.; Imai-Ogata, N.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *J. Org. Chem.* **2004**, *69*, 1144.

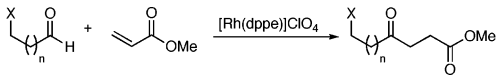
(22) Bendorf, H. D.; Colella, C. M.; Dixon, E. C.; Marchetti, M.; Matukonis, A. N.; Musselman, J. D.; Tiley, T. A. *Tetrahedron Lett.* **2002**, *43*, 7031.

(23) Willis, M. C.; Sapmaz, S. *Chem. Commun.* **2001**, 2558.

(24) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407.

(25) For the isolation of similar Tischenko products, see: (a) Bergens, S. H.; Fairlie, D. P.; Bosnich, B. *Organometallics* **1990**, *9*, 566. (b) Slough, G. A.; Ashbaugh, J. R.; Zannoni, L. A. *Organometallics*, **1994**, *13*, 3587.

TABLE 1. Aldehyde and Catalyst Evaluation[a]



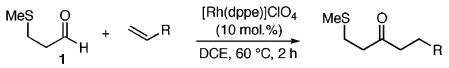
entry	aldehyde	solvent	temp. (°C)	conv. (%)[b]
1[c]		PhMe	80	0
2		CH_2Cl_2	40	0
3		CH_2Cl_2	40	9
4		CH_2Cl_2	40	36[d]
5		DCE	60	96
6		C_6H_6	60	0
7		THF	60	0
8[e]		DCE	60	91
9		DCE	60	0
10		DCE	60	0

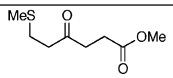
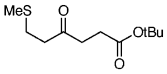
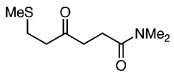
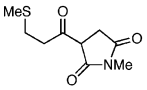
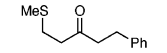
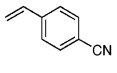
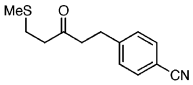
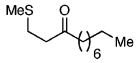
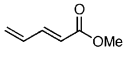
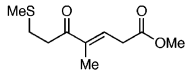
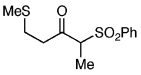
[a] Reaction conditions: catalyst (10 mol %), aldehyde (1.0 equiv), alkene (3.0 equiv). Catalysts $[Rh(dppe)]ClO_4$ and [Rh(dppe)]OTf where prepared in situ; see Supporting Information for details. [b] Determined by ^1H NMR. [c] $RhCl(PPh_3)_3$ used as catalyst. [d] Along with 27% Tischenko dimerization product (see ref 19a). [e] [Rh(dppe)]OTf used as catalyst.

(entry 5). Using benzene or THF as solvent completely suppressed the reaction (entries 6 and 7). Variation of the catalyst counterion has been shown to effect reaction efficiency in several intramolecular reactions;[10] however, using the triflate counterion in place of perchlorate had minimal effect in the present system (entry 8). Finally, we explored sulfide-substituted aldehydes that would lead to four- and six-membered chelates; however, neither delivered any of the desired products (entries 9 and 10).

With optimized conditions for the union of methyl sulfide substituted aldehyde **1** and methyl acrylate available, we next explored the scope of the process with respect to the alkene component (Table 2). A variety of functionalized alkenes could be employed, with ester, amide, and imide groups all being tolerated well (entries 1−4). Although styrene was a poor substrate, the more electron-poor 4-cyanostyrene delivered the HA adduct in good yield as a single regioisomer (entries 5 and 6). Simple, unfunctionalized alkenes are poor substrates, with significant decarbonylation occurring; octene provided the desired adduct in only 33% yield (entry 7). Dienyl substrates can been employed, with methyl pentadienoate providing the isomerized adduct in good yield (entry 8). Finally, sulfone functionality is also tolerated, with the adduct of aldehyde **1** and phenyl vinyl sulfone being isolated in 84% yield (entry 9). The sulfone adduct was obtained exclusively as the branched isomer. The reason for this difference in regioselectivity is unknown, although stabilization of an α-rhodium species by interaction with the sulfone group is a possibility. Enones are one class of electron-poor alkenes that as yet will not undergo HA reactions with β-sulfide-substituted aldehydes, instead favoring reaction along a reductive aldol pathway.[26] Acrylonitrile undergoes similar aldol chemistry. Disubstituted electron-poor

TABLE 2. Reaction of Aldehyde 1 with Various Alkenes[a]



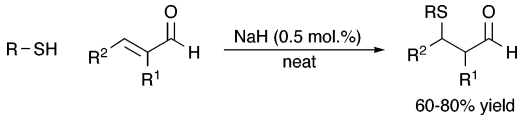
entry	alkene	product	l:b[b]	conv. (%)[b]	yield (%)[c]
1			4:1	96	71
2			5:1	95	81
3			20:1	90	82
4			-	91	73
5			20:1	64	41
6			20:1	77	66
7			20:1	50	33
8			10:1	65	45
9			20:1	100	84

[a] Reaction conditions: catalyst (10 mol %), aldehyde (1.0 equiv), alkene (5.0 equiv). [b] Regioselectivity (linear:branched), determined by ^1H NMR. [c] Isolated yield of pure regioisomer.

alkenes are also not effective substrates, with the introduction of α- or β-substituents resulting in no reaction.[27]

With good tolerance of alkene functional groups demonstrated in the reaction with aldehyde **1**, we wished to show that a variety of β-sulfide-substituted aldehydes would also function as HA substrates. The required aldehydes were readily prepared using a procedure based on that of Weber, involving the direct addition of a thiol to the relevant enal using catalytic sodium hydride (Scheme 3).[28] Variation of the sulfide group and the incorporation of α- and β-substituents were possible using this method.

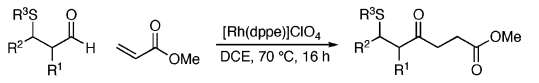
SCHEME 3

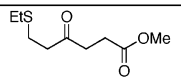
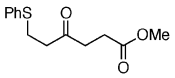
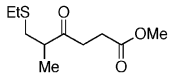
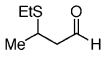
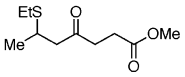
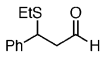
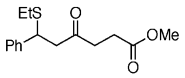
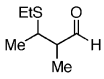
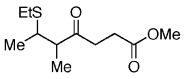


The substituted aldehydes were evaluated in the reaction with methyl acrylate (Table 3). Variation of the sulfide group from Me to Et and Ph resulted in minimal effect on the efficiency of the process, although the larger substituents provided a more regioselective process (entries 1 and 2). Single α- or β-substituents were also tolerated well (entries 3−5). Finally, the α,β-disubstituted aldehyde used in entry 6 delivered the expected HA adduct in good yield after increased reaction time.

(26) Willis, M. C.; Woodward, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 18012.
(27) For example, reaction with either methyl crotonate or methyl methacrylate resulted in no reaction.
(28) Weber, H. Patent DE855704, 1952.

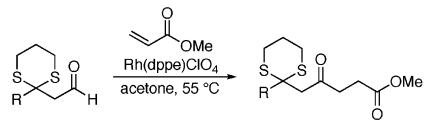
TABLE 3. Variation of β-Sulfide-Substituted Aldehyde Structure[a]

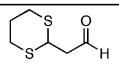
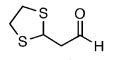
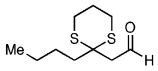
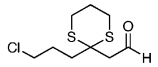
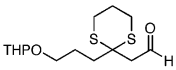
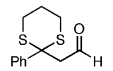
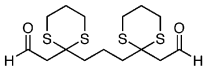


entry	aldehyde	product	l:b[b]	yield[c] (%)
1			6:1	80
2			20:1	92
3			20:1	83
4			20:1	77
5			20:1	87
6[d]			20:1	76[e,f]

[a] Reaction conditions: catalyst (10 mol %), aldehyde (1.0 equiv), methyl acrylate (3.0 equiv). [b] Determined by ^{1}H NMR. [c] Isolated yields. [d] Used as a 1:1 mixture of diastereomers. [e] Required 20 h reaction time. [f] Obtained as a 1:1 mixture of diastereomers.

TABLE 4. Scope of β-Thioacetal-Substituted Aldehydes[a]

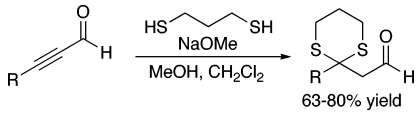


entry		aldehyde	time (h)	yield (%)[b,c]
1	**2a**		2	74
2	**2b**		4	71
3	**2c**		18	77
4	**2d**		18	72
5	**2e**		18	70
6	**2f**		18	0
7	**2g**		8	84

[a] Reaction conditions: aldehyde (1.0 equiv), methyl acrylate (4.0 equiv), catalyst (10 mol %), acetone, 50 °C. [b] Isolated yields. [c] Only linear isomers observed.

One of the initial aims of the project was to utilize aldehydes with substituents that could be readily functionalized after the HA reaction. Although there are a number of transformations available for sulfide groups, we sought a coordinating group that would offer more opportunities for synthetically useful functionalization. With the need to maintain a five-membered *S*-chelate we settled on the use of β-thioacetal-substituted aldehydes. The required aldehydes were readily available by the direct addition of a dithiol to the relevant ynal or in a two-step procedure by addition to an ynoate followed by reduction (Scheme 4).[29]

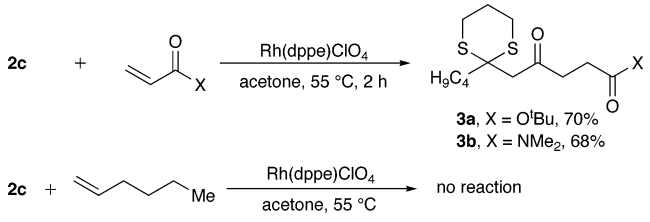
SCHEME 4



To determine the utility of the thioacetal-substituted aldehydes we evaluated their coupling reactions with methyl acrylate using the standard catalyst (Table 4).[30] Both dithiane- and dithiolane-substituted aldehydes delivered the desired HA adducts in good yields (entries 1 and 2). The products from both aldehydes were obtained as single linear regioisomers. This correlates with the use of the EtS- and PhS-substituted aldehydes (Table 3) in which the larger the substituent, the more selective the reaction for the linear adduct. Having established that β-thioacetal-substituted aldehydes undergo efficient HA reactions, we evaluated the range of additional functionality that could be incorporated. Simple alkyl chains, chloro-substituents, and acetal-protected alcohols were all tolerated well, delivering HA adducts in good yields as single regioisomers (entries 3−5). In general, the reactions employing these aldehydes required longer reaction times compared to the unsubstituted-thioacetal examples or the sulfide-substituted aldehydes. The reaction failed when a Ph-substituent was introduced to the aldehyde, presumably as a result of the greater steric bulk (entry 6). The final example demonstrates that a double HA reaction is possible if a bis-aldehyde is used as the substrate (entry 7).

The reduced reactivity of the thioacetal-substituted aldehydes, compared to their sulfide counterparts, affected the range of alkenes that could be used. Although variation of the ester group and the use of simple amides was possible, reaction with alternative electron-poor alkenes was prohibitively slow (Scheme 5).[31] Reactions with simple alkenes (i.e., 1-octene) were also unsuccessful.

SCHEME 5



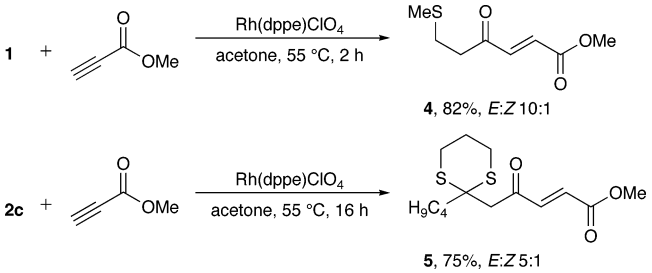
For HA reactions using alkene substrates there is the possibility of forming linear and branched isomers of the adduct. In the vast majority of examples involving β-*S*-substituted aldehydes, we observe good selectivity for the linear isomer.

(29) (a) Gaunt, M. J.; Sneddon, H. F.; Hewitt, P. R.; Orsini, P.; Hook, D. F.; Ley, S. V. *Org. Biomol. Chem.* **2003**, *1*, 15. (b) Sneddon, H. F.; Gaunt, M. J.; Ley, S. V. *Org. Lett.* **2003**, *5*, 1147. (c) Kuroda, H.; Tomita, I.; Endo, T. *Synth. Commun.* **1996**, *26*, 1539. (d) Ranu, B. C.; Bhar, S.; Chakraborti, R. *J. Org. Chem.* **1992**, *57*, 7349.

(30) Acetone is used as solvent as it allows easier generation of the catalyst due to a more pronounced color change. Reactions in DCE are also possible and give comparable results.

(31) For example, reaction with either phenyl vinyl sulfone or 4-cyanostyrene were unsuccessful.

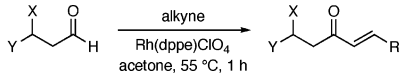
SCHEME 6

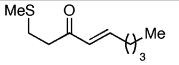
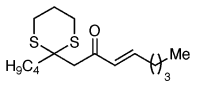
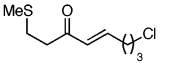
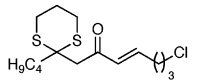
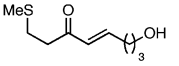
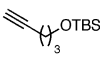
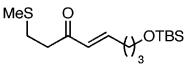
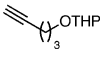
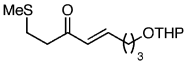
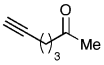
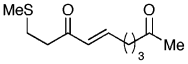
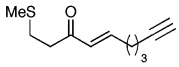
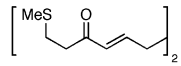
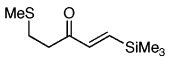
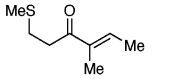
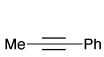
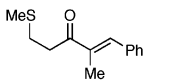
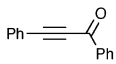
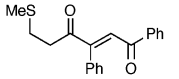
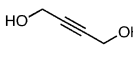
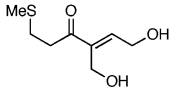
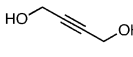
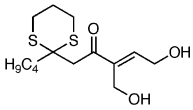
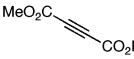
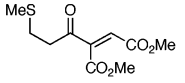
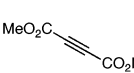
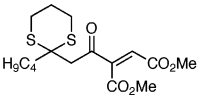


For reactions that employ alkyne substrates, there is the added possibility of the formation of *E*- and *Z*-geometrical isomers. We initially studied the reaction of a prototypical electron-poor alkyne, ethyl propynoate, with sulfide-substituted aldehyde **1** and thio-acetal-substituted aldehyde **2c** (Scheme 6). In both cases the linear regioisomers were produced in good yield with good to moderate selectivity for the *E*-isomer.

The synthetic utility of the enone products obtained from alkyne HA reactions prompted us to explore the scope of the process with respect to the alkyne unit (Table 5). A key difference between HA reactions employing alkynes, compared to alkenes, is that neutral alkynes (as opposed to electron-poor) are excellent substrates in reactions with *β*-*S*-substituted aldehydes. For example, the reaction of 1-hexyne with both aldehydes **1** and **2c** delivered the desired HA adducts in good yields as single isomers (entries 1 and 2). The selectivity for the formation of the liner regioisomers presumably arises from addition of the relatively large rhodium-acyl unit to the nonsubstituted end of the alkyne. The observed *E*-selectivity follows from a *syn*-addition of the rhodium-acyl and hydrogen atom to the alkyne. The ability to employ electronically neutral alkynes allowed a variety of functional groups to be incorporated into the HA process. For example, alkynes bearing chloro-substituents, free hydroxy groups, silyl ethers, THP ethers, and remote ketone groups could all be employed (entries 3−8). Reaction of a bis-alkyne (2 equiv) with aldehyde **1** provided the mono-coupled adduct in good yield (entry 9). The double HA adduct could be obtained by combining 0.5 equiv of bis-alkyne with the same aldehyde (entry 10). Synthetically useful vinylsilanes could be prepared efficiently by using trimethylsilylethyne as the coupling partner (entry 11). Internal alkynes can also be employed; for example, reaction of aldehyde **1** with 2-butyne provided the *E*-configured product in good yield (entry 12). Single regioisomers of products could also be obtained when unsymmetrical internal alkynes were used, with both sterically and electronically demanding groups proving to be effective control elements (entries 13 and 14). Entries 15 and 16 demonstrate that 2-butyne-1,4-diol can be effectively employed as a substrate in combination with both aldehydes **1** and **2c**, providing the corresponding diol-containing enone adducts in excellent yields as single isomers. Dimethyl acetylene dicarboxylate was the only internal alkyne to provide mixtures of isomers; the products from reaction with aldehyde **1** and **2c** were obtained as 2:1 and 3:1 mixtures, respectively (entries 17 and 18). The production of these mixtures correlates with the reactions between aldehydes **1** and **2c** and methyl propionate (Scheme 6), reactions that, although to a lesser extent, both produced mixtures of isomers. Experiments subjecting isolated pure *E*-isomers of product (Table 5, entries 17 and 18) to the reaction conditions have established that an *E*-to-*Z* isomerization does not take place during the reaction. Taken together, these reactions suggest that for alkynes conjugated directly with ester groups, the usual *syn*-addition of the acyl-rhodium species is not necessarily the only mechanism in operation.[32]

TABLE 5. Scope of Alkyne Component in HA Reactions with *β*-*S*-Aldehydes[a]

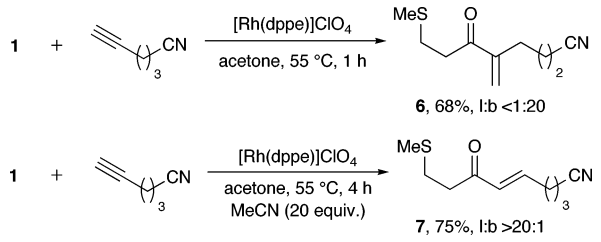


entry	aldehyde	alkyne	product	Yield (%)[c]
1	**1**			95
2[d]	**2c**			75
3	**1**			85
4[d]	**2c**			73
5	**1**			95
6	**1**			89
7	**1**			93
8	**1**			69
9	**1**			74
10[e]	**1**			60
11	**1**			89
12[d]	**1**			76
13[d]	**1**			67
14[d]	**1**			66
15[d]	**1**			75
16[d]	**2c**			83
17[d]	**1**			75[f]
18[d]	**2c**			71[g]

[a] Reaction conditions: catalyst (5 mol %), aldehyde (1.0 equiv), alkyne (2.0 equiv). [b] Determined by ^{1}H NMR. [c] Isolated yield of pure regioisomer. [d] 16 h reaction time. [e] 0.5 equiv of alkyne employed. [f] A 2:1 mixture of *Z*:*E* isomers. [g] A 3:1 mixture of *Z*:*E* isomers.

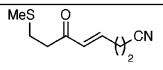
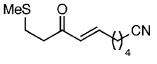
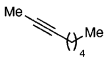
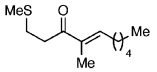
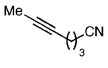
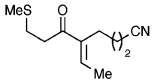
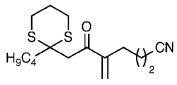
All of the reactions employing alkyl-substituted terminal alkynes delivered products as single regioisomers of *E*-config-

SCHEME 7



uration. We discovered an exception to this when 5-hexynenitrile was used in the reaction with methyl sulfide substituted aldehyde **1**, with the HA adduct being obtained with excellent selectivity for the branched regioisomer **6** (Scheme 7). We reasoned that this reversal in selectivity was due to coordination of the nitrile group to the rhodium center, with this interaction directing the rhodium-acyl to the 2-position of the alkyne. Support for this hypothesis was gained when the reaction was repeated using identical conditions but including 20 equiv of acetonitrile; the linear isomer **7** was obtained in 75% yield as a single product.

TABLE 6. Scope of Nitrile-Directing Effects in Alkyne HA Reactions[a]

entry	aldehyde	alkyne	product	l:b[b]	yield (%)[c]
1	**1**			1.5:1	77
2	**1**			1.5:1	81
3	**1**			3:1[d]	58
4	**1**			1:3.5[d]	70
5	**2c**			1:>20	68

[a] Reaction conditions: [Rh(dppe)]ClO_4 (5 mol %), aldehyde (1.0 equiv), alkyne (2.5 equiv), acetone, 55 °C. [b] Determined by ^1H NMR. [c] Isolated yield. [d] Only geometrical isomer observed.

Reports of remote nitrile substituents directing the stereo- or regioselectivity of transition-metal-catalyzed transformations are rare.[33,34] We undertook a brief study to determine the parameters over which the directing effect operated for our HA system (Table 6). When 4-propynenitrile and 6-heptynenitrile were reacted with aldehyde **1**, a less pronounced but still significant directing effect was observed, with both adducts being obtained as 1.5:1 mixtures of isomers in favor of the linear compound (entries 1 and 2). We were interested as to whether a similar directing effect would operate for internal alkynes. To establish a background selectivity for a nonsymmetrical dialkyl-substituted alkyne, we reacted 2-octyne with aldehyde **1**; the HA adduct was obtained as a 3:1 mixture of linear/branched regioisomers. When the 7-nitrile-substituted variant of this internal alkyne was reacted, the selectivity was reversed, to provide the adduct as a 3.5:1 mixture of isomers in favor of the branched compound (entry 4). Finally, we established that the directing effect was not limited to aldehyde **1**, with the reaction between aldehyde **2c** and 5-hexynenitrile providing the branched isomer with high selectivity (entry 5).

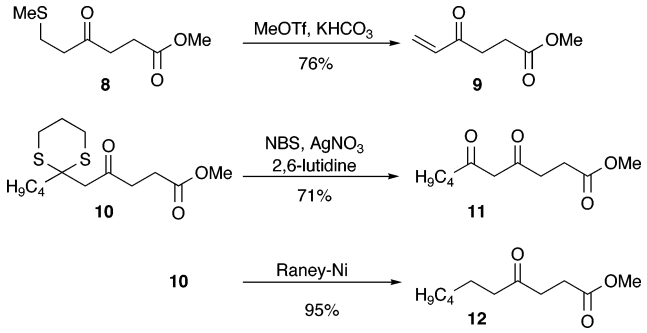
TABLE 7. Effect of Catalyst Loading on Reaction Time[a]

entry	aldehyde	alkene/ alkyne	cat. mol.%	time (h)	yield (%)[b]
1	**2a**		10	1	82
2	**2a**		2.5	12	71
3	**2a**		1	24	71
4	**1**		5	1	98
5[c]	**1**		5	1	93
6	**1**		1	17	81
7	**1**		0.1	36	78

[a] Reaction conditions: [Rh(dppe)]ClO_4, aldehyde (1.0 equiv), alkene (3.0 equiv) or alkyne (2.5 equiv). [b] Isolated yield. [c] Reaction conducted at 25 °C.

In all of the transformations discussed so far, catalyst loadings have been either 5 or 10 mol %. These loadings were selected as they allow convenient reaction times at moderate temperatures (usually 2−6 h at 50−65 °C). However, for larger scale reactions it was important that the catalyst loadings could be reduced. By extending the reaction times it was possible to significantly lower the catalyst loadings. Table 7 documents catalyst loadings against reaction time for an alkene and an alkyne HA system. As the final entry shows, for the more reactive alkyne reactions it is possible to use loadings as low as 0.1 mol % and still obtain the product in good yield. Loadings of 1.0 mol % represents the limit for reactions employing the less reactive methyl acrylate. For the alkyne substrates it is also possible to conduct the reactions with almost equal efficiency at lower temperatures. For example, the reaction between aldehyde **1** and 1-hexyne performed at 25 °C delivers the HA adduct in 93% (entry 5).

SCHEME 8



For synthetic utility it was important to demonstrate that the *β*-*S*-substituents could be modified after the key HA reactions. For the simple sulfide-substituted products this was achieved by effecting elimination. For example, sulfide **8** was treated with methyltriflate and potassium bicarbonate to deliver enone **9** in 76% yield (Scheme 8). There are many possibilities for derivatization of dithiane groups;[35] we have shown that hy-

(32) Experiments investigating this unusual selectivity are underway.

(33) For a review on directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(34) For the use of an *o*-nitrile group to direct ruthenium-catalyzed C−H functionalisation, see: Kakiuchi, F.; Sonoda, M.; Tsujimoto, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1999**, 1083.

drolysis using NBS and silver nitrate and reduction using Raney-nickel are both efficient processes on HA adduct **10**, providing diketone **11** and ketone **12**, respectiviely.

Conclusion

We have shown that aldehydes bearing a β-sulfide or β-thioacetal group are excellent substrates for intermolecular hydroacylation reactions. Electron-poor alkenes and both neutral and electron-poor alkynes serve as reaction partners to provide ketone-containing adducts in good yields with generally high levels of regio- and geometrical control. The mild reaction conditions, low catalyst loadings and excellent tolerance of both reactants to the introduction of functional groups combine to produce a synthetically useful hydroacylation system. The good reactivity of all of the β-*S*-substituted aldehydes described with electron-poor alkenes suggests that the corresponding acyl rhodium intermediates can be considered as acyl-anion equivalents. Studies aimed at exploring the further reactivity of these intermediates, developing asymmetric variants of the HA reaction, and investigating the mechanisms responsible for the regioselectivity of the process are underway.

Experimental Section

Procedures for three representative HA reactions employing combinations of different reaction partners are provided:

6-Ethylsulfanyl-4-oxo-6-phenyl-hexanoic Acid Methyl Ester (Table 3, entry 5). Acetone (2.0 mL) was added under argon to precatalyst [Rh(nbd)(dppe)]ClO_4 (5 mg, 0.0075 mmol). The catalyst was activated in situ by bubbling H_2 gas though the solution for 2 min until an orange to yellow color change was observed. After this time the solution was purged with argon. 3-Ethylsulfanyl-3-phenyl-propionaldehyde (29 mg, 0.15 mmol) was added to the resulting solution, followed by methyl acrylate (67 μL, 0.45 mmol). The resulting mixture was stirred and heated at 55 °C for 16 h. After this time the solution was concentrated in vacuo and purified by flash chromatography (20% EtOAc−hexane) to provide the ester product (37 mg, 87%). ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.29−7.12 (m, 5H), 4.29 (t, J = 7.3 Hz, 1H), 3.56 (s, 3H), 2.93 (d, J = 7.3 Hz, 2H), 2.71−2.43 (m, 4H), 2.30−2.18 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 205.2, 172.5, 141.4, 128.1 (2 CH), 127.2 (2 CH), 126.8, 51.3, 48.8, 43.3, 37.5, 27.1, 24.9, 13.9. IR (film): 3060, 1709, 1658, 1411, 1252, 903, 718 cm^{-1}. HRMS calcd for $C_{15}H_{20}O_3S$ $[M]^+$ 280.1128, found 280.1126.

(35) For a review on the applications of 1,3-dithianes in synthesis, see: Yus, M.; Najera, C.; Foubelo, F. *Tetrahedron* **2003**, 59, 6147.

1-(2-Butyl-[1,3]dithiane-2-yl)-oct-3-en-2-one (Table 5, entry 2). Acetone (2.0 mL) was added under argon to precatalyst [Rh-(nbd)(dppe)]ClO_4 (10 mg, 0.015 mmol). The catalyst was activated in situ by bubbling H_2 gas though the solution for 2 min until an orange to yellow color change was observed. After this time the solution was purged with argon. Aldehyde **2c** (30 mg, 0.13 mmol) was added to the resulting solution, followed by 1-hexyne (108 μL, 0.45 mmol). The resulting mixture was stirred and heated at 55 °C for 16 h. After this time the solution was concentrated in vacuo and purified by flash chromatography (20% EtOAc−hexane) to provide the enone product (31 mg, 75%). ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.80 (dt, J = 15.6, 6.9 Hz, 1H), 6.12 (dt, J = 15.6, 1.5 Hz, 1H), 3.06 (s, 2H), 2.82−2.77 (m, 4H), 2.15 (tdd, J = 7.0, 6.9, 1.4 Hz, 2H), 2.05−1.85 (m, 4H), 1.47−1.19 (m, 8H), 0.86 (t, J = 7.2 Hz, 3H), 0.84 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 196.4, 148.3, 131.4, 51.6, 47.8, 38.9, 32.6, 30.6, 26.9 (2 CH_2), 26.8, 25.5, 23.3, 22.7, 14.4, 14.2. IR (film): 2970, 1742, 1447, 1373, 1240, 1047 cm^{-1}. HRMS calcd for $C_{16}H_{29}OS_2$ $[M + H]^+$ 301.1651, found 301.1654.

1-Methylsulfanyl-5-phenyl-hex-4-en-3-one (Table 5, entry 13). Acetone (1.5 mL) was added under argon to precatalyst [Rh(nbd)-(dppe)]ClO_4 (5 mg, 0.0075 mmol). The catalyst was activated in situ by bubbling H_2 gas though the solution for 2 min until an orange to yellow color change was observed. After this time the solution was purged with argon. 3-Methylsulfanyl propanal **1** (15 μL, 0.15 mmol) was added to the resulting solution, followed by 1-phenyl-1-propyne (56 μL, 0.45 mmol). The resulting mixture was stirred and heated at 55 °C for 16 h. After this time the solution was concentrated in vacuo and purified by flash chromatography (20% EtOAc−hexane) to provide the enone product (22 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 1.4 Hz 1H), 7.43−7.35 (m, 5H), 3.14 (t, J = 7.6 Hz, 2H), 2.85 (t, J = 7.6 Hz, 2H), 2.17 (s, 3H), 2.07 (d, J = 1.4 Hz 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.2, 138.8, 137.0, 135.5, 129.5 (2CH), 128.4, 128.3 (2CH), 37.4, 28.9, 15.7, 12.9. IR (film): 2916, 2346, 1668, 1647, 1432, 1267, 1047, 728 cm^{-1}. HRMS calcd for $C_9H_{16}O_3S$ $[M + H]^+$ 221.0995, found 221.0996.

Acknowledgment. This work was supported by the EPSRC, AstraZeneca and GlaxoSmithKline. The EPSRC Mass Spectrometry Service at the University of Wales Swansea is also thanked for their assistance.

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

JO060582O