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Rhodium-Catalysed Intermolecular Alkyne Hydroacylation: The Enantioselective Synthesis of α- and β-Substituted Ketones by Kinetic Resolution

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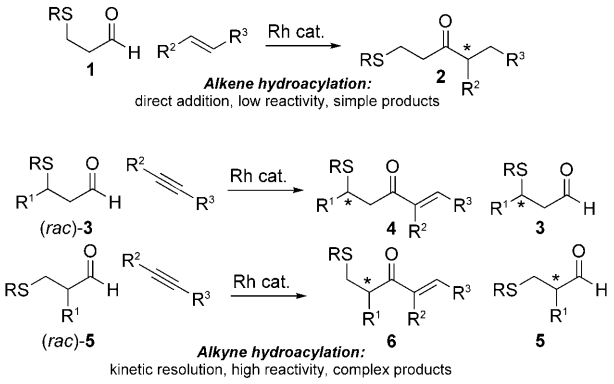
The potential utility of transition-metal-catalysed alkene and alkyne hydroacylation reactions—readily available substrates, synthetically useful products and inherently atom economic processes—has resulted in considerable interest in these transformations over the last decade.[1] During this time one of the main goals has been to develop efficient intermolecular variants that do not suffer decarbonylation. Stabilisation of key reaction intermediates by the use of chelating substrates has proven to be one successful approach,[2,3] albeit with certain substrate constraints remaining. In addition, a number of methods that avoid the need for chelation control have also been described.[4] Recently, attention has turned to the development of enantioselective variants of these processes, and although a number of intramolecular reactions are known,[5] examples of intermolecular transformations remain scarce. The enantioselective intermolecular reactions that have been reported all require specific substrate combinations: Bolm and Stemmler were the first to report an enantioselective intermolecular reaction; they employed norbornene-type alkenes in combination with salicylaldehyde derivatives to obtain varied selectivities and yields.[6] Suemune et al. have combined salicylaldehyde derivatives with dienes in a process that proceeds with moderate to good enantioselectivities but mixed regiocontrol.[7] Tanaka and Shibata have developed a highly enantioselective intermolecular process that requires the use of 1,1-substituted acrylamide derivatives as the alkene component.[8] Our own laboratory has also been active in this area and reported an enantioselective allene hydroacylation process that employed β-*S*-substituted aldehydes.[9,10] It follows that the need to employ specific substrate classes results in the formation of products with only limited substitution patterns.

The constraints in substrate choice needed to achieve an enantioselective intermolecular hydroacylation reaction result mainly from the relatively poor reactivity of disubstituted alkenes in these types of processes.[11] We postulated that the greater reactivity of alkyne substrates could result in a more general asymmetric process; however, to deliver products incorporating a stereogenic centre the reactions would need to operate as kinetic resolutions,[12] employing appropriately substituted, and racemic, aldehydes (Scheme 1). In addition to the greater reactivity we hoped to achieve by employing alkyne substrates, the proposed kinetic resolutions would also deliver more complex enone-containing products (compare **1**→**2** with **3**→**4** and **5**→**6**, Scheme 1). Although enantioselective intramolecular alkyne



Scheme 1. Enantioselective catalysis in alkene and alkyne hydroacylation reactions.

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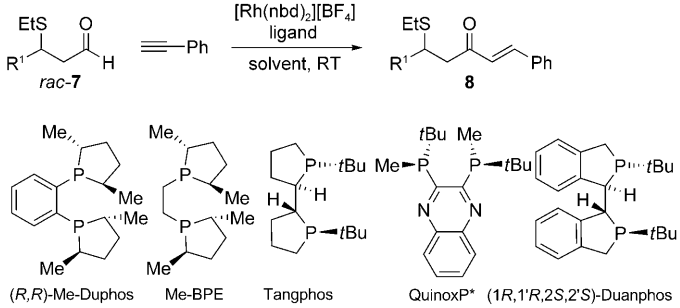
hydroacylation reactions have been described, as both kinetic resolutions and desymmetrisations,[13] there are no examples of the corresponding intermolecular reactions. Herein, we describe an effective alkyne-based kinetic resolution and demonstrate that both α- and β-substituted *S*-chelating aldehydes can be converted to the corresponding enones with high levels of selectivity.

Our initial investigation focused on the combination of 3-(ethylthio)butanal (**7a**) and phenylacetylene to obtain the unsaturated ketone **8a** (Table 1). Reactions were performed in DCE at room temperature and employed 5 mol% of a chiral Rh-catalyst, generated in situ from the combination of a diphosphine ligand and $[Rh(nbd)_2][BF_4]$ (nbd = norbornadiene) followed by hydrogenation. Several chiral bidentate phosphine ligands were employed, commencing with Me-Duphos, which was the optimal ligand in our enantioselective allene hydroacylation chemistry. When using Me-Duphos, ketone **8a** was obtained with a promising 82:18 e.r. and in a good yield (Table 1, entry 1).[14] Alternative Duphos ligands gave lower selectivity and/or reactivity (Table 1, entries 2 and 3); for example, with the bulky *i*Pr-Duphos only starting material was recovered. The related, ethylene-bridged diphosphine, Me-BPE, was also investigated, but gave no reaction (Table 1, entry 4). Both Tangphos[15] and QuinoxP*[16] gave good reactivity, but diminished selectivities relative to Me-Duphos (Table 1, entries 5 and 6). By using a preformed catalyst incorporating Me-Duphos, and performing the reaction at 0°C, the product was isolated in 40% yield with 85:15 e.r. (Table 1, entry 7). Finally, the use of the diphosphine Duanphos, recently used in ketone and ketoxime hydroacylation,[17,18] delivered material with 86:14 e.r. in 45% yield (Table 1, entry 8). Both Me-Duphos and Duanphos were then evaluated against the β-phenyl-substituted aldehyde **7b** in combination with phenylacetylene; Me-Duphos was found to generate the most effective catalyst for the aryl-substituted aldehyde, delivering the ketone product (**8b**) in 47% yield with an e.r. of 94:6 (Table 1, entries 9 and 10). The two most successful reactions in this series, employing Duanphos for the Me-substituted aldehyde (Table 1, entry 8), and Me-Duphos for the aryl aldehyde (Table 1, entry 9), were used to calculate representative selectivity factors for the process; $s = 13$ and 45, for the respective reactions.[19]

Table 1. Hydroacylation between *rac*-β-substituted aldehydes **7a**, **7b** and phenylacetylene.[a]



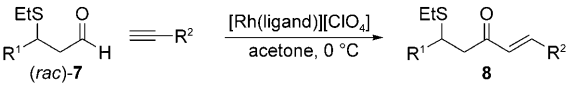
Entry	R^1	Ligand	Solvent[b]	Yield [%][c]	e.r.[d]
1	Me	Me-Duphos	DCE	45	82:18
2	Me	Et-Duphos	DCE	39	75:25
3	Me	*i*Pr-Duphos	DCE	0	–
4	Me	Me-BPE	DCE	0	–
5	Me	Tangphos	DCE	36	69:31
6	Me	QuinoxP*	DCE	47	79:21
7[e]	Me	Me-Duphos	DCE	40	85:15
8[e,f]	Me	Duanphos	acetone	45	86:14 ($s = 13$)
9[e,f]	Ph	Me-Duphos	DCE	47	94:6 ($s = 45$)
10[e]	Ph	Duanphos	acetone	45	86:14

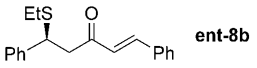
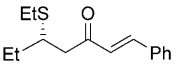
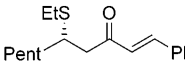
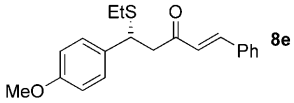
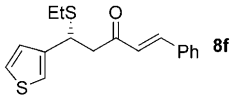
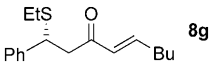
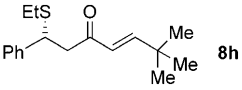
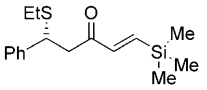
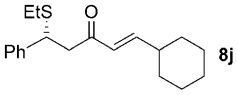
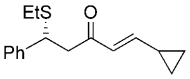
[a] Conditions: aldehyde (2.0 equiv), alkyne (1 equiv), $[Rh(nbd)_2][BF_4]$ (5 mol%), ligand (5 mol%), solvent, RT, 12 h. Catalysts activated by H_2. [b] DCE = dichloroethane. [c] Isolated yields. [d] The enantiomeric ratio (e.r.) was determined by chiral HPLC. [e] Preformed catalyst (5 mol%) was used and the reaction was performed at 0°C. [f] Selectivity factors (*s*) were calculated by using conversions and e.r. values of the ketone products.

Next we explored the generality of the reaction against a variety of β-substituted thioaldehydes **7b–f** and acetylenes (Table 2). The substituted aldehydes were easily prepared by a Et_3N-catalysed 1,4-addition of ethane thiol to the appropriate enal. All reactions were performed at 0°C by using acetone as solvent. Both the ethyl- and pentyl-substituted aldehydes were combined with phenylacetylene employing a Duanphos catalyst and performed similarly to the parent methyl aldehyde (91:9 and 88:12 e.r., respectively; Table 2, entries 2 and 3). For the remaining entries, which all feature aryl-substituted aldehydes, Me-Duphos catalysts were used. The results in Table 2, entries 4 and 5 demonstrate that a second aryl-substituted aldehyde, as well as a heteroaryl derivative, can be combined with phenylacetylene with good yields and selectivities. The next five entries illustrate that variation in the acetylene is also possible, with *n*-alkyl, *tert*-alkyl, cycloalkyl- and silyl-substituted examples all delivering the expected ketone products with high selectivities.

Having established an effective protocol for the kinetic resolution of β-substituted aldehydes, we turned our attention to the corresponding α-substituted substrates (Table 3). Reaction of the α-phenyl-substituted aldehyde (**9a**) with phenylacetylene was achieved by using a Me-Duphos-containing catalyst and delivered the enone product in 39% yield with an e.r. of 94:6 (Table 3, entry 1). The calculated selectivity factor for this reaction is $s = 34$.[19] Pleasingly, this level of selectivity demonstrated that the same catalyst system was effective for both the α- and β-substituted aldehydes. The remaining examples in Table 3 illustrate that variation of both the aldehyde and acetylene substituents is possible, while still maintaining high yields and selectivities. The exception is the *tert*-butyl-substituted aldehyde (**9c**), which although delivering the enone product in reasonable yield (43%), resulted in a reduced e.r. of 84:16 (Table 3, entry 3). As with the β-substituted aldehydes, all reactions with the α-substituted aldehyde substrates were performed at 0°C.

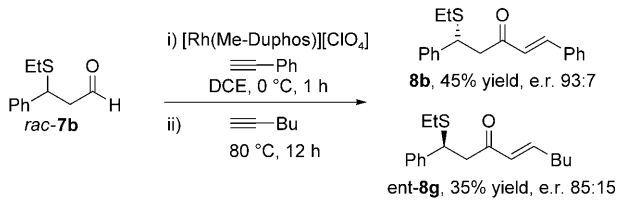
Table 2. Scope of alkyne hydroacylations employing *rac*-β-substituted aldehydes.[a]



Entry	R^1	R^2	Product	Yield [%][b]	e.r.[c]	s[d]
1[e,f]	Ph (**7b**)	Ph	 **ent-8b**	47	96:4	45
2[g]	Et (**7c**)	Ph	 **8c**	37	91:9	17
3[g]	Pent (**7d**)	Ph	 **8d**	34	88:12	12
4	4-MeO-Ph (**7e**)	Ph	 **8e**	42	87:13	12
5[e]	3-thienyl (**7f**)	Ph	 **8f**	40	90:10	16
6	Ph (**7b**)	Bu	 **8g**	48	92:8	30
7	Ph (**7b**)	*t*Bu	 **8h**	47	93:7	37
8	Ph (**7b**)	TMS	 **8i**	42	94:6	33
9	Ph (**7b**)	Cy	 **8j**	44	92:8	24
10	Ph (**7b**)	Cp	 **8k**	30	95:5	29

[a] Conditions: aldehyde (2.0 equiv), alkyne (1 equiv), [Rh(ligand)][ClO_4] (5 mol%), DCE, 0°C, 12 h. Catalyst generated in situ from [Rh(ligand)(nbd)][ClO_4] and H_2. Alkyl aldehydes used (1*R*,1′*R*,2*S*,2′*S*)-Duanphos; aryl aldehydes used (*R*,*R*)-Me-Duphos. [b] Isolated yields. [c] The e.r. values were determined by chiral HPLC. [d] Selectivity factors (s) were calculated by using conversions and e.r. values of the ketone products. [e] Absolute configuration determined by X-ray crystallography.[20] All other configurations are assigned by analogy. [f] (*S*,*S*)-Me-Duphos employed. [g] Acetone used as solvent.

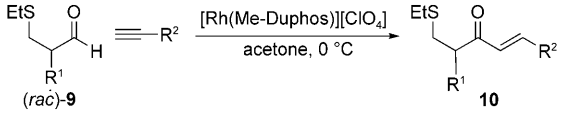
The primary focus of our investigation was to develop alkyne hydroacylation reactions to deliver complex enantiomerically enriched ketone products in good yields; the results presented in Tables 2 and 3 demonstrate that we have been successful in achieving this goal. However, apart from the desired ketone products, the kinetic resolution processes described above necessarily result in unreacted aldehyde remaining upon complete consumption of the alkyne coupling partner; if sufficiently high levels of selectivity are achieved, then both the product enone and the remaining aldehyde should be obtained with good enantioselectivity. For the more selective of the examples described above, this was the case. For example, the reaction between β-phenyl-substituted aldehyde **7b** and phenylacetylene (Table 2, entry 1) delivered the ketone product in 47% yield with an e.r. of 94:6, together with unreacted aldehyde with an e.r. of 89:11 in 34% yield. These levels of selectivity presented the opportunity to conduct two sequential alkyne hydroacylation reactions in the same vessel, with the goal of obtaining two distinct ketone products both with useful levels of enantiomeric enrichment. Scheme 2 illustrates this concept in practice: β-phenyl-substituted aldehyde **7b** was initially reacted with phenylacetylene at 0°C for 1 h. Hexyne was then introduced into the vessel and the reaction temperature was raised to 80°C; the reaction was continued for a further 12 h. The phenylacetylene-derived enone **8b** was obtained in 45% yield with an e.r. of 93:7 and the butyl-substituted enone (ent)-**8g** in 35% yield, but with an e.r. of 85:15. Importantly, and as expected, the major enantiomer of the butyl-substituted enone was opposite to that of the phenyl-substituted product **8b**. The levels of selectivity and yield achieved for the phenyl-substituted product are comparable to the simple kinetic resolution reaction. The lower enantioselectivity obtained for the butyl-substituted enone is possibly a consequence of the higher reaction temperature needed when employing the mismatched catalyst (a small amount of aldehyde racemisation is also a possibility).

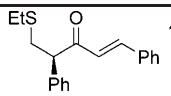
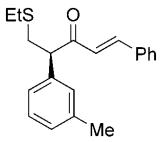
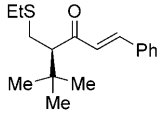
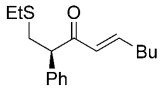
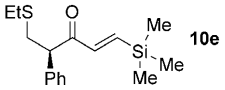


Scheme 2. Sequential alkyne hydroacylation reactions leading to pseudoenantiomeric products.

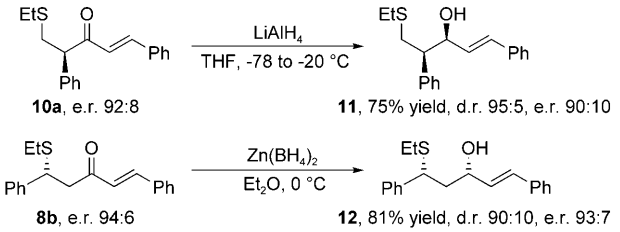
We have briefly explored the utility of the enone products in stereoselective functionalisation (Scheme 3); selective 1,2-reduction of either the α′- or β′-substituted enones was possible by using appropriate reagents. For example, reduction of enone **10a** with $LiAlH_4$ delivered alcohol **11** with a 95:5

Table 3. Scope of alkyne hydroacylation employing α-substituted aldehydes **9**.[a]



Entry	R^1	R^1	Product	Yield [%][b]	e.r.[c]	s[d]
1[e]	Ph (**9a**)	Ph	 **10a**	39	94:6	34
2	3-MePh (**9b**)	Ph	 **10b**	40	90:10	16
3	*t*Bu (**9c**)	Ph	 **10c**	43	84:16	9
4	Ph (**9a**)	Bu	 **10d**	49	89:11	19
5	Ph (**9a**)	TMS	 **10e**	42	90:10	17

[a] Conditions: aldehyde (2.0 equiv), alkyne (1 equiv), [Rh((*R*,*R*)-Me-Duphos)][ClO_4] (5 mol%), acetone, 0°C, 12 h. Catalyst generated in situ from [Rh(*R*,*R*)-Me-DuPhos)(nbd)][ClO_4] and H_2. [b] Isolated yields. [c] The e.r. values were determined by chiral HPLC. [d] Selectivity factors (s) were calculated by using conversions and e.r. values of the ketone products. [e] Absolute configuration indicated by X-ray crystallography.[20] All other configurations are assigned by analogy.



Scheme 3. Stereoselective reduction of enones **10a** and **8b**.

d.r., whereas reaction of enone **8b** with $Zn(BH_4)_2$ provided allylic alcohol **12** with 90:10 d.r.[21]

In summary, a new enantioselective rhodium-catalysed intermolecular alkyne hydroacylation reaction has been described. The process employs readily available substrates and delivers complex products; both α- and β-substituted *S*-chelating aldehydes are converted to enantioenriched α′- or β′-substituted α,β-unsaturated ketones, respectively. The products are obtained in high yields and with useful levels of enantioselectivity. This new kinetic resolution process significantly expands the range of products that can be accessed by using enantioselective intermolecular hydroacylation reactions.

Experimental Section

Typical experimental procedure (Table 2, entry 1): Acetone (2.0 mL) was added to the pre-catalyst [Rh(nbd)((*R*,*R*)-Me-Duphos)][ClO_4] (9 mg, 0.015 mmol) under nitrogen. The catalyst was activated in situ by passing H_2 though the solution for 2 min or until a colour change from orange to light yellow was observed. After this time the hydrogen atmosphere was purged by passing nitrogen through the solution for 0.5 min. Thioaldehyde **7b** (0.120 g, 0.6 mmol) was added to this solution at 0°C followed by phenylacetylene (0.033 mL, 0.3 mmol). The resulting mixture was stirred at 0°C for 2 h. After this time the solution was filtered through a silica plug and concentrated in vacuo. Purification by flash column chromatography through silica gel (diethyl ether/hexane 1:4) gave the product ketone **8b** (0.083 g, 47%) as a white solid.

Acknowledgment

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Keywords: homogeneous catalysis · hydroacylation · ketones · kinetic resolution · rhodium

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[20] Diffraction data for **8b**, **8f** and **10a** were collected at low temperature[22] by using an Enraf–Nonius KCCD diffractometer.[23] Structures were solved by using SIR92[24] and refined by using the CRYSTALS software suite[25] as per the Supporting Information (CIF file). The Flack x parameter[26] for **8b**, **8f** and **10a** were determined as −0.03(8), 0.004(90) and 0.01(14), respectively. Analysis of the Bijvoet pairs to gave Hooft y parameters of −0.04(5), 0.01(3) and 0.01(5), giving probabilities that the structure is the correct hand of better than 99.99% for all three crystals.[27] CCDC-782372, 782373, 782374, 782375 and 782376 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[21] X-ray crystal structures of the *p*-nitrobenzoates derived from alcohols **11** and **12** (**11'** and **12'** respectively) were used to establish relative configurations. Diffraction data were collected for **11'** on Beamline I19 (EH1) at the Diamond Light Source, Didcot, Oxfordshire, where raw frame data were processed (including unit cell refinement, multiscan absorption correction and inter-frame scaling) using CrystalClear;[28] data for **12'** were collected as for **8b**, **8f** and **10a**.[20] See the Supporting Information and the CIF file for further details.

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