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Catalytic Enantioselective Intermolecular Hydroacylation: Rhodium-Catalyzed Combination of β-*S*-Aldehydes and 1,3-Disubstituted Allenes

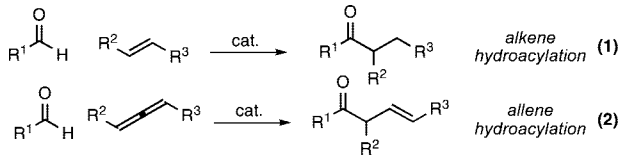
James D. Osborne,[†] Helen E. Randell-Sly,[‡] Gordon S. Currie,[§] Andrew R. Cowley,[†] and Michael C. Willis[†,*]

Department of Chemistry, University of Oxford, Chemical Research Laboratory, Mansfield Road, Oxford, U.K., Department of Chemistry, University of Bath, Bath, U.K., and AstraZeneca, Alderley Park, Macclesfield, Cheshire, U.K.

Received September 1, 2008; E-mail: michael.willis@chem.ox.ac.uk

Transition metal catalyzed alkene hydroacylation is an attractive method for the preparation of ketone derivatives; it is an atom economic process, employs readily available substrates, and can be achieved using relatively low catalyst loadings.[1] Intramolecular variants, particularly those leading to the formation of cyclopentanones, have been extensively studied,[2] and highly enantioselective variants have been developed.[3] Intermolecular reactions are more challenging, due mainly to competitive metal-catalyzed reductive decarbonylation.[4] One successful strategy to achieve these difficult transformations has been to stabilize the key acyl-metal intermediates using chelation control.[5] Although this has resulted in a number of useful reactions, the scope of these processes is still relatively narrow, with a particular limitation being the ability to routinely use disubstituted alkenes.[6] Given these difficulties it is not surprising that there is only a single report of enantioselective intermolecular hydroacylation, which, although efficient in terms of yield, offers only variable enantioselectivity.[7] Allenes have been demonstrated to provide useful reactivity in a growing number of transition metal catalyzed processes,[8] including enantioselective transformations,[9] although their use in hydroacylation reactions is virtually unexplored.[10] In this communication, we demonstrate that, by exchanging alkenes for allenes as substrates, an efficient and highly enantioselective catalytic intermolecular hydroacylation process can be achieved.

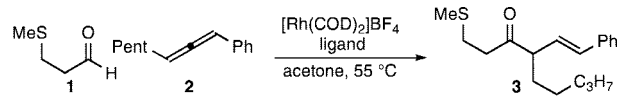
Recent results from our laboratories have established that β-*S*-substituted aldehydes are useful substrates in intermolecular Rh-catalyzed alkene and alkyne hydroacylation reactions, although, again, reactions with 1,1- or 1,2-disubstituted alkenes were generally unsuccessful.[11] We reasoned that employing 1,3-disubstituted allenes in intermolecular hydroacylation reactions should allow access to *substituted* nonconjugated enone products. This should provide a transformation potentially amenable to asymmetric catalysis, while avoiding the need to employ poorly reactive disubstituted alkenes as substrates (reactions 1 and 2). In following such an approach, the inherent axial chirality of 1,3-disubstituted allenes would need to be considered.



To assess the potential of the proposed asymmetric transformation we studied the combination of β-MeS-propanal (**1**) and racemic phenyl-pentyl-substituted allene **2**, leading to enone **3** (Table 1).[12]

[†] University of Oxford.
[‡] University of Bath.
[§] AstraZeneca.

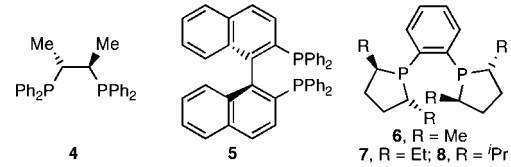
Table 1. Allene Hydroacylation: Ligand Evaluation[a]



entry	ligand	yield (%)[b]	ee (%)[c]
1	**4**	68	32
2	**5**	67	58
3	**6**	71	71
4	**7**	60	34
5	**8**	62	30
6[d]	**6**	65	80

[a] Conditions: aldehyde (1.0 equiv), allene (2.0 equiv), $[Rh(COD)_2]BF_4$ (10 mol%), ligand (10 mol%), acetone, 55 °C, 16 h. [b] Isolated yields. [c] Determined by chiral HPLC. [d] Reaction performed at 40 °C for 24 h.

Catalysts were generated *in situ* from $[Rh(COD)_2]BF_4$ and the appropriate diphosphine ligand. We selected ligands that had been successfully employed in enantioselective intramolecular reactions;[2b] Chiraphos (**4**), Binap (**5**), and Me-DuPhos (**6**). Although all three ligands generated effective catalysts, the complex incorporating Me-DuPhos displayed the highest levels of both reactivity and selectivity, delivering enone **3** in 71% yield and with a 71% ee (entries 1−3). Encouraged by these results we explored the Et- and ^{i}Pr-Duphos ligands (**7** and **8**); however, both generated less selective catalysts (entries 4 and 5). These initial ligand evaluations had been performed at 55 °C for 16 h. Simply reducing the temperature to 40 °C and running the reaction for 24 h allowed the product to be isolated with an improved 80% ee and only a slightly reduced yield (entry 6).



We next transferred our optimized conditions to aryl aldehyde **9**, with the expectation that the reduced mobility of the substrate would have a beneficial effect on the enantioselectivity of the process. Pleasingly, this proved to be the case, with the reaction between aldehyde **9** and allene **2** delivering the enone product in 92% ee (Table 2, entry 1). Variation of the alkyl-substituent of the allene, from pentyl to hexyl, butyl, and ethyl, had minimal impact on the efficiency or enantioselectivity of the process (entries 2−4). However, the smaller methyl-substituted allene delivered only a moderately selective reaction (entry 5). Reaction with the benzyl-phenyl-substituted allene was again highly selective (entry 6). We

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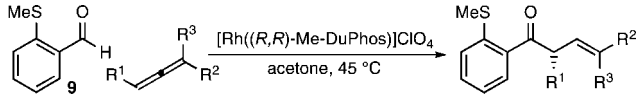
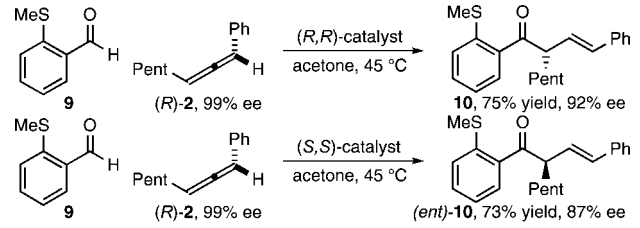
Table 2. Enantioselective Allene Hydroacylation: Allene Scope[a]



entry	R^1	R^2	R^3	yield (%)[b]	ee (%)[c]
1	Pent	Ph	H	81	92
2	Hex	Ph	H	88	94
3	But	Ph	H	83	93[d]
4	Et	Ph	H	76	91
5	Me	Ph	H	93	60
6	Bn	Ph	H	77	93
7	Hex	4-F_3C-C_6H_4	H	95	94
8	Et	4-F_3C-C_6H_4	H	94	90
9	Hex	3,5-F_3C-C_6H_4	H	79	96
10	Et	3,5-F_3C-C_6H_4	H	89	96
11	Hex	4-Me-C_6H_4	H	56	90
12	Et	4-Me-C_6H_4	H	64	89
13	Hex	Ph	Ph	25	94

[a] Conditions: aldehyde (1.0 equiv), allene (2.0 equiv), [Rh(*R*,*R*)-Me-DuPhos)]ClO_4 (10 mol.%), acetone, 45 °C, 24 h. Catalyst generated *in situ* from [Rh(*R*,*R*)-Me-DuPhos)(nbd)]ClO_4 and H_2. [b] Isolated yields. [c] Determined by chiral HPLC. [d] Absolute configuration determined from X-ray structure. See the Supporting Information for further details. All other configurations assigned by analogy.

Scheme 1. Enantioselective Hydroacylation: Nonracemic Allene



also explored variation of the electronics of the aromatic allene substituent; both electron-withdrawing (4-CF_3, 3,5-di-CF_3) and electron-donating (4-Me) groups could be introduced with minimal effect on the enantioselectivity of the processes, although the more electron-rich allene was less reactive (entries 7−12). The final example in Table 2 demonstrates the transformation remains highly enantioselective when an achiral allene is employed, with the indicated trisubstituted allene delivering the expected enone with 94% ee (entry 13). Unfortunately, trisubstituted allenes displayed significantly reduced reactivity, so although good enantioselectivity could be maintained, the yields were low (25% for this example).[13]

To begin to explore the nature of the observed asymmetric processes, we repeated an example from Table 2 (entry 4) but employed a single equivalent of racemic allene; after 48 h, the adduct was obtained in 77% yield, with 88% ee. We also reacted aldehyde **9** with enantiomerically enriched allene **2** using both enantiomers of the catalyst (Scheme 1). Catalyst control was observed in both reactions, with the two enantiomers of catalyst delivering enantiomeric products. Importantly, allenes recovered from both reactions had significantly reduced ee's, with the (*R*,*R*)-catalyst returning allene with −31% ee, and the (*S*,*S*)-catalyst delivering allene with 33% ee.[14,15] These reactions establish that the process is not a simple kinetic resolution of the allene; a dynamic kinetic asymmetric transformation, involving racemization of the allene during the reaction, is a more likely explanation.

In summary, by employing 1,3-disubstituted allenes and β-*S*-aldehydes, we have developed the first efficient and highly enantioselective intermolecular carbon−carbon double-bond hydroacylation process. Preliminary experiments suggest a dynamic kinetic asymmetric transformation is in operation; a detailed mechanistic study is underway.

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Supporting Information Available: Experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Single regio- and geometrical isomers were observed in all cases.
(13) Trialkyl-substituted allenes delivered no hydroacylation products when combined with aldehyde **9**.
(14) Both reactions illustrated in Scheme 1 were performed for 24 h. However, there was an observable difference in the rates of the two processes, with the (*S*,*S*)-catalyst delivering slower reactions. Comparative times to achieve 60% conversion: (*R*,*R*)-catalyst 11 h; (*S*,*S*)-catalyst 17 h.
(15) We have established that there is no product racemization under the standard reaction conditions.

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