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An enamine controlling group for rhodium-catalyzed intermolecular hydroacylation

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ABSTRACT

An enamine-controlled hydroacylation of alkynes using a rhodium(I)/dppe catalyst system is described. The reaction is highly selective, forming the linear enaminone products as single regioisomers in all examples. *In situ* hydrolysis of the enamine functionality generated α-substituted 1,3-diketone products, and Lewis-acid mediated intramolecular conjugate addition of the hydroacylation products gave substituted hexahydroquinolones.

1. Introduction

The discovery and optimization of atom efficient processes with which to construct functionalized organic scaffolds is at the forefront of modern Organic and Medicinal Chemistry.[1,2] The field of hydroacylation chemistry, the formal addition of a C–H bond across a π-bond, has grown over the past decade to not only become a robust method for the formation of ketones, enones, and esters,[3,4] but also a platform for the formation of heterocycles.[5–7] In the majority of cases, hydroacylation requires the use of a tethered directing group on either the aldehyde or alkene/alkyne coupling partner in order to avoid reductive decarbonylation.[8–17] Recent methodologies have enabled the use of a variety of functionalities as directing groups (Scheme 1), including but not limited to; phenols,[18–21] thioethers,[22–26] anilines,[27] and most recently, carbonyl groups.[28] A limitation of ester and ketone-directed hydroacylation is that the inherent acidity of the α-proton results in ready tautomerization under the reaction conditions, and this predominant enol form binds unproductively to the metal catalyst. This issue was alleviated by the use of α,α-disubstituted β-keto aldehydes and β-formyl esters, but α-mono-substituted substrates could not be used. Enamines have thus far not been explored as directing groups in hydroacylation reactions, yet they have the potential not only to form synthetically useful enaminones,[29–32] but also to act as carbonyl surrogates which, upon hydrolysis, would provide access to otherwise inaccessible dicarbonyl hydroacylation products. Our laboratory has previously reported amine-directed hydroacylation.[33] In these reactions, the Lewis-basicity of the amine was tempered by virtue of its phenyl substituents. We envisaged aniline-derived enamines exhibiting similar reactivity in controlling hydroacylation, but with the potential for further functionalization.

2. Results and discussion

After a brief evaluation of amine substituents, we chose to proceed in our investigations with cyclohexene β-aminoenal **1a**, which, in combination with 1-octyne, was submitted to rhodium(I) catalysis with a number of *bis*-phosphine ligands of varying bite-angle and phosphine substituent (Table 1). Catalyst systems comprised of narrow bite-angle ligands dcpm, dppm and PNP(Cy) led to low conversions of aldehyde substrate after 18 h at 55 °C, but gave high levels of regioselectivity for the linear product **2a** over the branched **3a** (Entries 1–3). Wider bite-angle ligands dcpe and dppe enhanced this selectivity and increased reactivity (Entries 4 and 5), with dppe generating the product in >20:1 rr and in 87% ^{1}H NMR yield. It was possible to isolate product **2a**, after purification on silica gel, as a single regioisomer in 73% yield, but it was found to hydrolyze to the 1,3-dicarbonyl product if exposed to silica for extended periods of time. Further increases to ligand bite-angle

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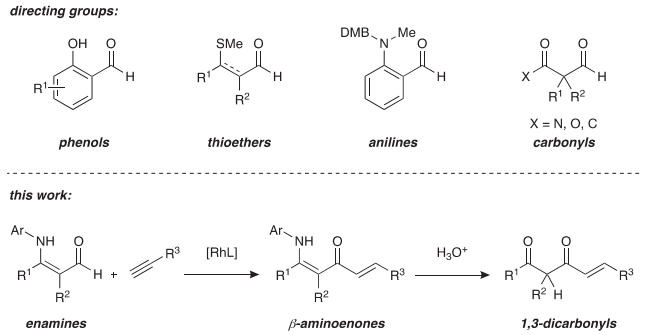
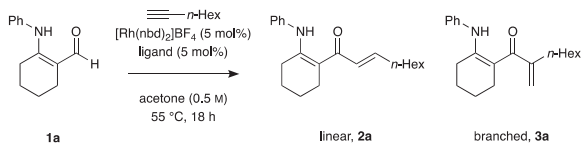
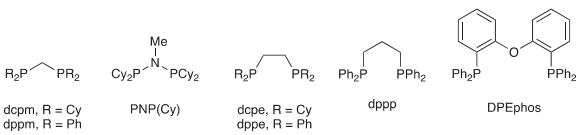


Scheme 1. Directing groups in intermolecular hydroacylation, and enamine-directed alkyne hydroacylation.

Table 1
Optimization of enamine-directed hydroacylation reaction conditions.[a]



Entry	Ligand	Ratio (2a:3a)[b]	Yield/%[b]
1	dcpm	9:1	40
2	dppm	9:1	15
3	PNP(Cy)	15:1	23
4	dcpe	>20:1	36
5	dppe	>20:1	87 (73)[c]
6	dppp	>20:1	53
7	DPEphos	9:1	7



[a] Reaction conditions: Rh $(nbd)_2BF_4$ (5 mol%), ligand (5 mol%), aldehyde (0.3 mmol, 1.0 equiv.), alkyne (1.5 equiv.), acetone (0.5 M), 55 °C for 18 h.
[b] Yield determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture, using 1,3,5-trimethoxybenzene as internal standard.
[c] Isolated yield of **2a**.

proved to be deleterious, with dppp and DPEphos both leading to reduction in reaction efficiency.

With an efficient catalytic manifold for enamine-directed hydroacylation in hand, we applied the optimized conditions to β-aminoenal **1a** in reaction with various alkynes (Table 2). Pleasingly, more sterically encumbered aliphatic alkynes were well tolerated; cyclohexyl and *tert*-butyl substituted alkynes delivered the desired enone products **2b** and **2d** in 77% and 85% yield respectively. In order to demonstrate the practicability of this methodology, reaction of **1a** with 3,3-dimethyl-1-butyne was performed on a 4 mmol scale, using only 2.5 mol% catalyst, which gave product **2d** in 87% yield (0.99 g) after 18 h at room temperature. Primary alkyl halides and silyl ether functionalities remained intact, with the corresponding products **2e** and **2f** isolated in high yields. It was found that hydroacylation of aryl alkynes was not possible under the reaction conditions, and that the aldehyde starting material could be cleanly recovered from reactions with both electron-rich and electron-poor phenyl-substituted alkynes. However, a phenyl-substituted aliphatic alkyne underwent the desired hydroacylation, generating the product **2g** in 46% yield. Phthalimide product **2i** could also be obtained in moderate yield. We next examined variation of the aldehyde component in reaction with 1-octyne. Deviation of ring size to 5- or 7-membered rings resulted in complete loss of reactivity, which is likely due to a subtle electronic effect of the cyclohexene β-aminoenal, which is disrupted by changes in geometry. Likewise, substitution to the cyclohexene ring was unfavorable and only tolerated at the 4-position. Reaction of **1b**-**c** required 10 mol% catalyst loading, but nevertheless delivered products **2j**-**l** in good yields. Complete linear regioselectivity (>20:1 rr) was observed in all cases, and low yielding examples were only as a result of incomplete consumption of aldehyde starting material.

Having developed the enamine-directed hydroacylation methodology and applied it to a number of combinations of aldehydes and alkynes, we next turned our attention to isolating the hydrolyzed enamine products from a one-pot hydroacylation/hydrolysis process (Table 3). It was found that direct addition of aqueous hydrochloric acid to the reaction vessel, following successful hydroacylation, facilitated rapid enamine hydrolysis (*ca* 2 h). The α-mono-substituted 1,3-dicarbonyl products **4a**-**h** were generated in good to excellent yields and were indeed found to exist entirely as the enol tautomer (**5**), as was observed by ^{1}H NMR spectroscopy in $CDCl_3$, and confirmed by HMBC analysis.

Finally, we investigated the possibility of further utilizing the enamine functionality in a Lewis acid-catalyzed aza-conjugate addition process,[34] in order to construct functionalized hexahydroquinolinones (Table 4). Pleasingly, using catalytic antimony (III) trichloride in acetonitrile for 18 h at 55 °C, the isolated hydroacylation products (**2**) underwent the desired intramolecular cyclisation to generate bicyclic products **6a**-**c** in high yields. In the case of **6b** and **6c**, which bore substituents on the cyclohexene ring, low diastereoselectivity was observed in the conjugate addition (1.5:1 dr and 1.8:1 dr respectively). This was perhaps due to the planarity of the enamine preventing effective chirality relay in the formation of the new stereocentre.

3. Conclusions

We have demonstrated enamines as efficient directing groups for intermolecular hydroacylation of alkynes. Using a rhodium(I)/dppe catalyst system, the enaminone products were generated as single regioisomers (>20:1 rr), and isolated in moderate to high yields. These products could alternatively be hydrolyzed *in situ* to access the corresponding 1,3-dicarbonyl products, previously inaccessible using carbonyl-directed hydoacylation, or cyclized *via* intramolecular aza-conjugate addition to generate synthetically attractive hetero-bicyclic systems.

4. Experimental

4.1. General information

All reactions were performed under argon using standard Schlenk techniques. ^{1}H and ^{13}C NMR spectra were obtained on a Brüker AVIII400 (400 MHz) spectrometer using the residual solvent signal as an internal standard ($CDCl_3$: $\delta_H = 7.26$ ppm, $\delta_C = 77.16$ ppm). All coupling constants (*J* values) were reported in Hertz (Hz). Multiplicities were reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; m, multiplet. High-resolution mass spectrometry (HRMS) measurements were recorded on a Bruker Daltronics microTOF (ESI) spectrometer. Infrared spectra were recorded as thin films on a Bruker Tensor 27 FT-IR spectrometer. Flash chromatography was carried out using matrix 60 silica. All alkynes were distilled prior to use. Acetone was dried over Drierite™ overnight, distilled at atmospheric pressure, and

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