Palladium-catalyzed enantioselective Heck alkenylation of trisubstituted allylic alkenols: a redox-relay strategy to construct vicinal stereocenters†

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An enantioselective, redox-relay Heck alkenylation of trisubstituted allylic alkenol substrates has been developed. This process enables the construction of vicinal stereocenters in high diastereo- and enantioselectivity and allows the formation of enolizable α-carbonyl methyl-substituted stereocenters with no observed epimerization under the reported reaction conditions.

Introduction

In a Heck reaction using multi-substituted alkenes, the initial syn-carbopalladation sets two vicinal stereocenters by virtue of the migratory insertion process. Unfortunately, the resultant Pd-alkyl undergoes facile β-hydride elimination, which generally eliminates the stereochemistry imparted by migratory insertion. Recently, we have reported a modern variant of the Heck reaction, wherein the directionality and stereochemical fidelity of β-hydride elimination can be controlled and, thus, the initial stereochemical consequence of migratory insertion is not lost. Termed redox-relay Heck reactions, the unsaturation of the alkene is conserved as it is transferred to a different position on the alkyl chain, most commonly by oxidation of an alcohol to a carbonyl. These reactions have been rendered enantioselective and are effective on both disubstituted alkenes to form tertiary stereocenters and trisubstituted alkenes to form quaternary stereocenters (Scheme 1A). However, the potential power of the syn migratory insertion has not been realized as only a single stereocenter has been set. Therefore, we set out to investigate whether vicinal centers can be forged through the use of trisubstituted alkenols of type 2 in enantioselective redox-relay Heck reactions (Scheme 1B). In this case, such stereocenters could be strategically constructed if we took advantage of the propensity for the alkenyl electrophile 1 to add at the alkene carbon distal to the alcohol functionality, producing a new Csp2–Csp3 bond and set an adjacent stereocenter in a single migratory insertion event. In order to render this transformation enantioselective, the chiral Pd-ligand complex must differentiate the two similar prochiral faces of sterically encumbered trisubstituted alkenol 2, which can be challenging on the basis of past reports.

Mechanistically, we propose the reaction initiates with oxidative addition of alkenyl triflate 1 with Pd(0) to produce cationic Pd-alkenyl intermediate 4 (Scheme 1C). Alkenol 2 can undergo migratory insertion into the Pd-alkenyl bond to...
furnish Pd–alkyl intermediate 5. The cationic Pd–alkyl species 5 undergoes β-hydride elimination to deliver Pd–enol intermediate 6, which subsequently leads to reinsertion to yield intermediate 7. This type of Pd–alkyl intermediate is unique since the alcohol and Pd-catalyst are bonded to the same carbon atom. As a result, alcohol oxidation occurs (either through β-hydride elimination or an E2-type elimination\(^9\)), reminiscent of the final step in the Wacker process.\(^{10}\) This yields final product 3 and Pd(0), closing the catalytic cycle.

**Results and discussion**

Preliminary investigations to develop this process were conducted with trisubstituted alkenol 2a using reaction conditions previously shown to effectively promote such processes. Unfortunately, commonly employed amide solvents, such as dimethyleacetamide (DMA) and dimethylformamide (DMF), produced the desired redox-relay Heck product 3a in low yield and enantioselectivity (entries 1 and 2, Table 1). A variety of solvents were then evaluated and only ester-derived solvents resulted in significant improvements. For example, ethyl acetate (EtOAc) enhanced the yield of product 3a to 45% and enantioselectivity to 94 : 6 (entry 3). Isopropyl acetate (i-PrOAc) and ethyl isobutyrate also resulted in similar yield and selectivity (entries 4 and 5). However, changing the solvent to ethyl pivalate delivered product 3a in 62% yield and 95 : 5 er. It should be noted that the enantioselectivity can be correlated to the natural bond orbital (NBO) charge of the oxygen or nitrogen atom of the ester or amide functional group of the solvent (see ESI for details).\(^{11}\) Next, an assortment of bases was screened, as an equivalent of triflic acid is formed with each catalytic turnover. The addition of 1.5 equivalents of NEt\(_3\) slowed the desired reaction and resulted in trace product formation (entry 7). In contrast, adding 1.5 equivalents of Li\(_2\)CO\(_3\) improved the yield of product 3a to 74% with no erosion in selectivity (entry 8). Exchanging the cation of the carbonate base from lithium to sodium or potassium resulted in slightly lower yields (entries 9 and 10).

Using ethyl pivalate as solvent and Li\(_2\)CO\(_3\) as base, the substrate scope of trisubstituted allylic alkenols was investigated (Table 2). Simple alkyl groups, such as methyl (3a) and ethyl (3b), at the R\(^1\) position on the alkene resulted in 74% and 84% yields, respectively. Introduction of a phenethyl moiety (3c) at the R\(^2\) position gave the desired product in 41% yield and 95 : 5 er. The inclusion of methyl (3d) and ethyl (3e) at the R\(^3\) position provided the corresponding ketone products in 60% and 54% yields, with increased enantioselectivity (97 : 3 and 98 : 2 er, respectively). An n-octyl alkyl group was examined giving 51% yield of 3f with 98 : 2 er. Evaluation of phenethyl (3g), benzyl (3h), and phenyl (3i) at R\(^1\) indicated that, as the phenyl group was positioned closer to the resulting carbonyl moiety, slightly lower yields and enantioselectivities were observed. In addition, the reaction could tolerate an isopropyl (i-Pr) group at the R\(^2\) position furnishing product 3j in 45% yield and 98 : 2 er. A trimethylsilyl (TMS) group could also be positioned α to the resultant carbonyl in high enantioselectivity, albeit in 19% yield (3k). The absolute configuration of product

### Table 1 Reaction optimization\(^a\)

| Entry | Solvent | Base    | % Yield | dr  | er  |
|-------|---------|---------|---------|-----|-----|
| 1     | DMA     | —       | 14      | >20 : 1 | 71 : 29 |
| 2     | DMF     | —       | 15      | >20 : 1 | 75 : 25 |
| 3     | EtOAc   | —       | 45      | >20 : 1 | 94 : 6  |
| 4     | i-ProOAc| —       | 39      | >20 : 1 | 94 : 6  |
| 5     | Ethyl isobutyrate | — | 49 | >20 : 1 | 95 : 5  |
| 6     | Ethyl pivalate | — | 62 | >20 : 1 | 95 : 5  |
| 7     | Ethyl pivalate | NEt\(_3\) | trace | — | —  |
| 8     | Ethyl pivalate | Li\(_2\)CO\(_3\) | 74 | >20 : 1 | 93 : 5  |
| 9     | Ethyl pivalate | Na\(_2\)CO\(_3\) | 70 | >20 : 1 | 93 : 5  |
| 10    | Ethyl pivalate | K\(_2\)CO\(_3\) | 61 | >20 : 1 | 93 : 5  |

\(^a\) Each entry represents the isolated yield on 0.25 mmol scale. er values were determined by SFC or HPLC. Entries 7–10 used 1.5 equiv of base.

### Table 2 Evaluation of alkenol substrates\(^a\)

| Product | Yield | Er           |
|---------|-------|--------------|
| 3a      | 74%   | 95:5 er, >20:1 dr |
| 3b      | 84%   | 94:6 er, >20:1 dr |
| 3c      | 41%   | 95:5 er, >20:1 dr |
| 3d      | 60%   | 97:3 er, >20:1 dr |
| 3e      | 54%   | 98:2 er, >20:1 dr |
| 3f      | 49%   | 98:2 er, >20:1 dr |
| 3g      | 51%   | 96:4 er, >20:1 dr |
| 3h      | 46%   | 97:3 er, >20:1 dr |
| 3i      | 19%   | 97:3 er, >20:1 dr |

\(^a\) Each entry represents the isolated yield on 0.25 mmol scale. er values were determined by SFC or HPLC.
was determined to be (2S,3S) using electronic circular dichroism (see ESI for details)). The other products were assigned by analogy to product 3d.

When cyclopropyl-containing substrate 2l was subjected to the reaction conditions, the ring opening product (3l) was isolated in 40% yield and 97 : 3 er (Scheme 2). This α,β-unsaturated product could arise through Pd-mediated ring opening of β-cyclopropyl Pd-alkyl intermediate 8 to yield enol 9 that could tautomerize to ketone 10. Primary Pd-alkyl intermediate 10 can then undergo β-hydride elimination to produce a terminal alkene that isomerizes to the internal position to produce α,β-unsaturated product 3l. Ultimately, this confirms that the Pd-center migrates to the carbon attached to the alcohol.

Next, the scope of alkenyl triflates was explored including a variety of tri- and tetrasubstituted alkenyl triflates (1, Table 3). Starting with 2-substituted cyclohexenone triflates, an 85% yield was isolated for the ethyl-substituted product (3m) as the apparent steric impact of the aliphatic group was increased to Bn (3n) and i-Pr (3o), lower product yields were observed. In the case of a 2-bromo-substituted triflate, only 22% yield was isolated (3p). Enol triflates containing a methyl-substituted cyclopentenone (1q) and 5-membered lactone (1r) delivered the corresponding products in excellent yield and good selectivity. Reaction with β-keto ester derived (Z)-enol triflate yielded the (Z)-alkene product in 72% yield (3s). In contrast, reaction with the (E)-enol triflate gave a near equal mixture of (E)- and (Z)-tetrasubstituted alkene products in 56% yield (3t). Interestingly, the (E)-alkene product isomer has a 97 : 3 er, while the (Z)-alkene isomer product has a 91 : 9 er, the same er as observed when (Z)-enol triflate 1s was used. This result can be explained through isomerization of (E)-enol triflate 1t producing a mixture of (E)- and (Z)-enol triflates. Reaction with Pd(0) would produce distinct Pd-alkenyl species and ultimately deliver alkenes isomeric products with different enantioselectivities (97 : 3 and 91 : 9 er). In addition, a TMS-containing enol triflate furnished product 3u in 86% yield and 90 : 10 er. An enol triflate containing a pthalimide provided product 3v in 58% yield and 91 : 9 er. Furthermore, (+)-nootkatone derivative 3w was produced in 31% yield and 8 : 1 dr. Estrone derivative 3x was synthesized in 79% yield and >20 : 1 dr. Lastly, the enol triflate derived from cholesterol delivered product 3y in 26% yield and 8 : 1 dr. During our investigation of chiral triflate reagents (1w–1y), we found that the (R)-t-BuPyroX ligand gave superior diastereoselectivities (see ESI for additional details†).

In an effort to expand this redox-relay strategy beyond allylic alkenols, homoallylic alkenol 2z was subjected to the optimized reaction conditions and gave product 3z in 31% yield and 89 : 11 er. This result, albeit promising, suggests the current system is optimized for allylic substrates.

As this alkene class is distinct from others previously evaluated, we were interested in exploring how related substructures performed under these reaction conditions.
Accordingly, several alkenes with unique substitution patterns were studied (Table 4). The model substrate, (E)-alkenol 2a, yielded the desired redox-relay product in 95 : 5 er. In contrast, (Z)-alkenol 2aa delivered the product in a significantly reduced enantioselectivity (57 : 43 er), underscoring the importance of the substitution pattern on the trisubstituted alkene for face selection. For comparison, disubstituted alkenone 2ab provided the corresponding product in 89 : 11 er, while 1,1-disubstituted alkenone 2ac gave product in 79 : 21 er.

The structural origin of the difference in enantioselectivity between the (E) and the (Z)-alkenones was elucidated computationally in analogy to our previous work. The different conformations and configurations at the metal center in the stereodetermining alkene migratory insertion step for (E)-alkenone 2a and (Z)-alkenone 2aa with electrophile 1a mediated by a Pd-PyrOx catalyst were calculated using the M06/6-31+G**/LANL2DZ level of theory in G09 (for details see ESI†). The lowest energy transition structures leading to the (S) and (R)-products starting from 2a are shown in Fig. 1A. TSA is 1.5 kcal mol⁻¹ higher in free energy than TSA, in good agreement with the experimentally determined selectivity (95 : 5 er, 1.74 kcal mol⁻¹). This free energy difference is due to a through-space steric repulsion between a hydrogen on the carbon α to the hydroxyl group on the (E)-alkenone substrate and the t-Bu group next to the t-Bu oxazoline portion of the ligand. As a result, a potentially stabilizing interaction between a hydrogen on the electron deficient pyridine ring and the hydroxyl group of the alkenone substrate with an H–O distance of 2.11 Å and a C–H–O angle of 144.9° is observed.

Fig. 1B shows the lowest energy transition structures TSBS and TSBR leading to the (S)- and (R)-products for (Z)-alkenone 2aa. TSBS is only 0.7 kcal mol⁻¹ higher in free energy than TSBR. This difference matches, within the expected error of the calculations, the experimentally determined selectivity (57 : 43 er). The free energy difference is smaller for 2aa due to a combination of several unfavorable interactions present in both transition structures. In TSBR, there are two close contacts between the t-Bu group on the ligand and the alkyl on substrate (H–H = 2.16 Å and H–H = 2.18 Å). In TSBS, there is a close contact between a hydrogen on an alkyl methyl group and a hydrogen on the pyridine ring of the ligand (H–H = 1.96 Å). The same potentially stabilizing interaction between a hydrogen on the electron deficient pyridine ring of the ligand and the hydroxyl group of the alkyl substrate seen in TSA was also observed in both structures. The similarity of the interactions in TSBS and TSBR leads to the low selectivity observed experimentally for this substrate.

### Conclusions

In summary, we have developed an enantioselective redox-relay Heck reaction of trisubstituted allylic alkenones to deliver vicinal stereocenters in generally high enantio- and diastereoselectivity. This reaction is conducted under mild reaction conditions that allows the construction of enolizable α-carbonyl methyl-substituted stereocenters with no or little observed epimerization. Systematic evaluation of the substitution pattern on the alkenone substrate has revealed the importance of the double bond geometry to achieve high enantioselectivity. Computational studies were used to explore this finding and showcase a significantly different network of interactions responsible for high enantioselectivity. This information will be utilized in the development of new variants of this reaction with an eye towards expansion to homoallylic alcohols and related substrate classes.

| Table 4 Evaluation of alkenone substitution |
|---------------------------------------------|

| OMe | R1 | R2 | 2-ButPyrOx (5 mol %) | Li2CO3 (1.5 equiv) | 3 A MS, 24 h |
|-----|----|----|----------------------|-------------------|------------|
| OMe | R1 | R2 | 2-ButPyrOx (15 mol %) | Ethyl vinyl | 3 A MS, 24 h |
| 2a  | Me | Me | 95.5 er, 20.1 dr | 57.43 er, 20.1 dr | 89.11 er |
| 2ac | Me | Me | 79.21 er | 89% | 89% |

a The isolated yields of products 3a–3ac are shown. Each entry represents the isolated yield on 0.25 mmol scale. er values were determined by SFC or HPLC.
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