Dual Catalysis

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Stereodivergent Dual Catalytic α-Allylation of Protected α-Amino- and α-Hydroxyacetaldehydes

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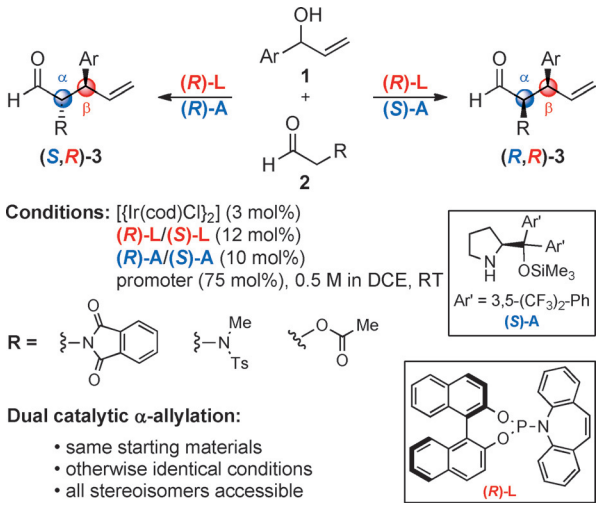
Abstract: *Fully stereodivergent dual-catalytic α-allylation of protected α-amino- and α-hydroxyacetaldehydes is achieved through iridium- and amine-catalyzed substitution of racemic allylic alcohols with chiral enamines generated in situ. The operationally simple method furnishes useful aldehyde building blocks in good yields, more than 99% ee, and with d.r. values greater than 20:1 in some cases. Additionally, the γ,δ-unsaturated products can be further functionalized in a stereodivergent fashion with high selectivity and with preservation of stereochemical integrity at the C_α position.*

Formation of multiple stereogenic centers in a single chemical transformation with complete control of absolute and relative configuration represents a significant challenge in asymmetric synthesis.[1] We recently described the concept of stereodivergent dual catalysis, whereby two distinct chiral catalysts operate concurrently, yet independently, to promote bond formation with full control over the configuration of two new stereogenic centers.[2] Simultaneous use of a chiral Ir(P,olefin) complex and a chiral amine allowed implementation of this concept in the stereodivergent α-allylation of branched and linear alkanals as well as γ-allylation of cyclic α,β-unsaturated aldehydes.[3] Herein, we report the enantio- and diastereodivergent α-allylation of protected α-amino- and α-hydroxyacetaldehydes through dual iridium/amine catalysis (Scheme 1). The resulting α-*N*/*O*-substituted unsaturated aldehyde products are amenable to further elaboration under mild conditions with high selectivity.

Aldehydes have been examined as substrates in amine/transition-metal catalyzed α-allylation reactions to furnish general and useful approaches to optically active adducts.[4] Most prominently featured in these studies are α-alkyl-substituted branched and linear aldehydes. However, noticeably absent is the use of protected α-amino- and α-hydroxyacetaldehydes.[5] There are merely four reactions reported to date, which involve Pd-catalyzed allylation to afford γ,δ-unsaturated adducts in racemic form[5a,b] or at best 46% *ee*.[5c] The use of a suitably protected α-aminoacetaldehyde in a dual catalytic process of the type shown in Scheme 1 could result in a fully stereodivergent synthesis of β,β′-disubstituted α-amino acid derivatives. The sustained interest in this class of



Scheme 1. Stereodivergent dual catalytic α-allylation of protected α-amino- and α-hydroxyacetaldehydes. Ts = *p*-toluenesulfonyl; DCE = 1,2-dichloroethane.

compounds as synthetic intermediates and conformational constraints in the development of peptidomimetics continues to stimulate the development of methods for their synthesis.[6,7] Currently available routes to these structures typically give only one of the two possible diastereomers in high enantio- and diastereoselectivity.[8] In those processes that enable synthesis of the complementary diastereomer, the switch in the sense of diastereoselectivity is usually the result of a change in the catalyst[9] or substrate,[10] or stems from ad hoc adjustment of the reaction conditions.[11] In contrast to these approaches, at the outset of this study we sought to identify one-step, fully stereodivergent access to α-amino β-substituted γ,δ-unsaturated aldehydes. Furthermore, we expected that the lessons learned would subsequently find use with other α-heteroatom-substituted aldehydes, enabling the stereodivergent synthesis of a diverse set of enantioenriched building blocks. The process would thus complement established methods for the one-step catalytic enantioselective synthesis of γ,δ-unsaturated carbonyls with α-*N*/*O* substituents, such as hydrogenation of β,β′-disubstituted dehydroamino acids,[8] nucleophilic addition to imino esters,[8] transition-metal-catalyzed allylic substitutions involving enolate nucleophiles,[12] as well as [2,3] and [3,3] sigmatropic rearrangements.[13]

The investigation was initiated with phenyl vinyl carbinol **1a** and 2-phthalimidoacetaldehyde (**2a**) as test substrates for an allylation reaction. We examined conditions previously reported for alkanals, namely, [{Ir(cod)Cl}$_2$] (3 mol%), (*R*)-**L**

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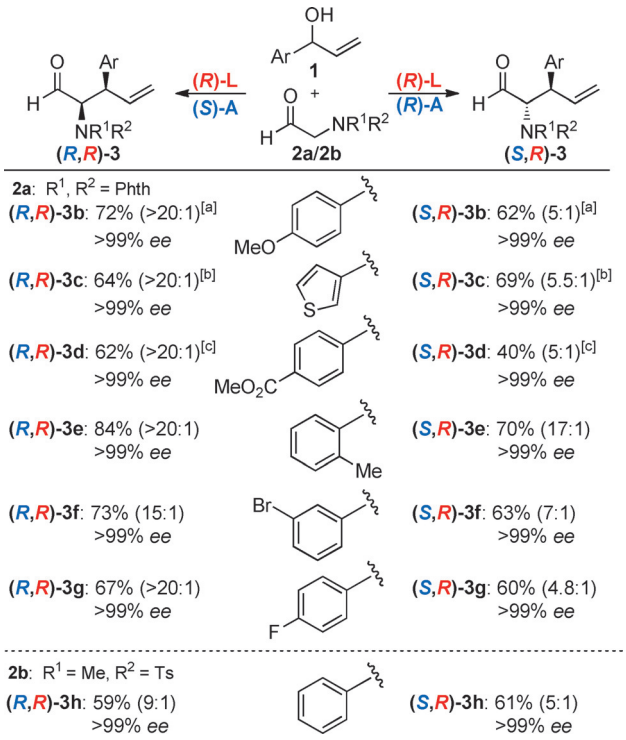
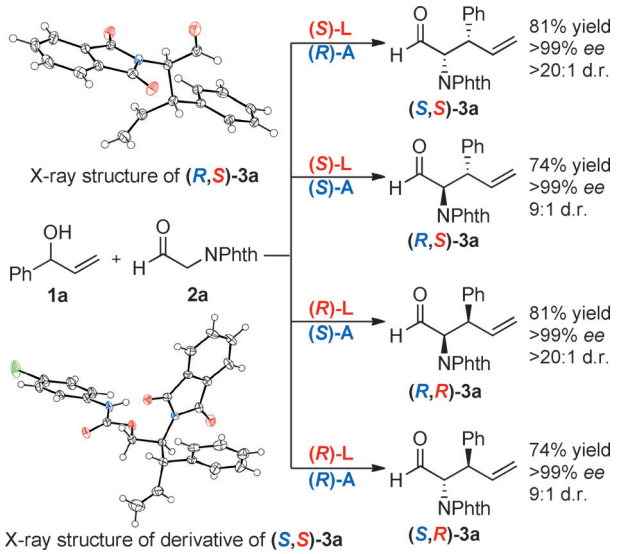
(12 mol%), and (*S*)-**A** (10 mol%) in 1,2-dichloroethane with dimethyl hydrogen phosphate as promoter. Under these conditions, product (*R*,*R*)-**3a** was formed in 85% yield, more than 20:1 d.r., and 99% *ee*. Although the reaction proceeded to give (*S*,*R*)-**3a** as the product (1:7 d.r.) when conducted with the (*R*)-**L** complex/(*R*)-**A** catalyst combination under otherwise identical conditions, it merely went to 20% conversion after 14 h, which precludes the original conditions for further development of a stereodivergent process with substrates **2**.

We have previously noted that the nature of the Brønsted or Lewis acid promoter has pronounced effects on the reaction outcome.[3b] Although at present the underlying reasons for such effects are not clear, indeed, optimization studies revealed that in the presence of dichloroacetic acid (75 mol%) the reaction afforded product (*R*,*R*)-**3a** in 81% yield, more than 99% *ee*, and with a d.r. value greater than 20:1 when catalyzed by the (*R*)-**L** complex/(*S*)-**A** combination (Scheme 2).[14,15] Significantly, the use of this acid allowed preparation of diastereoisomer (*R*,*S*)-**3a** in 74% yield, more than 99% *ee*, and 9:1 d.r. The remaining two stereoisomers were prepared in equally high yields and selectivities, thus establishing the operation of a fully stereodivergent process. The identity and configuration of both diastereomers was confirmed by X-ray crystallography.[16] It is also important to note that the sensitive aldehyde products were isolated by flash chromatography without epimerization at the C_α position, allowing their direct use in subsequent manipulations.



Scheme 3. Scope of substrates in the dual catalytic α-allylation of **2a** and **2b**. See Scheme 2 for details. Diastereomeric ratios shown in parentheses. [a] Cl_2HCCO_2H (30 mol%). [b] Cl_2HCCO_2H (50 mol%). [c] Cl_3CCO_2H (50 mol%).

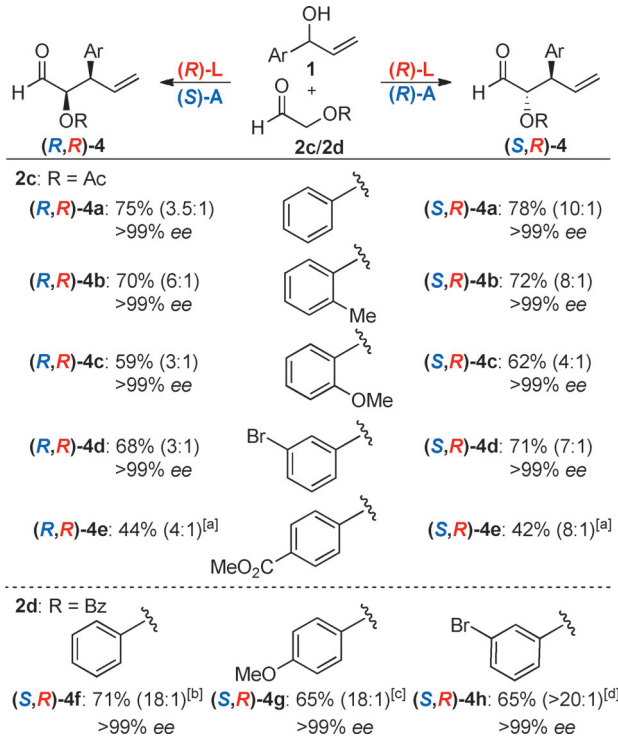


Scheme 2. Synthesis of all stereoisomers of **3a**. Reactions performed on 0.25 mmol scale under the following conditions: [{Ir(cod)Cl}$_2$] (3 mol%), (*R*)-**L** or (*S*)-**L** (12 mol%), (*R*)-**A** or (*S*)-**A** (10 mol%), **1a** (0.25 mmol), **2a** (2.0 equiv), Cl_2HCCO_2H (75 mol%), $(CH_2Cl)_2$ (0.5 M), RT. Yields refer to isolated products after purification by flash chromatography. Diastereomeric ratios determined by ^{1}H NMR analysis of the unpurified reaction mixture. Enantiomeric excesses determined by supercritical fluid chromatography (SFC) on a chiral stationary phase after reduction to the corresponding primary alcohol. Absolute configuration assigned by X-ray crystallography of a derivative of (*S*,*S*)-**3a** (C gray, H white, O red, N blue, Br green).[16] Phth = phthalimide; cod = 1,5-cyclooctadiene.

With optimized conditions in hand, the substrate scope of the dual catalytic allylation was explored (Scheme 3). Allylic alcohols with electron-rich aryl substituents (**3b**, **3c**) afforded products in good yields, 5:1 to more than 20:1 d.r., and with *ee* values greater than 99%. A substrate with an electron-withdrawing substituent (**3d**) required the use of a stronger acid as promoter (trichloroacetic acid) to furnish the product with high diastereoselectivity and more than 99% *ee*. Allylic alcohols incorporating alkyl (**3e**) and halogen substituents (**3f**, **3g**) on the arene also proved to be good substrates for the reaction, giving the corresponding products in 60–84% yield, 4.8:1 to more than 20:1 d.r., and with *ee* values greater than 99%.[17] Aldehyde **2b**, with a methyl substituent and *p*-toluenesulfonyl protecting group on nitrogen, was also found to be a suitable substrate for the reaction, affording (*S*,*R*)-**3h** and (*R*,*R*)-**3h** in good yields, more than 99% *ee*, and d.r. values of 5:1 and 9:1, respectively. This considerably expands the utility of the developed procedure as it allows direct introduction of a wide range of amine derivatives.

Attention was then focused on the use of α-hydroxyacetaldehydes. Extensive experimentation revealed that α-hydroxyacetaldehydes with protecting groups such as silyl ethers, alkyl ethers, esters, carbonates, and carbamates furnished the desired products (see the Supporting Information for details). The combination of *O*-acetyl-α-hydroxyacetaldehyde (**2c**) and dibenzenesulfonimide was identified as most suitable for the dual catalytic allylation in good yield, diastereoselectivity, and high enantioselectivity. Overall, the observed diastereoselectivities were somewhat lower than in

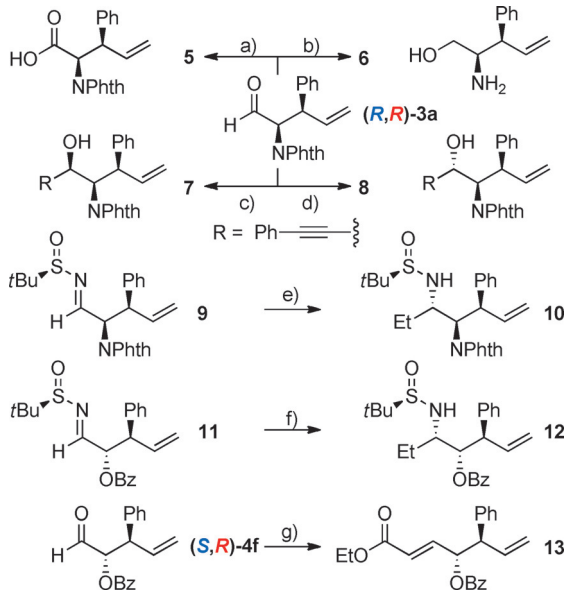
the case of 2-phthalimidoacetaldehyde. Interestingly, the (*R*,*R*)-diastereomers, which are usually produced in higher diastereoselectivity with α-aminoacetaldehydes, formed in lower diastereomeric ratios than their (*S*,*R*)-configured counterparts. Thus, (*S*,*R*)-**4a** was isolated in 78% yield, 10:1 d.r., and more than 99% *ee* (Scheme 4). In the reaction with



Scheme 4. Scope of allylic alcohol substrates in the dual catalytic allylation of **2c** and **2d**. All reactions were performed on 0.25 mmol scale under the following conditions: [{Ir(cod)Cl}$_2$] (3 mol%), (*R*)-**L** (12 mol%), (*R*)-**A** or (*S*)-**A** (10 mol%), **1** (0.25 mmol), **2** (2.0 equiv), dibenzenesulfonimide (50 mol%), 1,2-dichloroethane (0.5 M), RT. Yields refer to isolated products after purification by flash chromatography. For details, see the Supporting Information. Ac = acetyl; Bz = benzoyl. [a] ee value not determined; [b] Cl_2HCCO_2H (75 mol%); [c] Cl_2HCCO_2H (50 mol%); [d] Cl_3CCO_2H (50 mol%).

enantiomeric amine catalyst (*S*)-**A**, (*R*,*R*)-**4a** was produced in 75% yield, 3.5:1 d.r. and more than 99% *ee*. Allylic alcohols with alkyl (**4b**), electron-donating (**4c**), and halogen substituents (**4d**) all afforded the corresponding γ,δ-unsaturated products in good yields, synthetically useful diastereoselectivities of 3:1–8:1 d.r., and with *ee* values of more than 99%. An allylic alcohol incorporating an electron-withdrawing ester group also served as substrate (**4e**), but its diminished reactivity led to modest yields of 42% and 44%. During the optimization studies, it was discovered that using *O*-benzoyl-α-hydroxyacetaldehyde (**2d**) resulted in formation of one diastereomer of the product in high selectivity (up to >20:1 d.r.). It was, however, not possible to switch the preferred sense of diastereoselectivity. Thus, the preparation of the (*S*,*R*) diastereoisomer in highly diastereoselective fashion is possible as shown for three representative substrates (**4f**–**4h**) in Scheme 4.

The utility of the γ,δ-unsaturated aldehyde products as building blocks for further elaboration is demonstrated in Scheme 5. While Pinnick oxidation of aldehyde (*R*,*R*)-**3a**



Scheme 5. Functionalization of γ,δ-unsaturated aldehyde products. Reagents and conditions: a) $NaClO_2$ (3.3 equiv), NaH_2PO_4 (3.3 equiv), 2-methyl-2-butene (30 equiv), THF/*t*BuOH/H_2O (4:4:1 v/v), RT, 2 h, 76%; b) 1. $NaBH_4$ (2.0 equiv), CH_2Cl_2/MeOH (2:1 v/v), −78 °C; 2. $(CH_2NH_2)_2$ (4.0 equiv), EtOH, 90 °C, 30 min, 55% over 2 steps; c) $Zn(OTf)_2$ (1.1 equiv), (−)-ephedrine (1.2 equiv), phenylacetylene (1.2 equiv), NEt_3 (1.2 equiv), toluene, RT, 5 h, 11:1 d.r., 83% yield (single diastereomer); d) $Zn(OTf)_2$ (1.1 equiv), (+)-ephedrine (1.2 equiv), phenylacetylene (1.2 equiv), NEt_3 (1.2 equiv), toluene, RT, 5 h, >20:1 d.r., 78% yield (single diastereomer); e) $ZnMe_2$ (2.6 equiv), EtMgBr (2.2 equiv), THF, RT, 15 min; then **9**, −78 °C, 1 h, 64% (single diastereomer); f) $ZnMe_2$ (2.6 equiv), EtMgBr (2.2 equiv), THF, RT, 15 min; then **11**, −78 °C, 1 h, 66% (single diastereomer); g) $EtO_2CCH_2PO(OPh)_2$ (1.3 equiv), NaH (1.1 equiv), THF, 0 °C, 30 min; then (*S*,*R*)-**4f**, RT, 2 h, 78% (12:1 d.r.).

afforded carboxylic acid **5**,[18] $NaBH_4$ reduction followed by cleavage of the phthalimide moiety furnished β-amino alcohol **6** in 55% yield over two steps. We were particularly interested in exploring the potential of the α-amino- and α-hydroxyaldehyde products to serve as precursors for a variety of vicinal amino alcohols and diamines, which are of interest in the development of catalysts and pharmaceuticals. We observed that a procedure originally developed for the enantioselective addition of zinc(II) acetylides to aldehydes was well-suited for fully stereocontrolled addition of phenylacetylene to aldehyde (*R*,*R*)-**3a**.[19,20] Thus, by selection of the appropriate ephedrine ligand, both protected amino alcohol diastereomers **7** and **8** could be prepared in 83% and 78% yield and 11:1 d.r. and more than 20:1 d.r., respectively.

A strategy that combines stereodivergent dual catalysis with subsequent reagent/auxiliary control imparts an additional degree of stereodivergence to the overall process. The strategy was extended to imine functionalization; thus, addition of an organozincate derived from ethylmagnesium bromide to Ellman's sulfinyl imine derivative **9** afforded

protected vicinal diamine **10** in 64% yield and more than 20:1 d.r.[21] Similarly, protected amino alcohol **12** was prepared from Ellman's sulfinyl imine derivative **11** in 66% yield and with a d.r. value of more than 20:1. Finally, (*S*,*R*)-**4 f** underwent Horner–Wadsworth–Emmons olefination to give α,β-unsaturated ester **13** in 78% yield.

In summary, we have documented the development of a fully stereodivergent, dual iridium/amine catalyzed α-allylation of protected α-amino- and α-hydroxyacetaldehydes. The method delivers γ,δ-unsaturated aldehydes in good yield, with *ee* values of more than 99%, and with synthetically useful diastereoselectivities. The products can be further functionalized in a stereodivergent manner to give a set of protected amino alcohols and diamines with superb selectivity. The work delineated herein underscores the power of stereodivergent dual catalysis as a concept in the development of practical and highly selective catalytic transformations.

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