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Stereodivergent α-Allylation of Linear Aldehydes with Dual Iridium and Amine Catalysis

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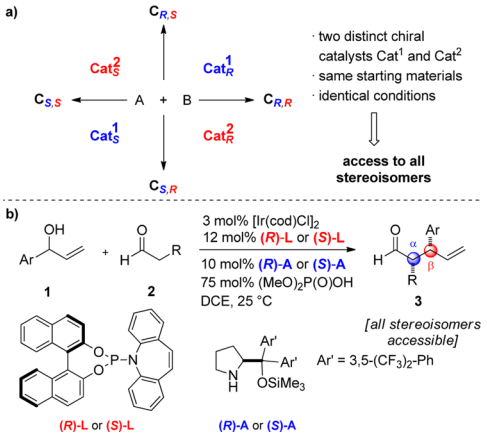
Supporting Information

ABSTRACT: We describe the fully stereodivergent, dual catalytic α-allylation of linear aldehydes. The reaction proceeds via direct iridium-catalyzed substitution of racemic allylic alcohols with enamines generated in situ. The use of an Ir(P,olefin) complex and a diarylsilyl prolinol ether as catalysts in the presence of dimethylhydrogen phosphate as the promoter proved to be crucial for achieving high enantio- and diastereoselectivity (>99% ee, up to >20:1 dr). The utility of the method is demonstrated in a concise enantioselective synthesis of the antidepressant (−)-paroxetine.

Despite impressive advances in the field of asymmetric synthesis,[1] the development of processes that enable at will the generation of any stereoisomer of a molecule bearing multiple stereogenic centers remains a challenge.[2] We recently introduced the concept of stereodivergent dual catalysis, which entails the simultaneous use of two distinct chiral catalysts to furnish products with full control over the configuration of two stereogenic centers (Scheme 1a).[3] The concept was successfully applied in the α-allylation of branched aldehydes catalyzed by a chiral Ir(P,olefin) complex and a chiral cinchona-alkaloid derived primary amine.[4] Herein, we report the development of enantio- and diastereodivergent α-allylation of linear aldehydes, which considerably expands the implementation of stereodivergent dual catalysis conceptually and preparatively. The full complement of product stereoisomers is prepared from the same set of starting materials and under identical conditions simply by the use of the four available catalyst permutations in a pairwise fashion (Scheme 1b). The utility of the method is showcased in a concise synthesis of the antidepressant (−)-paroxetine.

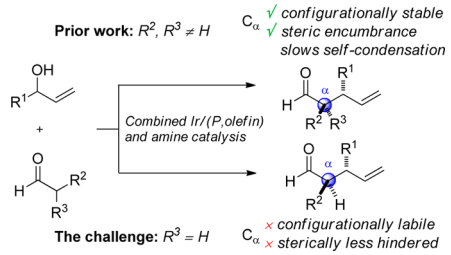
Scheme 1. Stereodivergent Dual Catalytic Allylation of Linear Aldehydes



Since the initial report by Tsuji on the Pd-catalyzed reaction of allyl acetates with stoichiometric amounts of enamines,[5] the method has been developed further to provide enantioselectively allylated ketones and aldehydes.[6] In addition, there are a number of reports describing transition metal catalyzed enantioselective intermolecular allylation of linear aldehydes that are also catalytic in amine.[7,8] However, these methods exert control over just one stereogenic center. By contrast, catalytic enantio- and diastereoselective methods providing access to γ,δ-unsaturated carbonyls in a single step with control of configuration of *two* vicinal stereogenic centers are rare and limited to variants of the asymmetric Claisen rearrangement.[9]

A notable difficulty associated with the stereoselective α-functionalization of linear aldehydes is that the products bear an enolizable stereogenic center, rendering them prone to epimerization (Scheme 2). This is especially the case for adducts generated under the reaction conditions developed to date in the context of stereodivergent, dual catalytic allylations for which acidic promoters and amine catalysts are prescribed.[3] Our earlier report involving the allylation of branched aldehydes circumvented this critical stereochemical issue because products were generated incorporating C_α quaternary stereocenters (Scheme 2). Additionally, the more hindered starting materials and products are considerably less prone to participate in side reactions, such as self-condensation, which take place at the expense of product yield. Filling this gap in the method was deemed important toward the development of fully stereodivergent allylation reactions of linear aldehydes. More

Scheme 2. Antecedents and Challenges in Reaction Development for Stereodivergent Dual Catalysis



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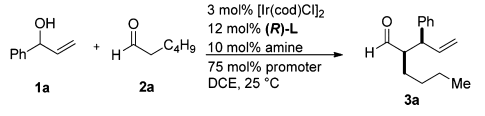
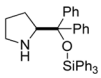
significantly, it would underline and expand the generality of stereodivergent dual catalysis as a concept. In addition, the allylation of unbranched aldehydes would constitute an enantio- and diastereodivergent equivalent to the venerable Ireland–Claisen rearrangement in which independent control of two stereogenic centers can be effected by the selection of enolate geometry (*E* versus *Z*) and alcohol configuration.

In line with our earlier studies, initial experiments were focused on intercepting reactive π-allyliridium intermediates[10−12] with enamines derived from C_α monosubstituted acetaldehydes. In contrast to the work involving branched aldehydes, which necessitated the use of a primary amine organocatalyst, we examined the use of secondary amines such as (*S*)-**A** (Scheme 1), which has been shown to enable the highly enantioselective α-functionalization of aldehydes via enamine catalysis.[13] In the initial prospecting experiments, the reaction of phenyl vinyl carbinol **1a** and hexanal **2a** in the presence of acetic acid as the promoter along with (*S*)-**A** and [Ir/(*R*)-**L**] as catalysts afforded the desired product **3a** in 26% ^{1}H NMR yield and >20:1 dr (Table 1, entry 1). The use of benzoic acid improved the outcome only slightly (entry 2). In both cases, the reactions did not go to completion and were plagued by self-aldol condensation of the aldehyde starting material.

Table 1. Variation of Reaction Parameters[a]



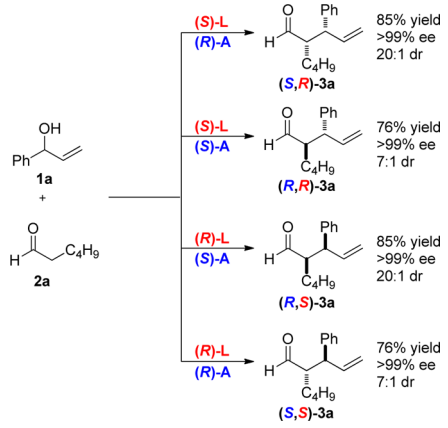
entry	promoter	amine	dr[b,c]	yield (%)[d]	
1	AcOH	(*S*)-**A**	>20:1	26	Side products
2	$PhCO_2H$	(*S*)-**A**	>20:1	42	
3	*p*-TsOH[e]	(*S*)-**A**	2:3	26	
4	$(BuO)_2PO_2H$	(*S*)-**A**	13:1	25	
5	$(PhO)_2PO_2H$	(*S*)-**A**	2:1	86	
6	$(MeO)_2PO_2H$	(*S*)-**A**	20:1	90	
7	$(MeO)_2PO_2H$	(*R*)-**A**	1:7	80	
8	$(MeO)_2PO_2H$		1.3:1	73	Poor dr
9	$(MeO)_2PO_2H$		2:1	75	

[a]Reactions run on 0.25 mmol scale under the standard conditions (see SI). [b]dr determined by ^{1}H NMR analysis of crude reaction mixture. [c]ee of the corresponding primary alcohol determined by SFC on a chiral stationary phase; for entries 1−3, ee not determined; for entries 4−9, ee >99%; absolute configuration determination described in SI. [d]Yields determined by ^{1}H NMR with 1,4-$(NO_2)_2C_6H_4$ as internal standard. [e]50 mol %.

Stronger acids such as *p*-toluenesulfonic acid led to product formation, albeit with a drop in diastereoselectivity and equally poor yield due to further reactions of the product (entry 3). The use of dibutylhydrogen phosphate gave the desired product with good stereoselectivity (>99% ee, 13:1 dr) but in low yield (25%). Careful analysis of the reaction mixture revealed that no aldol byproduct had been formed (entry 4). Consequently, we turned our attention to the use of phosphoric acid diesters as coactivators. While diphenylhydrogen phosphate gave clean and full conversion to the desired product, the observed dr dropped to 2:1 (entry 5). The use of dimethylhydrogen phosphate (pK_a = 1.29 in H_2O), by contrast, gave **3a** in 90% yield by ^{1}H NMR analysis (85% isolated yield), >99% ee, and 20:1 dr (entry 6).[14] Although the reaction was complete after 6 h, it is noteworthy that when it is stirred for an additional 12 h only a modest drop in diastereoselectivity to 14:1 is observed. This indicates that epimerization under these conditions post C−C bond formation is slow relative to the time scale of the reaction. This is significant because at the outset of our studies when stronger acids, such as *p*-TsOH (pK_a = −2.8 in H_2O) or TFA (pK_a = 0.23 in H_2O), were employed we observed substantial epimerization at C_α following C−C bond formation. Additional investigations revealed that the *anti* diastereomer of **3a** could be produced in good yield and stereoselectivity (>99% ee, 7:1 dr) by employing the enantiomeric amine catalyst (*R*)-**A** (entry 7). This switch in the sense of diastereoselectivity indicates that the two chiral catalysts are capable of independent control over the configuration of the two stereocenters, the defining feature of stereodivergent, dual catalysis. A number of other amine catalysts were also employed in the presence of dimethylhydrogen phosphate as the promoter but gave inferior results in terms of diastereoselectivity (entries 8 and 9) and the extent of the diastereochemical switch (see Supporting Information (SI) for details).

With a suitable set of conditions in hand, we went on to establish that all four stereoisomers of γ,δ-unsaturated aldehyde **3a** can be prepared (Scheme 3). From the same set of starting materials **1a** and **2a** and under identical reaction conditions, all four products are obtained in good yields, excellent enantioselectivity (>99% ee), and good diastereoselectivity (7:1 to 20:1 dr) by simply selecting from the various pairwise catalyst combinations.

Scheme 3. Synthesis of All Stereoisomers of 3a



We then set out to explore the scope of the α-allylation with regard to the allylic alcohol component (Table 2). A range of allylic alcohols substituted with arenes bearing alkyl and electron-donating substituents furnish products (**3b**−**3d**) in good yields, 7:1 to >20:1 dr, and >99% ee. In addition, an allylic alcohol incorporating a thiophene (**3e**) proved to be a good substrate for the reaction. Allylic alcohols incorporating arenes with halogen or electron-withdrawing substituents also participated in the reaction, but they required the use of a stronger promoter such as trichloroacetic acid (**3f** and **3g**) to give good yields.[15]

We then turned our attention to investigating the scope of the reaction with regard to the aldehyde component (Table 3). A range of unfunctionalized linear aldehydes give the desired

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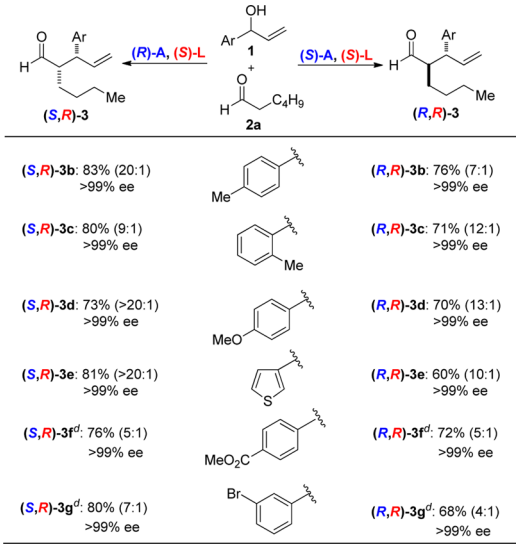
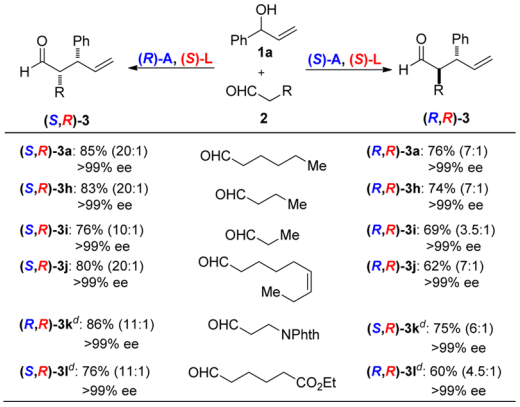
Table 2. Allylic Alcohol Scope of the Allylation[a,b,c]



[a]All reactions were run on 0.25 mmol scale under the standard conditions. [b]Yields of isolated products (diastereomeric mixture) after purification by flash chromatography. [c]ee of the corresponding primary alcohol determined by SFC on a chiral stationary phase; dr (shown in parentheses) determined by ^{1}H NMR analysis of crude reaction mixture. Absolute stereochemistry determined by analogy. [d]50 mol % of trichloroacetic acid instead of dimethyl hydrogen phosphate.

Table 3. Aldehyde Scope of the Allylation[a,b,c]

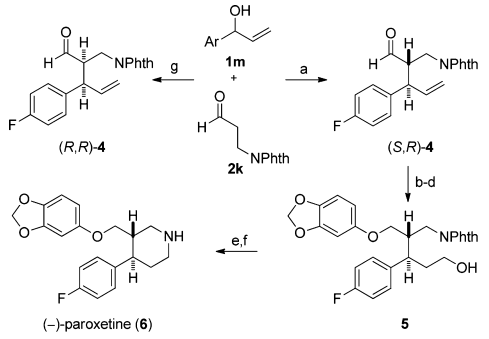


[a]Reactions were run on 0.25 mmol scale under the standard conditions. [b]Yields of isolated products (diastereomeric mixture) after purification by flash chromatography. [c]ee determined by SFC on a chiral stationary phase; dr (shown in parentheses) determined by ^{1}H NMR analysis of crude reaction mixture. Absolute configuration determined by analogy. [d]100 mol % dimethyl hydrogen phosphate.

products (**3a**, **3h**−**3j**) in good yields and 3.5 to >20:1 diastereoselectivity. In addition, common functional groups such as a phthalimide and an ester were tolerated (**3k**, **3l**).

Finally, in an effort to demonstrate the practicality and utility of this stereodivergent dual catalytic process, we examined the application to the synthesis of a high-profile target. (−)-Paroxetine, a selective serotonin reuptake inhibitor, is commonly used in the treatment of depression, obsessive compulsive disorders, and panic disorders.[15] Ir((*S*)-**L**)/(*S*)-**A** catalyzed allylation of aldehyde **2k** with 4-fluorophenyl vinyl carbinol **1m** afforded γ,δ-unsaturated aldehyde (*S*,*R*)-**4** in 64% yield, >99% ee, and 6:1 dr (gram scale, Scheme 4). Separation of the diastereomers was achieved after reduction to the corresponding primary alcohol,

Scheme 4. Concise Synthesis of (−)-Paroxetine[a]



[a]Reagents and conditions: (a) 3 mol % $[Ir(cod)Cl]_2$, 12 mol % (*S*)-**L**, 10 mol % (*S*)-**A**, 50 mol % Cl_3CCO_2H, DCE, rt, 16 h, 64%, >99% ee, 6:1 dr. (b) $NaBH_4$, CH_2Cl_2/MeOH (2/1), −78 °C, 20 min, 73% (single diastereomer). (c) DEAD, PPh_3, sesamol, THF/toluene (6/1), reflux, 10 h, 74%. (d) 9-BBN, THF, rt, 2 h; then $NaBO_3$, 1 h, 67%. (e) $N_2H_4{\cdot}H_2O$, EtOH, reflux, 30 min, 79%. (f) PPh_3, DIAD, 0 °C to rt, 2.5 h, 71%. (g) 3 mol % $[Ir(cod)Cl]_2$, 12 mol % (*S*)-**L**, 10 mol % (*R*)-**A**, 50 mol % Cl_3CCO_2H, DCE, rt, 18 h, 78%, >99% ee, 8:1 dr.

which was then displaced to give the corresponding aryl ether. Hydroboration/oxidation of the terminal olefin furnished **5**. Cleavage of the phthalimide followed by cyclization then afforded (−)-paroxetine **6**.[16] It is noteworthy that stereoisomer (*R*,*R*)-**4** could also be prepared in enantiomerically pure form and in a single step from the same starting materials **1m** and **2k**, thus enabling the synthesis of the diastereomer of (−)-paroxetine. We anticipate that this feature of stereodivergent dual catalytic methods will make them highly attractive for use in medicinal chemistry in establishing structure−activity relationships.

In summary, we have disclosed a stereodivergent dual catalytic α-allylation of linear aldehydes that relies on the combination of iridium and amine catalysis. The method enables the preparation of a range of γ,δ-unsaturated aldehydes bearing two vicinal stereogenic centers. The appropriate combination of chiral catalysts provides any given product stereoisomer from the same set of starting materials under identical conditions. The synthetic utility of the method was showcased in a concise synthesis of (−)-paroxetine. Studies to further establish the concept of stereodivergent dual catalysis are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all reactions and products, including ^{1}H and ^{13}C NMR spectra as well as SFC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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