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Formaldehyde *N,N*-Dialkylhydrazones as Neutral Formyl Anion Equivalents in Iridium-Catalyzed Asymmetric Allylic Substitution

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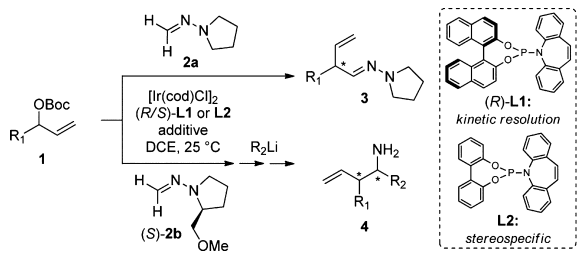
Supporting Information

ABSTRACT: The use of formaldehyde *N,N*-dialkylhydrazones as neutral C1-nucleophiles in the iridium-catalyzed substitution of allylic carbonates is described for two processes. Kinetic resolution or, alternatively, stereospecific substitution affords configurationally stable α,α-disubstituted aldehyde hydrazones in high enantiomeric excess and yield. This umpolung approach allows for the construction of optically active allylic nitriles and dithiolanes as well as branched α-aryl aldehydes. A catalyst-controlled reaction with Enders' chiral hydrazone derivatives followed by diastereoselective nucleophilic addition to the hydrazone products constitutes a two-step stereodivergent synthesis of chiral amines.

The concept of reversing the inherent electrophilic reactivity of acyl groups was first formulated by Corey and Seebach and later termed "umpolung". This construct has enabled chemists to craft a host of novel strategies for the synthesis of complex molecules.[1,2] Among these is the development of d^1-reagents, such as cyanide, thioacetals, or cyanohydrins. Despite progress in this area, there remain untapped opportunities in the application of these reagents in asymmetric catalysis. For example, transition-metal catalyzed enantioselective allylic substitution reactions of C1-formyl anion equivalents are unknown. Given the utility of the optically active, branched, α-vinyl formyl products and the difficulty of accessing them by conventional methods, development of such reactions would be highly desirable.[3] Herein, we report the first asymmetric formylation of allylic carbonates with formaldehyde *N,N*-dialkylhydrazones catalyzed by an iridium-(P,olefin) complex to afford formylated products **3** (Scheme 1). The reaction can be employed in two different modes: (1) in enantioselective kinetic resolution of racemic starting materials ((*R*/*S*)-**L1**) or, alternatively, (2) in stereospecific allylic substitution of optically active carbonates (**L2**). The versatile products can be further converted to allylic nitriles and dithiolanes without racemization, and highly enantioenriched, saturated α-aryl aldehydes are accessible by this method. We show that diastereoselective nucleophilic addition to products derived from Enders' chiral formaldehyde hydrazone **2b** enables stereodivergent access to α,β-branched chiral amines **4**.

Scheme 1. Ir-Catalyzed Asymmetric Formylation of Allylic Carbonates with Formaldehyde *N,N*-Dialkylhydrazones



Transition-metal catalyzed asymmetric allylic substitution (AAS) reactions represent a versatile approach for enantioselective synthesis, and recent advances have dramatically increased the utility of such methods.[4] However, challenges remain, such as the enantioselective substitution using carbonyl anion equivalents.[5] Only four classes of reverse-polarity nucleophiles for the synthesis of α-branched carbonyl products by AAS have been reported to date (Figure 1). Two of these approaches have been the subject of methodological studies in which stabilized enolates are employed as methoxy carbonyl anion equivalents. Acetoxymalonates have been utilized in the Pd-catalyzed AAS by Trost and Helmchen to afford methyl esters after oxidative degradation procedures.[6] Esters were also obtained by Helmchen through oxidation of malononitriles, arising from iridium-catalyzed AAS.[7] However, reports of masked acyl anion equivalents in AAS have been scarce. A single example utilizing 1-phenylsulfonyl-1-nitroethane in conjunction with palladium catalysis for the enantioselective introduction of an acetyl group has been reported in the synthesis of hygromycin analogues.[8] More recently, P. A. Evans described a study of stereospecific, rhodium-catalyzed allylic substitutions with silylated cyanohydrins, which were subjected to *in situ* deprotection to afford α,α-disubstituted arylketones.[9]

As part of our ongoing program to extend the scope and utility of iridium-catalyzed AAS under nonanionic conditions,[10] we became interested in examining a reverse-polarity nucleophile for

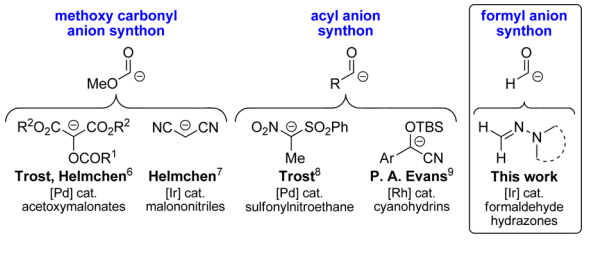


Figure 1. Carbonyl anion equivalents in AAS.

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previously unknown asymmetric formylation reactions. Crucial to the success of such an endeavor would be the identification of a suitable formyl anion equivalent. We were drawn to the use of formaldehyde *N,N*-dialkylhydrazones, pioneered by Brehme[11] and further developed by Enders and Lassaletta.[12] The aza-enamine character makes them neutral formyl anion equivalents, which have been shown to be effective nucleophiles in the presence of both Brønsted and Lewis acids.[13]

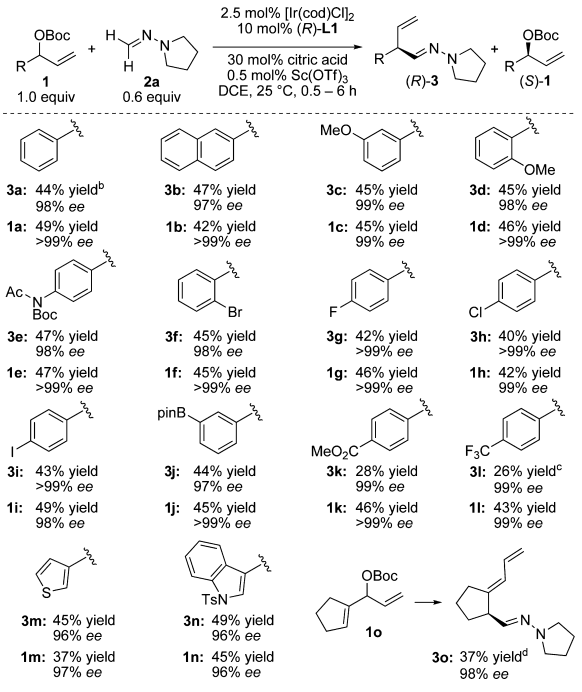
In our study of nucleophilic formylation of allyl-iridium complexes formed from $[Ir(cod)Cl]_2$ and ligand (*S*)-**L1**, the formaldehyde hydrazone of 1-aminopyrrolidine (**2a**) was chosen for its availability and relatively high nucleophilicity.[14] Free allylic alcohols were found to be unsuitable substrates under either Lewis acid (e.g., $Sc(OTf)_3$)[10b] or Brønsted acid (e.g., $(BuO)_2PO_2H$, CSA) assistance.[15] A search for alternative substrates revealed allylic *tert*-butyl carbonates **1** to be viable electrophile precursors for the catalytic system. Reactions with carbonate **1a** (R = Ph) proceeded cleanly to afford the desired product (**3a**). We noted that the reaction rate became sluggish and the *ee* of the product deteriorated with increasing conversion. We initially attributed the erosion in optical purity to racemization of the product over the course of the reaction. Yet, in experiments with isolated, optically active products, no change in *ee* could be observed under the reaction conditions. Optimization efforts revealed that the addition of weak Brønsted acids (e.g., formic acid, citric acid) led to a highly enantioselective kinetic resolution process. The use of citric acid was especially advantageous as a consequence of competing formate addition when formic acid was employed. The addition of 0.5 mol % of $Sc(OTf)_3$ was found to increase reaction rates and lead to higher yields of recovered starting material.[16]

With the optimized conditions in hand, we set out to explore the scope of the asymmetric allylic formylation (Table 1). Various electron-neutral and -rich aromatic substrates afforded the desired products **3a**–**3e** in good yield and 97–99% *ee* along with the recovery of optically enriched (99% *ee*) carbonates **1a**–**1e**. Carbonates incorporating halogenated arenes were found to be equally suitable substrates (**1f**–**1i**) even when substituted in the *ortho*-position (**1f**), furnishing products **3f**–**3i** in 98–99% *ee*. Pinacolboronate esters were also well tolerated under the reaction conditions (**1j** → **3j**, 97% *ee*). Substrates bearing electron-deficient arenes participated in the reaction to give **3k**–**3l** (99% *ee*), albeit with lower efficiency.[17] Additionally, heteroaryl-bearing allylic carbonates proved to be excellent substrates for the reaction, affording hydrazone products **3m**–**3n** in high yield and 96% *ee*. Finally, starting from bisallylic carbonate **1o**, the conjugated diene **3o** was obtained in 37% yield (95:5 regioselectivity) and 98% enantioselectivity. The kinetic resolution described is highly efficient with calculated selectivity factors (*s*) of >600, except for **3m** (*s* = 232) and **3n** (*s* = 218).[18] Additionally, the procedure, which enjoys the benefits of being oxygen- and moisture-tolerant, was also found to be scalable, and the catalyst loadings could be further decreased to 1 mol % for gram-scale synthesis of hydrazone product **3a** without deleterious effects.[19,20]

The recovered enantioenriched carbonates **1** proved to readily undergo stereospecific substitution under the influence of a catalyst formed from iridium and achiral **L2** (Scheme 1), affording optically active hydrazone adducts **3** (Table 2).[21] Apart from catalytic $Sc(OTf)_3$, no additional additives were necessary, and catalyst loadings as low as 1 mol % $[Ir(cod)Cl]_2$ were found to be sufficient. All allylic carbonates recovered from the kinetic resolution underwent the stereospecific allylic formylation in good to excellent yield with high enantiospecificity (96–99% *es*). The possibility of reuse of the recovered starting materials significantly enhances the utility of our method, as it makes both enantiomers of the products available from the same batch of racemic allylic carbonates.

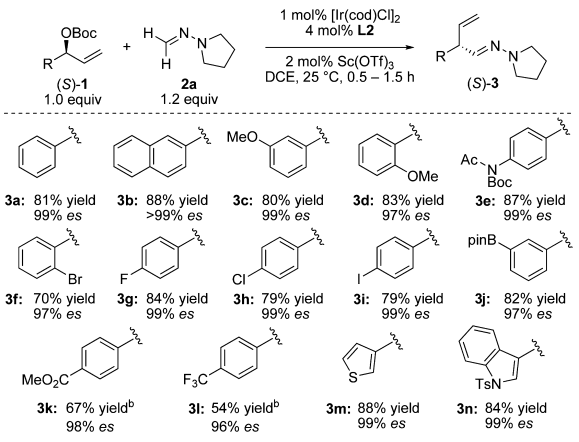
The hydrazone products **3** are versatile entities, which can be subjected to further synthetic manipulations. They can be

Table 1. Allylic Carbonate Scope of the Kinetic Resolution[a]



[a]Unless otherwise noted, reactions were carried out at 1 mmol scale. Yield of the isolated products and starting materials after purification by chromatography on silica gel. The *ee* was determined by SFC or HPLC on a chiral stationary phase. [b]Conducted at 10 mmol scale with 1 mol % $[Ir(cod)Cl]_2$ and 4 mol % (*R*)-**L1**. [c]5 mol % $[Ir(cod)Cl]_2$, 20 mol % (*R*)-**L1** employed. [d]Conducted at 0.5 mmol scale. The starting material was recovered in 41% yield as a regioisomeric mixture.

Table 2. Scope of the Stereospecific Allylic Formylation[a]



[a]Unless otherwise noted, reactions were conducted at 0.25 mmol scale. Yield of the isolated products after purification by chromatography on silica gel. The *es* was determined by SFC or HPLC on a chiral stationary phase. [b]3 mol % $[Ir(cod)Cl]_2$, 12 mol % **L2** used.

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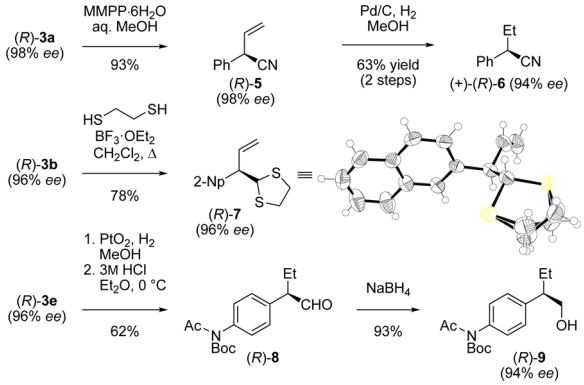
Scheme 2. Elaboration of Hydrazone Products



transformed to the corresponding allylic nitrile under oxidative conditions without racemization or double bond migration, as exemplified by the conversion of (*R*)-**3a** (98% *ee*) to (*R*)-**5** (98% *ee*) (Scheme 2).[22] Selective hydrogenation of the double bond afforded known (+)-(*R*)-**6** (94% *ee*), enabling the determination of its absolute configuration. Additionally, hydrazone (*R*)-**3b** (96% *ee*) could be converted to dithiolane (*R*)-**7** (96% *ee*) without racemization.[23] It is noteworthy that neither cyanide nor dithiolane anions have been utilized for the stereoselective construction of structures such as **5** or **7** by AAS. Moreover, α-vinylation or α-arylation of the corresponding nitriles or dithiolanes is unknown. Finally, biphasic hydrolysis of the hydrogenation product of (*R*)-**3e** (96% *ee*) afforded α-aryl aldehyde (*R*)-**8** which can be isolated and reduced to the alcohol (*R*)-**9** in high yield with negligible racemization (94% *ee*).

We next investigated chiral formaldehyde hydrazone derivatives in the allylic substitution reaction. Drawing on the experience of previous work on dual iridium-enamine catalysis[10e,g] and the analogous aza-enamine character of the nucleophile **2b**, we anticipated high stereocontrol by the Ir catalyst at the allylic stereocenter. Nonetheless, we were interested in examining whether matching and mismatching effects between the chiral hydrazone and allyl-iridium intermediate would be observed. In the experiment, when the formaldehyde hydrazone of Enders' hydrazine[24] ((*S*)-**2b**, Scheme 3) was employed in the kinetic resolution reaction, both (*S*,*R*)-**10** (from (*R*)-**L1**) and (*S*,*S*)-**10** (from (*S*)-**L1**) were obtained as single diastereomers with 99% *ee*. Given the results, the use of either enantiomer of the chiral hydrazone allows maximum leeway for stereocontrol by the hydrazone auxiliary in subsequent diastereodivergent nucleophilic additions. Accordingly, treatment of **10** with MeLi in the presence of $LaCl_3$·2LiCl in THF furnished trifluoroacethydrazides **11** in 88% yield.[25] The diastereoselectivity is efficiently controlled by the chiral auxiliary with *d.r.* > 20:1 for (*S*,2*R*,3*R*)-**11** and *d.r.* = 10:1 for (*S*,2*R*,3*S*)-**11**, as judged from the analysis of the ^{1}H NMR spectra (unpurified products). X-ray crystallographic analysis of (*S*,2*R*,3*R*)-**11** unambiguously confirmed the absolute and relative configuration of the products.[26] Trifluoroacethydrazides have been demonstrated to undergo reduction of the *N*,*N*-bond by SmI_2.[27,28] Following this procedure afforded trifluoroacetamides (2*R*,3*S*)-**12** and (2*S*,3*S*)-**12** in good yields without racemization. Treatment of (2*R*,3*S*)-**12** and (2*S*,3*S*)-**12** with K_2CO_3 in aqueous methanol led to the hydrolysis of the trifluoroacetamides. Overall, (2*R*,3*S*)-**4** and (2*S*,3*S*)-**4** were obtained as their hydrochloride salts in 55% and 64% yield from the formylation products **10**, respectively. This procedure thus represents a two-step (**1a** → **10** → **11**) diastereodivergent synthesis of substituted arylethyl amines. Notably, the reported procedure makes available all four stereoisomers of this biologically important structural motif, depending on the choice of ligand and chiral hydrazone.[29]

In summary, we have developed an asymmetric allylic formylation which combines an umpolung approach with Ir catalysis. Formaldehyde *N*,*N*-dialkylhydrazones were shown to be competent nucleophiles for the allylic substitution reaction in both a kinetic resolution and stereospecific setting, and the products can be further transformed to α,α-disubstituted nitriles, dithiolanes, and saturated, branched α-aryl aldehydes in high enantiomeric excess. Chiral formaldehyde hydrazone derivatives were demonstrated to undergo catalyst-controlled substitution, and their use enables a highly flexible stereodivergent approach to chiral homoallylic amines. Further studies and applications of the versatile hydrazone products are currently 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 and HPLC traces and X-ray crystallographic data, are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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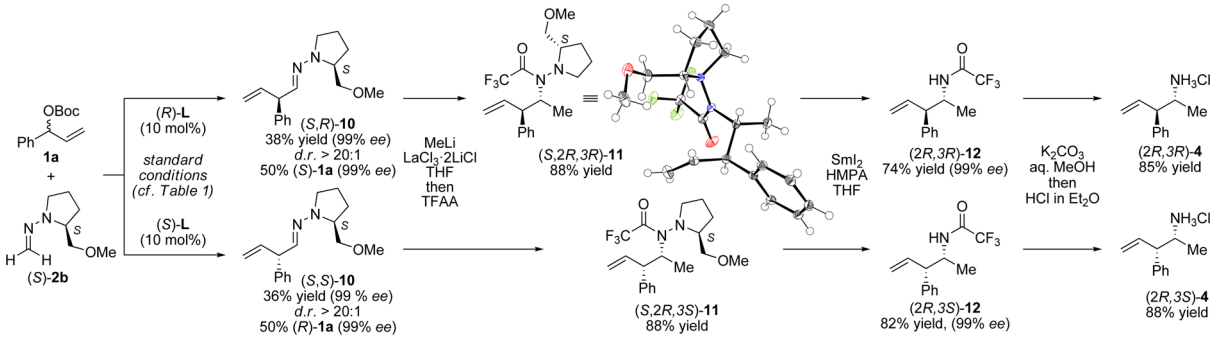
Notes

The authors declare no competing financial interest.

Scheme 3. Diastereodivergent Synthesis of Chiral Amines



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