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Rhodium/Yanphos-Catalyzed Asymmetric Interrupted Intramolecular Hydroaminomethylation of *trans*-1,2-Disubstituted Alkenes

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Supporting Information

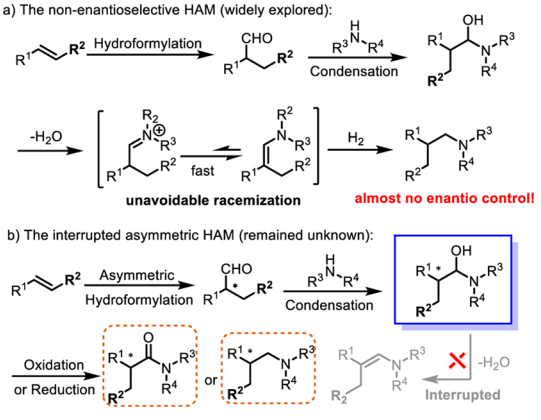
ABSTRACT: The first interrupted asymmetric hydroaminomethylation reaction was developed. The challenging *trans*-1,2-disubstituted olefins were employed as substrates, and a series of valuable chiral pyrrolidinones and pyrrolidines were obtained in high yields with high regioselectivities and excellent enantioselectivities. Several synthetic transformations were conducted, demonstrating the high synthetic utility of our method. A creative route for the synthesis of vernakalant and Enablex was also developed.

Since the first discovery by Reppe et al. at BASF in the early 1950s,[1] hydroaminomethylation (HAM) has been one of the most efficient reactions to synthesize valuable amines with important biological and medicinal properties for the construction of drugs and fine chemicals from readily available alkenes and amines in the presence of syngas with high atom economy.[2] A typical HAM reaction includes the hydroformylation of an alkene, the subsequent condensation of the aldehyde with the amine, and the final hydrogenation of the resulting imine or enamine to give the desired amine (Scheme 1a). In that respect, linear HAM has been widely explored, and recent progress has been summarized in several reviews.[3]

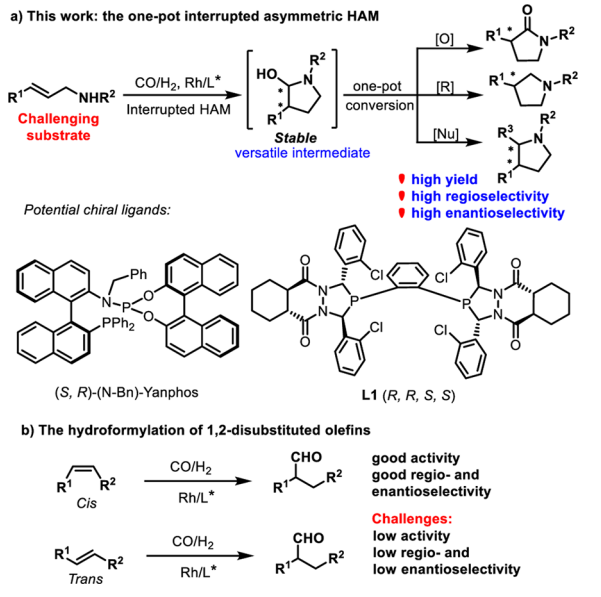
With respect to asymmetric HAM, unavoidable racemization of the chiral iminium often occurs through fast isomerization to the nonchiral enamine (Scheme 1a). Consequently, reports on asymmetric HAM are very rare.[4] Recently, Kalck and co-workers tried asymmetric HAM catalyzed by rhodium complexes with chiral diphosphine ligands.[4a] However, only racemic amine was obtained. The results were explained by a detailed computational study, which revealed that the hydrogenation of the imine intermediate follows a similar energetic pathway regardless of the chiral ligand used.[4a] On the basis of our long-term interest in HAM,[5] we envisioned that the chiral product could be obtained by interrupting the reaction through stabilization of the chiral hemiacetal intermediate, leaving the chiral carbon untouched. Importantly, the one-pot workup using an oxidant or reductant would generate the valuable chiral amides or amines (Scheme 1b).

With regard to stabilization of the intermediate, we perceived that the cyclic five-membered-ring hemiacetal is very stable,[6] which makes the interrupted asymmetric HAM possible in an intramolecular version using the protected 3-substituted allylamine as substrate along with our previously developed Yanphos ligand[7] or the steric bulky ligand **L1**[8] (Scheme 2a). As mentioned above, the five-membered-ring hemiacetal intermediate can be

Scheme 1. Widely Explored HAM Reaction and the New Interrupted Asymmetric HAM Reaction



Scheme 2. Interrupted HAM of 3-Substituted Allylamines with Potential Chiral Ligands and Hydroformylation of 1,2-Disubstituted Olefins



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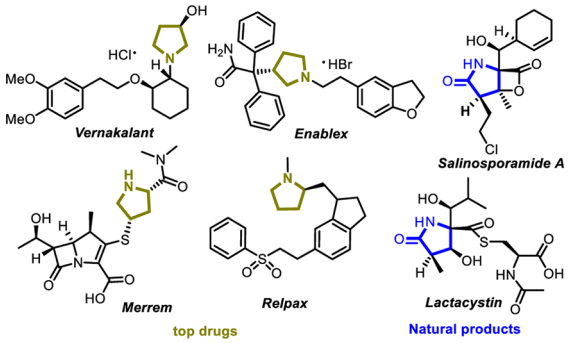
easily converted to valuable pyrrolidinones and pyrrolidines, which are common motifs in many top-200 brand-name drugs and natural products, such as the top drugs vernakalant,[9] Enablex,[10] Merrem,[11] and Relpax[12] and the natural products salinosporamide A and lactacystin[13] (Scheme 3). As a result, the

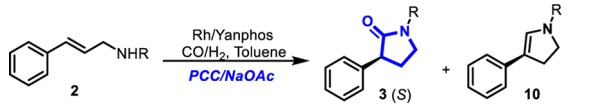
Scheme 3. Representative Top-200 Brand-Name Drugs and Natural Products Featuring the Pyrrolidine and Pyrrolidinone Motifs



interrupted asymmetric HAM of protected 3-substituted allylamines will be highly desirable. However, the first step of the asymmetric HAM of protected 3-substituted allylamines, the asymmetric hydroformylation of 1,2-disubstituted olefins, remains a very challenging problem.[14] To date, only a few examples have been reported.[15] Among these examples, the asymmetric hydroformylation of *cis*-1,2-disubstituted olefins was realized with good regioselectivities and enantioselectivities.[15a,b,f] However, the hydroformylation of the readily available *trans*-1,2-disubstituted olefins was shown to be much more challenging, and generally lower reactivities and enantioselectivities were observed (Scheme 2b).[15b,f] Herein we report the first rhodium (*N*-Bn)-Yanphos (Scheme 2a)-catalyzed interrupted asymmetric HAM of the very challenging substrates, *trans*-1,2-disubstuted olefins, to afford valuable chiral pyrrolidinones and pyrrolidines in one pot with excellent regio- (>99:1) and enantioselectivities (up to 96% *ee*).

The reaction was initiated by investigating the one-pot method for the preparation of chiral pyrrolidinones. We were pleased to find that the one-pot reaction proceeded smoothly upon the addition of pyridinium chlorochromate (PCC)/NaOAc to the reaction system once the hydroformylation reaction stopped, with high yield and excellent regioselectivity (for the screeing of oxidants, see the Supporting Information (SI)). In the presence of Rh/Yanphos, the reaction took place only at the α position, affording the desired chiral pyrrolidinone **3a** exclusively with 93% *ee* (Table 1, entry 1). The effects of the reaction conditions on the one-pot interrupted asymmetric HAM were subsequently investigated. Lowering of the L/Rh ratio gave a higher yield, but the *ee* dropped significantly (entries 1−3). The yield dropped sharply when the syngas pressure was lowered, although slightly higher *ee* was observed (entry 4). Increasing the syngas pressure to 20:20 bar gave rise to the presence of the dehydrated product in 30% yield, and moreover, the *ee* dropped sharply (entry 5). Increasing the temperature gave a higher yield but a lower *ee*, while in contrast, lowering the temperature gave a lower yield but slightly higher *ee* (entries 6 and 7). It was also found that a shorter reaction time and lower catalyst loading gave a lower yield while the *ee* almost remained the same (entries 8 and 9). The steric bulky ligand **L1** (Scheme 2) was also tested (for the screening of other ligands, see the SI), but only the dehydrated product was

Table 1. Screening of Conditions for the One-Pot Interrupted Asymmetric HAM To Afford Chiral Pyrrolidinones[a]



entry	R[b]	L/Rh	CO:H_2 (bar)	T (°C)	yield (%)[c]	*ee* (%)[d]
1	Ts	2.0	10:10	70	93 (**3**)	93
2	Ts	1.5	10:10	70	95 (**3**)	84
3	Ts	1.1	10:10	70	98 (**3**)	12
4	Ts	2.0	5:5	70	41 (**3**)	95
5[e]	Ts	2.0	20:20	70	66 (**3**)	10
6	Ts	2.0	10:10	80	97 (**3**)	90
7	Ts	2.0	10:10	60	57 (**3**)	94
8[f]	Ts	2.0	10:10	70	77 (**3**)	94
9[g]	Ts	2.0	10:10	70	81 (**3**)	93
10[h]	Ts	2.0	10:10	70	85 (**10**)	–
11[i]	Ts(OMe)	2.0	10:10	70	89 (**10**)	–
12[j]	Bn	2.0	10:10	70	94 (**10**)	–
13	Boc	2.0	10:10	70	90 (**3**)	41
14	Bz	2.0	10:10	70	86 (**3**)	56

[a]The reaction was conducted on a 0.1 mmol scale in 0.5 mL of toluene with $Rh(acac)(CO)_2$ (acac = acetylacetone) as the metal precursor, (*S*,*R*)-(*N*-Bn)-Yanphos as the ligand, S/C = 20, a reaction time of 70 h, PCC (0.2 mmol), and NaOAc (0.2 mmol). [b]Ts = 4-methylbenzenesulfonyl; Ts(OMe) = 4-methoxybenzenesulfonyl; Bn = benzyl; Boc = *tert*-butoxycarbonyl; Bz = benzoyl. [c]Isolated yields of the chiral pyrrolidinones. [d]Enantiomeric excesses of the products as determined by chiral HPLC. [e]The dehydrated product was isolated in 30% yield. [f]Reaction time = 48 h; [g]S/C = 50. [h]**L1** was used as the ligand; only the dehydrated product was obtained in 85% yield without using the oxidant PCC/NaOAc. [i]Only the new aldehyde product was obtained in 89% yield. [j]Only the dehydrated product was obtained in 94% yield without using the oxidant PCC/NaOAc.

obtained (entry 10). We further investigated the effect of the substituents on the amine moiety. It was found that no desired product was observed when the Ts group was changed to a Ts(OMe) group (entry 11). Instead, the hemiacetal intermediate dehydrated and was further oxidized by PCC to give a new aldehyde (see the SI). With the electron-donating benzyl group attached to the substrate, the dehydrated product was obtained exclusively in high yield (entry 12).[5e] Only when the electron-withdrawing Boc or Bz group was attached to the substrate did the desired chiral pyrrolidinones form (entries 13 and 14). However, the *ee* dropped significantly, which is probably due to fast racemization of the hemiacetal product when the strong electron-withdrawing group is attached to the substrate. These results indicated that the protecting group on the amine moiety is very critical to the reaction and that only electron-withdrawing groups give the desired products. The Ts group was selected as the best in terms of the high enantioselectivity.

With the optimized reaction conditions in hand, the substrate scope of the one-pot asymmetric HAM to afford chiral pyrrolidinones was investigated. As summarized in Table 2, a series of chiral pyrrolidinones were obtained in high yields with excellent *ee*. It was found that electron-donating groups on the benzene ring tended to deactivate the substrates, affording lower isolated yields, but the *ee* remained very high (**3a**−**c**). In contrast, with electron-withdrawing groups attached to the benzene ring, the substrates were activated, and shorter reaction times were needed while the *ee* was not influenced (**3d**−**h**). For example, when the trifluoromethyl group or three fluorine atoms were

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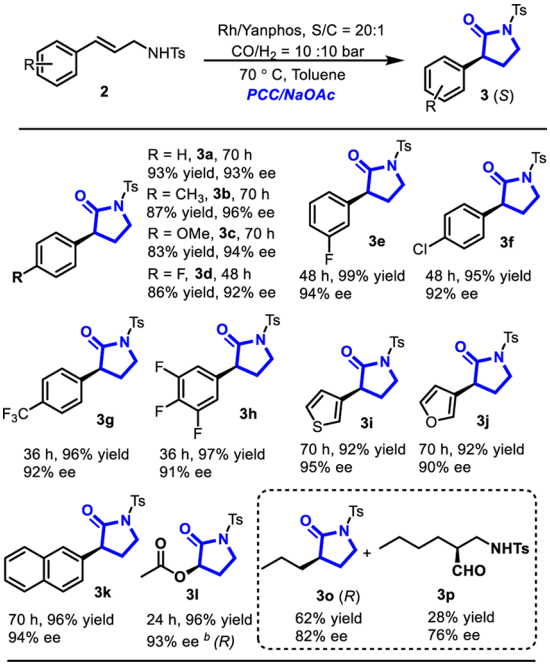
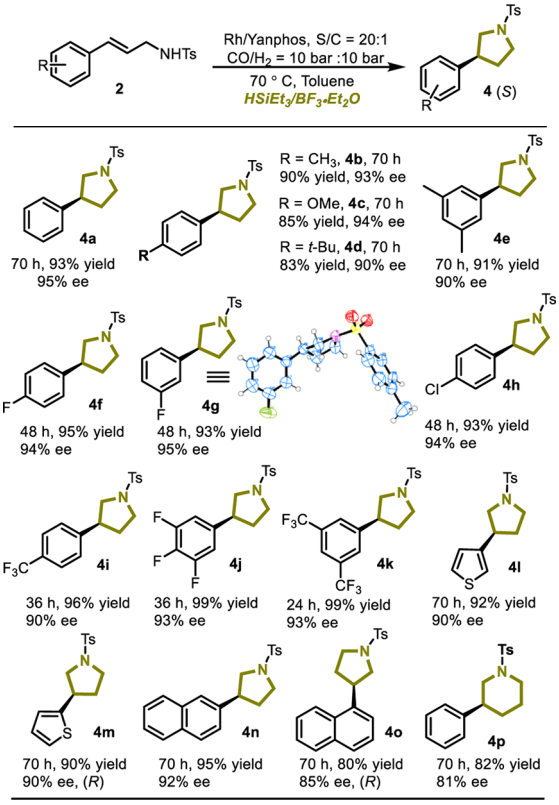
Table 2. Substrate Scope for the Preparation of Chiral Pyrrolidinones through the Interrupted Asymmetric HAM[a]



[a]The reaction was conducted on a 0.1 mmol scale in 0.5 mL of toluene with $Rh(acac)(CO)_2$ as the metal precursor, (*S*,*R*)-(*N*-Bn)-Yanphos as the ligand, $CO:H_2$ = 10:10 bar, S/C = 20, PCC (0.2 mmol), and NaOAc (0.2 mmol). The configuration of all of the products was determined to be *S*, and only the desired regioisomer was obtained as determined by NMR analysis. [b]The *cis*-configured substrate was used with S/C = 100.

Table 3. Substrate Scope for the Preparation of Chiral Pyrrolidines through the Interrupted Asymmetric HAM[a]



[a]The reaction was conducted on a 0.1 mmol scale in 0.5 mL of toluene with $Rh(acac)(CO)_2$ as the metal precursor, (*S*,*R*)-(*N*-Bn)-Yanphos as the ligand, $CO:H_2$ = 10:10 bar, S/C = 20, $HSiEt_3$ (0.3 mmol), and $BF_3.Et_2O$ (0.3 mmol). The configuration of all of the products was determined to be *S*, except for **4m** and **4o**; only the desired regioisomer was obtained as determined by NMR analysis.

attached to the substrate, only 36 h was needed for full conversion (**3g** and **3h**). Interestingly, thienyl, furyl, and naphthyl substrates were also tolerated, and the corresponding valuable products **3i**, **3j**, and **3k** were obtained in very high yields with excellent *ee*. Importantly, the *cis*-configured acetoxy substrate **2l** was also smoothly converted with much lower catalyst loading and much shorter reaction time, giving the product **3l** in very high yield and *ee*. Furthermore, 3-propyl allylic amine was also employed as the substrate. To our delight, the desired chiral pyrrolidinone product **3o** was obtained in good yield, albeit with the formation of the aldehyde product **3p**.

With regard to the preparation of chiral pyrrolidines, the one-pot method was also developed simply by adding $HSiEt_3$ and $BF_3{\cdot}Et_2O$ to the reaction system at low temperature (−10 °C) when the hydroformylation reaction stopped, without isolation of the hemiacetal intermediate. The substrate scope for the preparation of chiral pyrrolidines through the interrupted asymmetric HAM was also investigated. As summarized in Table 3, the one-pot interrupted HAM method to afford chiral pyrrolidines has a broad substrate scope. A series of chiral pyrrolidines were obtained in very high yields with excellent *ee* (>90%), regardless of whether the substituents on the pyrrolidine ring were electron-donating (**4a**−**e**), electron-withdrawing (**4f**−**k**), heterocyclic (**4l** and **4m**), or naphthyl (**4n**). However, when 1-substituted naphthalene was employed as the substrate, a lower yield and *ee* were observed (**4o**), which is probably due to the ortho steric hindrance of the substituted ring. Interestingly, the reaction also tolerated a homoallylic amine, giving the chiral piperidine product **4p** in good yield and *ee*. As aforementioned, electron-donating groups on the substrate gave a lower reaction rate, and electron-withdrawing groups gave a higher reaction rate requiring a much shorter reaction time. Moreover, in order to determine the absolute configuration of the products, X-ray analysis of **4g** was conducted, and the configuration was determined to be *S*.[16]

In order to further demonstrate the synthetic utility of the interrupted asymmetric HAM, several transformations were conducted, as summarized in Scheme 4. Interestingly, we found that the *ee* remained the same regardless of whether the substrate is *cis* or a *cis*/*trans* mixture, which makes the method very convenient without the tedious isolation of the *cis*/*trans* mixture (Scheme 4a). The interrupted asymmetric HAM reaction was also conducted on a gram scale with a lower catalyst loading (Scheme 4b). Satisfyingly, we found that the hemiacetal **5** was very stable and was isolated in high yield with excellent regio- and enantioselectivity, albeit with a low dr. Hemiacetal **5** was subsequently treated with indole or allyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$. It was found that the desired products **6** and **7** were obtained in high yields without loss of *ee* (Scheme 4c). Importantly, a very high dr was observed when **5** was treated with indole. Moreover, the chiral pyrrolidine **4a** was deprotected efficiently in high yield without loss of *ee* (Scheme 4d).

Furthermore, a creative synthetic route for vernakalant and Enablex was developed. Starting from **2l**, the one-pot interrupted HAM reaction proceeded smoothly to give **4q** in very high yield with excellent *ee* (Scheme 5). Deprotection of the acetoxy group

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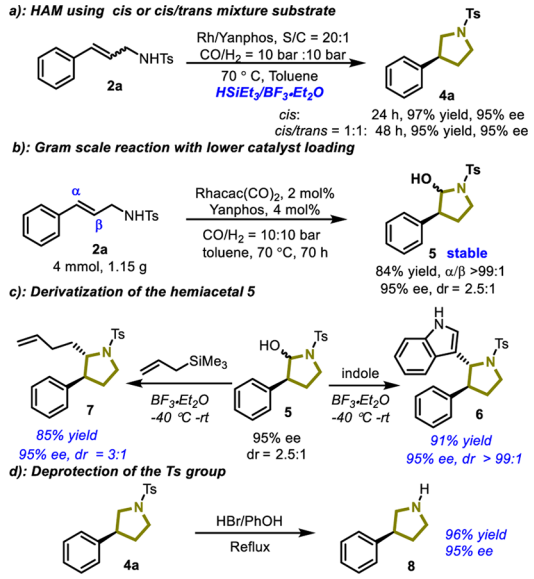
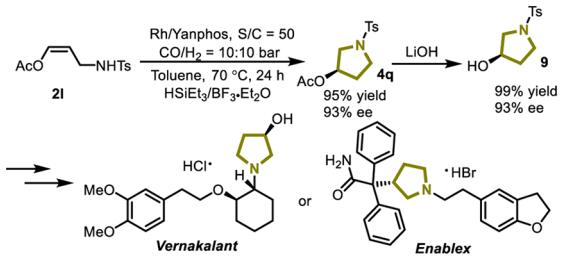
Scheme 4. Synthetic Transformations



gave **9** in high yield without loss of *ee*. Starting from **9**, vernakalant[17] and Enablex[10] can be synthesized readily following literature procedures.

Scheme 5. Creative Synthesis of Vernakalant and Enablex



In summary, the first interrupted asymmetric HAM reaction has been developed. The challenging *trans*-1,2-disubstituted olefins were employed as substrates, and a series of valuable chiral pyrrolidinones and pyrrolidines were obtained in high yields with high regioselectivities and excellent *ee*. It was found that the *ee* remained the same regardless of whether the substrate was *cis* or *trans*. Several synthetic transformations were conducted, demonstrating the high synthetic utility of the current reaction. A creative route for the synthesis of venakalant and Enablex was also developed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03596.

Procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(16) The X-ray crystal data for **4g** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1468105. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: +44 (1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

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