Communication

Rhodium/Yanphos-catalyzed Asymmetric Interrupted Intramolecular Hydroaminomethylation of Trans-1, 2-disubstituted Alkenes

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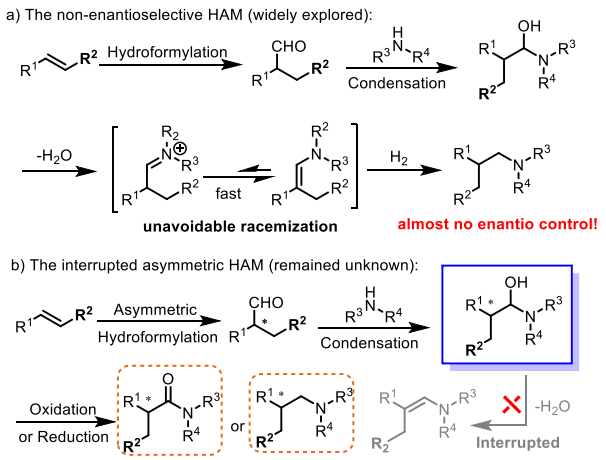
Rhodium/Yanphos-Catalyzed Asymmetric Interrupted Intramolecular Hydroaminomethylation of *Trans*-1, 2-disubstituted Alkenes

Caiyou Chen, Shicheng Jin, Zhefan Zhang, Biao Wei, Heng Wang, Kai Zhang, Hui Lv,* Xiu-Qin Dong,* and Xumu Zhang*

College of Chemistry and Molecular Sciences, Wuhan University, 430072, Wuhan, (P. R. China).

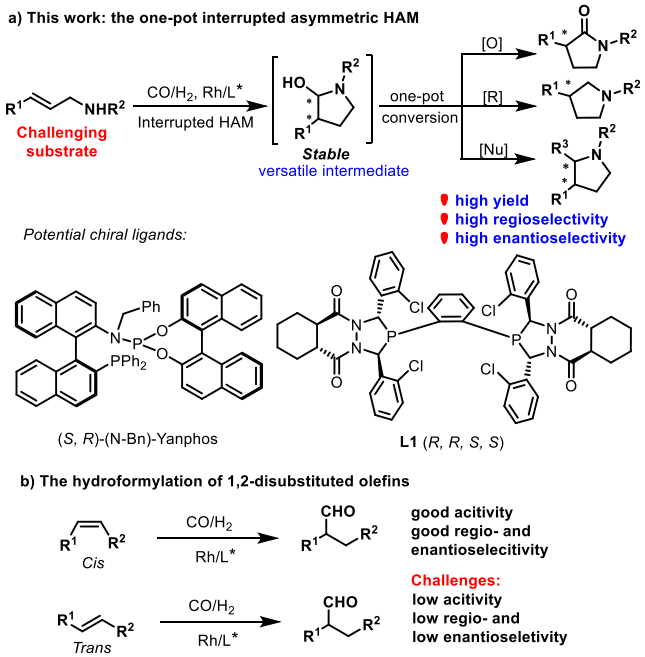
ABSTRACT: The first interrupted asymmetric HAM reaction was developed. The challenging *trans*-1, 2-disubstituted olefins were employed as substrates and a series of valuable chiral pyrrolidinones and pyrrolidines were obtained in high yields, high regioslectivities and excellent *ee*. Several synthetic 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 the 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 with one carbon elongation (Scheme 1a). In that respect, linear HAM is widely explored and recent progress has been summarized in several reviews.[3]



Scheme 1. The widely explored HAM reaction and the new interrupted asymmetric HAM reaction.

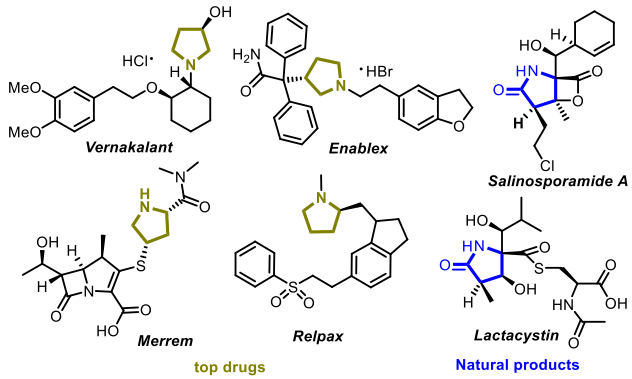
With respect to the asymmetric HAM, unavoidable racemization of the chiral iminium often occurs through the fast isomerization to the non-chiral enamine (Scheme 1a). Consequently, very rare work was reported in terms of the asymmetric HAM.[4] Recently, Kalck *et al.* tried the rhodium complex with chiral diphosphine ligands catalyzed asymmetric HAM.[4a] However, only racemic amine was obtained. The results were explained by the detailed computational study which revealed that the hydrogenation of the imine intermediate follows the similar energetic pathway regardless of the chiral ligands used.[4a] Owing to our long-term interest in HAM,[5] we envision that the chiral product can be obtained by interrupting the reaction through stabilization of the chiral hemiacetal intermediate leaving the chiral carbon untouched. And importantly, the one-pot work-up using oxidant or reductant will generate the valuable chiral amides or amines (Scheme 1b).



Scheme 2. Interrupted HAM of 3-substituted allylamines with the potential chiral ligands and the hydroformylation of 1, 2-disubstituted olefins.

With regard to the stabilization of the intermediate, we perceived that the cyclic five member ring hemiacetal is very stable[6] which makes the interrupted asymmetric HAM to be possible in an intramolecular version by using the protected 3-substituted allylamine as substrate utilizing our previously developed Yanphos [7] or the steric bulky ligand **L1**[8] (Scheme 2a). As mentioned above, the five member ring hemiacetal intermediate can be easily converted to the valuable pyrrolidinones and pyrrolidines which are common motifs in many top 200 brand name drugs and natural products, such as top drugs Vernakalant,[9] Enablex,[10] Merrem,[11] Relpax[12] and natural products Salinosporamide A, Lactacystin [13] (Scheme 3). As a result, the interrupted asymmetric HAM of protected 3-substituted allylamine will be highly desirable. However, the first step of the asymmetric HAM of the protected 3-substituted allylamines, the asymmetric hydroformylation of 1, 2-disubstituted olefins, remains a very challenging problem.[14] Up to now, only a few examples were reported.[15] Among these examples, the asymmetric hydroformylation of the *cis*-1,2-disubstituted olefins were realized with good regioselectivities and enantioselectivities.[15a-b, 15f], However, with respect to the hydroformylation of the readily available *trans*-1,2-disubstituted olefins, it was shown to be much more challenging and generally lower reactivities and enan-

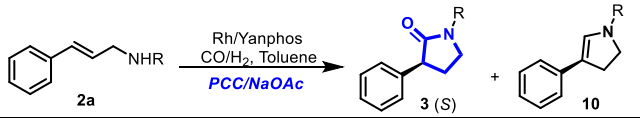
tioselectivities were observed (Scheme 2b).[15b, 15f] Herein, we report the first rhodium (N-Bn)-Yanphos (Scheme 2a) catalyzed interrupted asymmetric HAM of the very challenging substrates, *trans*-1,2-disubstuted olefins, to afford the valuable chiral pyrrolidinones and pyrrolidines in one-pot with excellent regio- (>99:1) and enantioselectivities (up to 96% *ee*).



Scheme 3. Representative top 200 brand name drugs and natural products featuring the pyrrolidine and pyrrolidinone motifs.

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 by adding PCC (pyridinium chlorochromate)/NaOAc to the reaction system once the hydroformylation reaction stopped with high yield and excellent regioselectivity (for the screeing of oxidants, see supporting information). In the presence of Rh/Yanphos, the reaction only took place in the α position with the desired chiral pyrrolidinone **3a** obtained exclusively in 93% *ee* (Table 1, entry 1). The effects of reaction conditions on the one-pot interrupted asymmetric HAM were subsequently investigated. As shown in table 1, lowering of the L/Rh ratio gave higher yield, on the contrast of which, the *ee* dropped significantly (Table 1, entries 1-3). The yield dropped sharply by lowering the syngas pressure although slightly higher *ee* was observed (Table 1, entry 4). Increasing of 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 (Table 1, entry 5). Increasing of the temperature gave higher yield but lower *ee* while lowering of the temperature, on the contrast, gave lower yield but slightly higher *ee* (Table 1, entries 6-7). It was also found that shorter reaction time and lower catalyst loading gave lower yield while the *ee* almost remained the same (Table 1, entries 8-9). The steric bulky ligand **L1** (Scheme 2) was also tested (for the screening of other ligands, see supporting information), however, only the dehydrated product was obtained (Table 1, entry 10). We further investigated the effect of the substituents on the amine moiety. It was found that no desired product was observed by changing the Ts group into the Ts(OMe) group (Table 1, entry 11). Instead, the hemiacetal intermediate dehydrated and was further oxidized by PCC to give a new aldehyde (See supporting information). With the electron-donating benzyl group attached to the substrate, the dehydrated product was obtained exclusively in high yield (Table 1, entry 12) [5e]. It is only when the electron-withdrawing Boc or Bz group attached to the substrate that the desired chiral pyrrolidinones formed (Table 2, entries 13-14). However, the *ee* dropped significantly, which is probably due to the fast racemization of the hemiacetal product when the strong electron-withdrawing group attached to the substrate. These results indicated that the protecting group on the amine moiety was very critical to the reaction and only the electron-withdrawing groups give the desired products. Ts group was selected as the best in terms of the high enantioselectivity.

Table 1. Screening of the conditions for the one-pot interrupted asymmetric HAM to afford chiral pyrrolidinone [a]



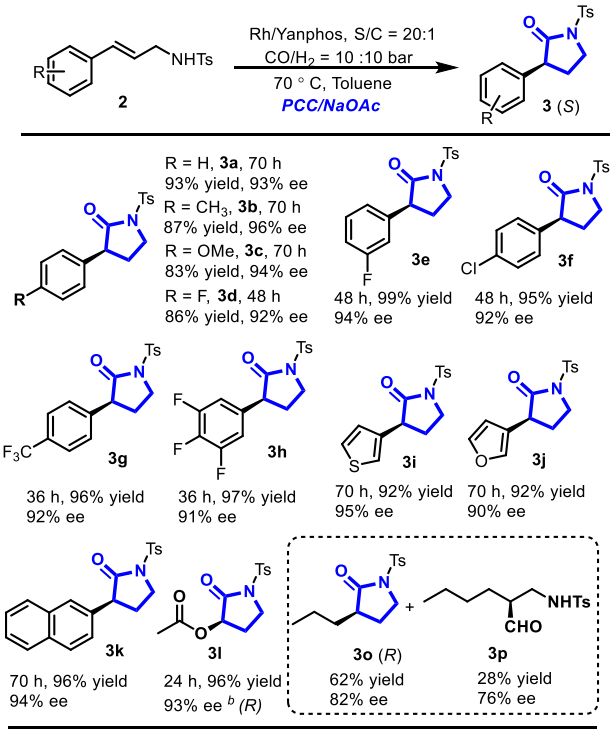
Entry	R[b]	L/Rh	CO/H_2 (bar)	Temp. (℃)	Iso. Yield%[c]	*Ee*%[d]
1	Ts	2.0	10:10	70	93 (**3**)	93
2	Ts	1.5	10:10	70	95 (**3**)	84
3	Ts	1.1	10:10	70	98 (**3**)	12
4	Ts	2.0	5:5	70	41 (**3**)	95
5[e]	Ts	2.0	20:20	70	66 (**3**)	10
6	Ts	2.0	10:10	80	97 (**3**)	90
7	Ts	2.0	10:10	60	57 (**3**)	94
8[f]	Ts	2.0	10:10	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 in 0.1 mmol scale in 0.5 mL of toluene, $Rhacac(CO)_2$ (acac = acetylacetone) was used as metal precursor, (*S, R*)-(N-Bn)-Yanphos as ligand, S/C = 20, reaction time = 70 h, PCC = 0.2 mmol, NaOAc = 0.2 mmol. [b] Ts = 4-methylbenzenesulfonyl, Ts(OMe) = 4-methoxybenzenesulfonyl, Bn = benzyl, Boc = *t*-butyl oxide carbonyl, Bz =benzoyl. [c] Isolated yield of the chiral pyrrolidinones. [d] Enantiomeric excess of the product, 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 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.

With the optimized reaction conditions in hand, substrate scope of the one-pot asymmetric HAM to afford chiral pyrrolindinones was simultaneously investigated. As summarized in table 2, a series of chiral pyrrolidinones were obtained in high yields and excellent *ee* (For all the products, *ee* was higher than 90%). It was found that, electron-donating groups on the benzene ring tended to deactivate the substrates affording lower isolated yields, however, the *ee* remained very high (Table 2, **3a**-**3c**). On the contrast, with the electron-withdrawing groups attached to the benzene ring, the substrate was activated and shorter reaction time was needed while the *ee* was not influenced (Table 2, **3d**-**3h**). For example, when the trifluoromethyl group or three fluorine atoms were attached to the substrates, only 36 h was needed for full conversion (Table 2, **3g**, **3h**). Interestingly, the

thienyl, furyl, and naphthyl substrates were also tolerated and the corresponding valuable products **3i**, **3j** and **3k** were obtained in very high yields and 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**. It is notable that, in all cases, the reaction proceeded in very high regioselectivity with only the desired regio-isomer observed as determined by NMR analysis, demonstrating the high efficiency of our catalytic system.

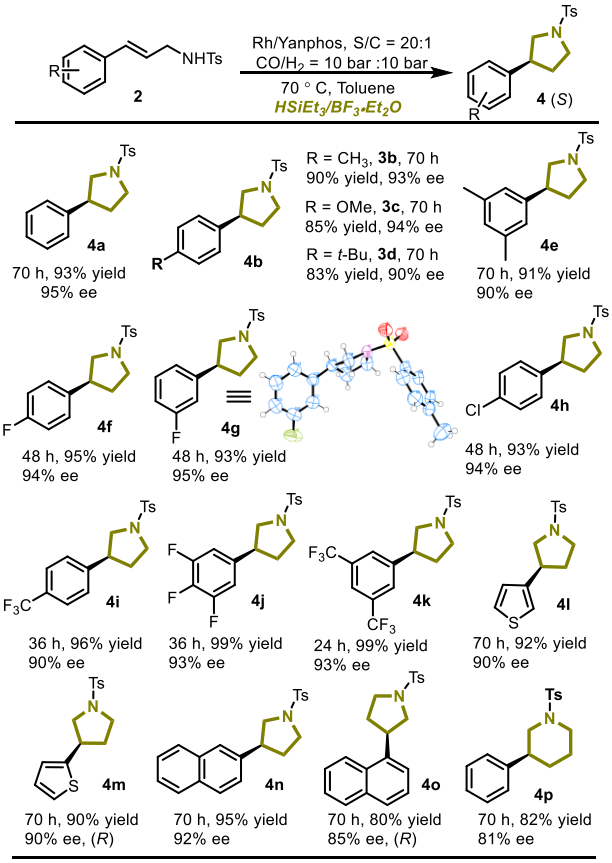
Table 2. Substrate scope of the preparation of chiral pyrrolidinones through the interrupted asymmetric HAM [a]



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

With regard to the preparation of the chiral pyrrolidines, the one-pot method was also developed simply by adding $HSiEt_3$ and BF_3·Et_2O to the reaction system under low temperature (-10 ℃) when the hydroformylation reaction stopped without isolation of the hemiacetal intermediate. The substrate scope for the preparation of the chiral pyrrolidines through the interrupted asymmetric HAM was also investigated. Due to the common feature of chiral pyrrolidines in many drug structures, apart from the representative substrates in table 2, some other substrates were also tested. 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 was obtained in very high yields and excellent *ee* (>90%), regardless of the substituents on the pyrrolidine ring were electron-donating (Table 3, **4a**-**4e**), electron-withdrawing (Table 3, **4f**-**4k**), heterocyclic (Table 3, **4l**, **4m**) or naphthyl (Table 3, **4n**). However, when the 1-substituted naphthalene was employed as the substrate, lower yield and *ee* were observed (Table 3, **4o**), which is probably due to the *ortho* steric hindrance of the substituted ring. Interestingly, the reaction also tolerated the homoallylic amines giving the chiral piperidine product **4p** in good yield and *ee*. As aforementioned, electron-donating groups on the substrate gave lower reaction rate and electron-withdrawing groups gave higher reaction rate requiring much shorter reaction time. It is noteworthy that, the *ee*

Table 3. Substrate scope of the preparation of chiral pyrrolidines through the interrupted asymmetric HAM [a]

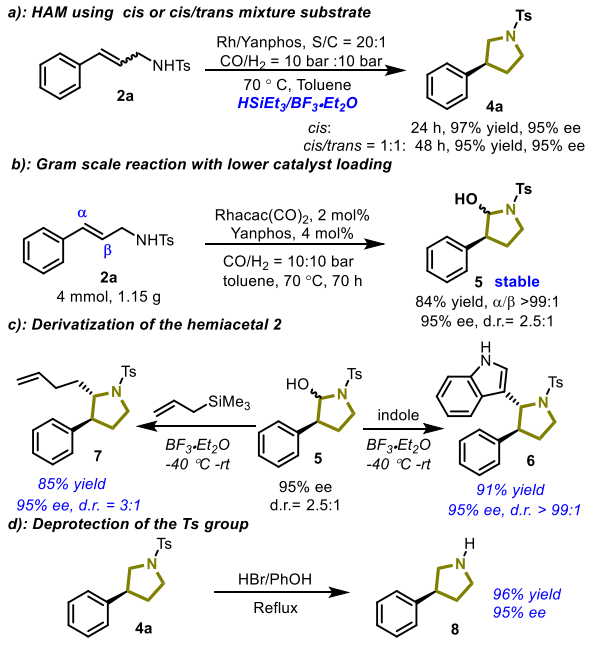


[a] The reaction was conducted in 0.1 mmol scale in 0.5 mL of toluene, $Rhacac(CO)_2$ (acac = acetylacetone) as metal precursor, (*S, R*)-(N-Bn)-Yanphos as ligand, CO/H_2 = 10:10 bar, S/C = 20, $HSiEt_3$ = 0.3 mmol, $BF_3.Et_2O$ = 0.3 mmol, the configuration of all the products was determined as (*S*)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

obtained in the preparation of the chiral pyrrolidines was generally higher than that obtained in the preparation of the chiral pyrrolidinones when strong electron-withdrawing groups were attached to the substrates. This is probably due to the slow racemization of the chiral pyrrolidinones. Similar to the preparation of the chiral pyrrolidinones, for all the substrates tested in table 3, only one regio-isomer was observed as determined by NMR analysis. Moreover, in order to determine the absolute configuration of the products, X-ray analysis of **4g** was conducted and the configuration was determined as (*S*). [16]

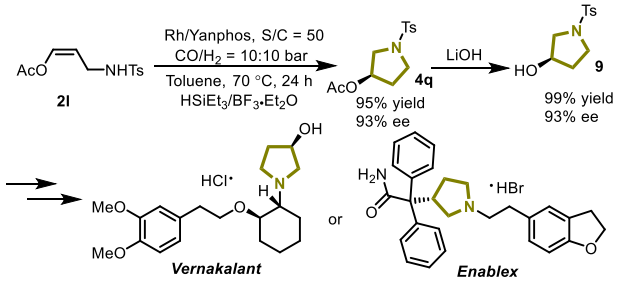
In order to further demonstrate the synthetic utility of the interrupted asymmetric HAM, several transformations were conducted as summarized in scheme 4. Interestingly, we

found that the *ee* remained the same regardless of whether the substrate is *cis* or *cis*/*trans* mixture, which makes the method to be very convenient without the tedious isolation of the *cis*/*trans* mixture (Scheme 4a). The interrupted asymmetric HAM reaction was also conducted on gram scale with lower catalyst loading (Scheme 4b). Satisfyingly, we found that the hemiacetal **5** was very stable and was isolated in high yield and excellent regio- and enantioselectivity *albeit* with low dr ratio. The hemiacetal **5** was subsequently treated with indole or allyltrimethylsilane in the presence of BF_3·Et_2O. It was found that the desired products **6** and **7** were obtained in high yields without losing any *ee* (Scheme 4c). Importantly, very high *d.r.* value was observed when **2a** was treated with indole. Moreover, the chiral pyrrolidine **4a** was deprotected efficiently in high yield without losing any *ee* (Scheme 4d).



Scheme 4. Synthetic transformation.

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 and excellent *ee* (Scheme 5). Deprotection of the acetoxy group gave **9** in high yield without losing any *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 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, high regioslectivities and excellent *ee*. It was found that the *ee* remained the same regardless of whether the substrate is *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

Experimental procedures and compound characterization data. This material is available free of charge *via* the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

xumu@whu.edu.cn; xiuqindong@whu.edu.cn;
huilv@whu.edu.cn

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(16) The X-ray crystal data of **4g** has 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, UK [Fax: +44 (1223)336033 or E-mail: deposit@ccdc.cam.ac.uk].

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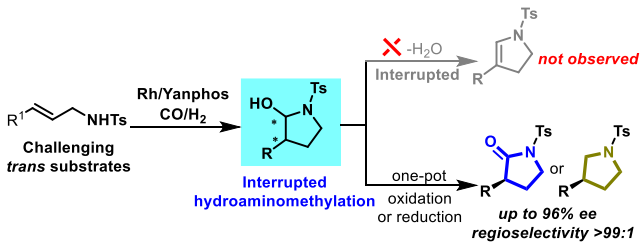
Rh/Yanphos
CO/H2
NHTs
Challenging
trans substrates
HO
Ts
N
R
Interrupted
hydroaminomethylation
-H2O
Interrupted
not observed
one-pot
oxidation
or reduction
O
or
up to 96% ee
regioselectivity >99:1