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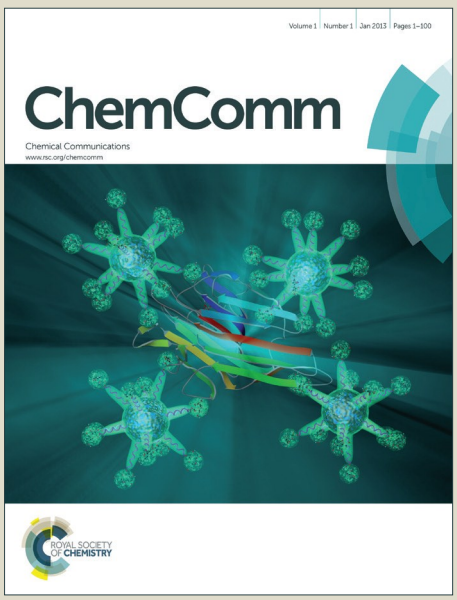

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COMMUNICATION

Enantioselective synthesis of ß-substituted Chiral Allylic Amines via Rh-Catalyzed Asymmetric Hydrogenation

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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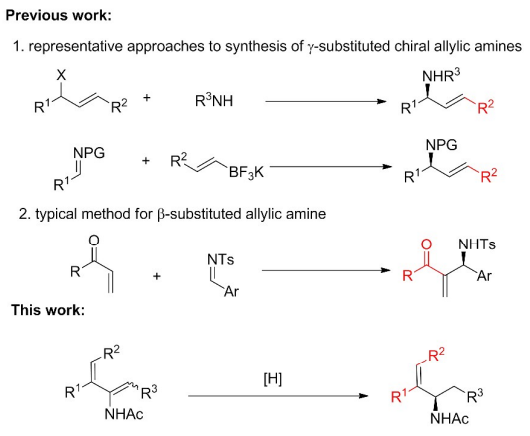
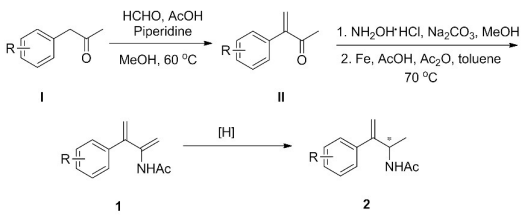
Rh-DuanPhos complex-catalyzed asymmetric mono-hydrogenation of 2-acetamido-1,3-dienes has been developed, which provides a readily accessible approach to chiral allylic amines with excellent enantioselectivities and high regioselectivities. The products are valuable chiral building blocks in chiral pharmaceuticals.

Chiral allylic amines are versatile building blocks in organic chemistry and be widely used in synthesis of pharmaceuticals and biologically active compounds.[1-2] Considerable efforts have been devoted to exploring efficient methods for the synthesis of chiral allylic amines and many approaches have been developed. Among them, the methods for γ-substituted chiral allylic amines are well documented, and the representative approaches include transition-metal catalyzed allylic substitution reaction (Scheme1, 1),[3] vinylation of imines,[4] direct allylic amination of simple alkenes,[5] aza-Claisen rearrangement of allylic trichloroacetimidates,[6] and kinetic resolution of primary allylic amines.[7] However, access to ß-substituted chiral allylic amines is rare, and the main approach heavily relies on an asymmetric aza-Morita-Baylis-Hillman reaction (Scheme1, 2), despite the inherent drawbacks, such as limited substrate scope and long reaction time.[8] Developing efficient methods for enantioselecitive synthesis of ß-substituted allylic amines is highly desired but remains a challenge.



Scheme 1 Methods for Synthesis chiral allylic amines



Scheme 2 Design and Synthesis of Chiral Allylic Amines

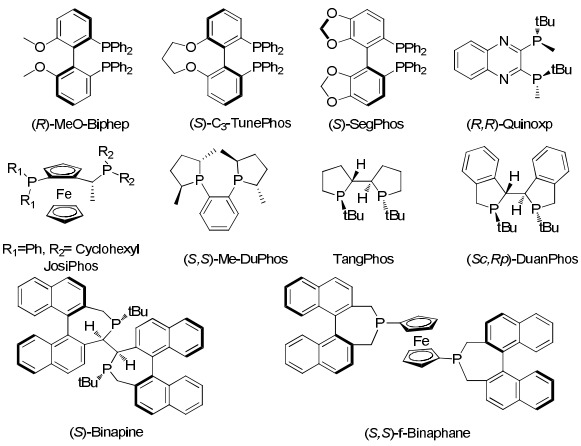


Fig. 1 Structures of the phosphine ligands for hydrogenation of **1a**.

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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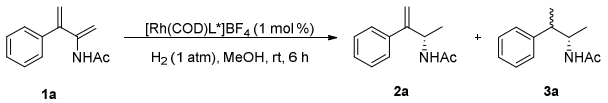
Table 1 Ligand Screening for Rh-Catalyzed Asymmetric Hydrogenation of **1a**[a]

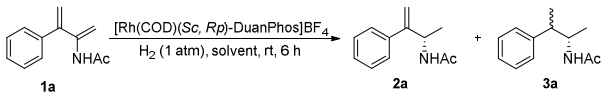


1a 2a 3a

entry	ligand	Conv. (%)[b]	2a:3a[b]	ee(%)[c]
1	(*R*)-MeO-Biphep	35	>98:2	28
2	(*S*)-C_3-TunePhos	38	>98:2	11
3	(*S*)-SegPhos	46	>98:2	27
4	JosiPhos	>99	37:63	50
5	(*S,S*)-f-Binaphane	60	40:60	48
6	(*R.R*)-Quinoxp	29	>98:2	92
7	(*S,S*)-Me-DuPhos	7	>98:2	67
8	(*S*)-Binapine	50	90:10	43
9	TangPhos	67	>98:2	95
10	(*Sc,Rp*)-DuanPhos	>99	>98:2	96

[a]Unless otherwise mentioned, all reactions were carried out with a $[Rh(cod)_2]BF_4$/ligand/substrate ratio of 1:1.1:100, in 1 mL MeOH at room temperature under 1 atm H_2 for 6 h. [b]Determined by ^1H NMR spectroscopy. [c]Determined by HPLC analysis using a chiral stationary phase.

Table 2 Solvent Screening for Rh-Catalyzed Asymmetric Hydrogenation of 1a[a]



1a 2a 3a

entry	solvent	Conv. (%)[b]	2a:3a[b]	ee(%)[c,]
1	MeOH	>99	>98:2	96
2[d]	MeOH	>99	91:9	96
3	*i*-PrOH	76	>98:2	93
4	EtOH	78	>98:2	90
5	CF_3CH_2OH	>99	80:20	98
6	EA	98	>98:2	96
7	THF	46	95:5	96
8	toluene	>99	90:10	94
9	CH_2Cl_2	>99	91:9	97

[a]Unless otherwise mentioned, all reactions were carried out with a catalyst/substrate ratio of 1:100, in 1 mL of solvent at rt under 1 atm H_2 for 6 h. [b]Determined by ^1H NMR spectroscopy. [c]Determined by HPLC analysis using a chiral stationary phase. [d]24h.

In the past decades, asymmetric hydrogenation,[9] due to its atom economy, cost effectiveness and environmentally friendly nature, has become one of the most powerful strategies for the synthesis of chiral compounds. In this context, our group has developed several efficient catalysts for asymmetric hydrogenation and successfully synthesized a series of chiral amines and alcohols.[10] Recently, our group developed the protocols to synthesize γ, δ-unsaturated amino acids,[11] γ-substituted allylic amines,[12] α-amino ketones[13] by regioselective asymmetric hydrogenation of different substituted functionalized enamides. Intrigued by the success of these examples, we envisioned that ß-substituted chiral allylic amines may also be obtained by regio- and enantioselective hydrogenation of 3-branched 2-acetamido-1,3-dienes. Herein, we report a new approach for asymmetric synthesis of chiral allylic amines via Rh-catalyzed regio- and enantioselectivitive hydrogenation.

Our strategy for the synthesis of chiral allylic amines is listed in Scheme 2. Initially, N-(3-phenylbuta-1,3-dien-2-yl)acetamide **1a** was prepared and chosen as a model substrate to optimize the reaction conditions. First of all, the effect of ligands on the reaction was investigated at room temperature under 1 atm H_2 in methanol in the presence of 1 mol% $[Rh(cod)_2]BF_4$. As shown in Table 1, axial chiral biphosphrous ligands, such as (*R*)-MeO-Biphep, (*S*)-C_3-TunePhos and (*S*)-SegPhos, exhibited poor reactivities and enantioselectivities but excellent regioselectivities (entries 1-3). When planar chiral ligands, such as Josiphos and (*S,S*)-f-Binaphane, were used, the reactivity improved dramatically, but the regioselectivity and enatioselectivity were disappointing (entries 4-5). To our delight, excellent regioselectivity and high enantioselectivity were obtained when P-chiral ligand (*R, R*)-Quinoxp was employed, though the yield is very low. Subsequently, a series of P-chiral diphophine ligands developed in our group were screened, electron-donating and rigid (*Sc, Rp*)-DuanPhos was proved to be the best ligand to give the desired product with full conversion and excellent regio- , enantioselectivity (entries 7-10). The solvent effects on this reaction was also evaluated. As shown in Table 2, the solvent screening revealed that MeOH was the best choice (Table 2, entries 1-9).

Under the optimized reaction conditions (1 mol% [Rh(cod)(*Rc*, *Sp*)-DuanPhos]BF_4 , in MeOH at rt under 1 atm H_2), the substrate scope was examined. As shown in Table 3, all of the 2-acetamido-1,3-dienes examined here were good substrates for this reaction and afforded the corresponding β-substituted allylic amines with high yields and good enantioselectivities.[14] When R^1 was aromatic group, the substituent on the phenyl ring, no matter electron-donating group or electron-withdrawing group, had no effect on the yields and enantioselectivities except for *p*-F or *p*-Br substituted substrates with slightly lower enantioselectivity (**2a**-**2h**). 2-naphthyl substituted dienamide can also be hydrogenated under this reaction condition but the enantioselectivity was decreased dramatically and need a longer reaction time to get a good yield (**2i**). When phenyl group was replaced by Bn group, the reaction went smoothly and gave the desired product with good yield and excellent ee (**2j**). When R^2 was aromatic group, the reaction also worked very well (**2k**, **2l**). (*E*)-*N*-(5-benzylidenecyclopent-1-en-1-yl)acetamide was also well tolerated for this reaction albeit the enantioselectivity decreased to some extent (**2m**).

To demonstrate the potential utility of this method, the asymmetric hydrogenation of N-(3-(4-methoxyphenyl)buta-1,3-dien-2-yl)acetamide (**2d**) was carried out on preparative scale, and 0.65 gram desired product was obtained smoothly without any loss in yield and enantioselectivity. Notably, when the reaction was carried out under 50 atm hydrogen pressure

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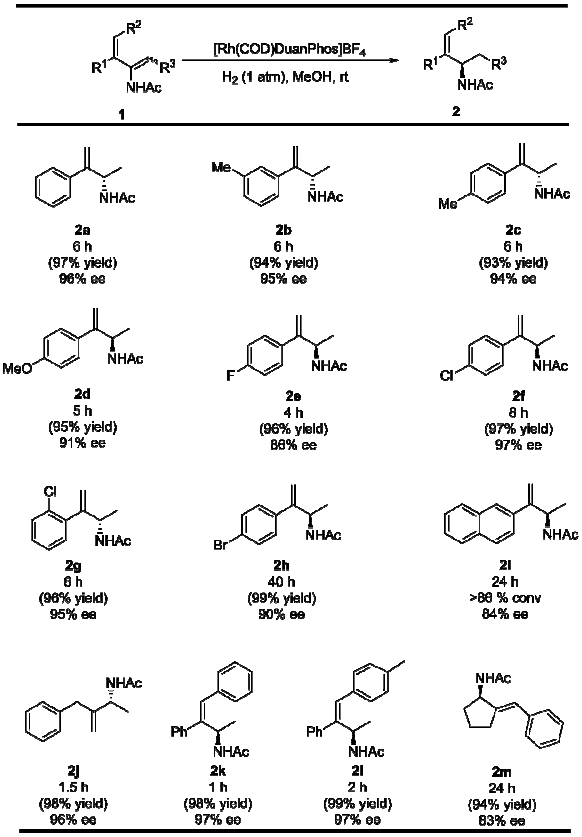
Table 3 Rh-Catalyzed Asymmetric Hydrogenation of Various Dienamides[a, f, g]

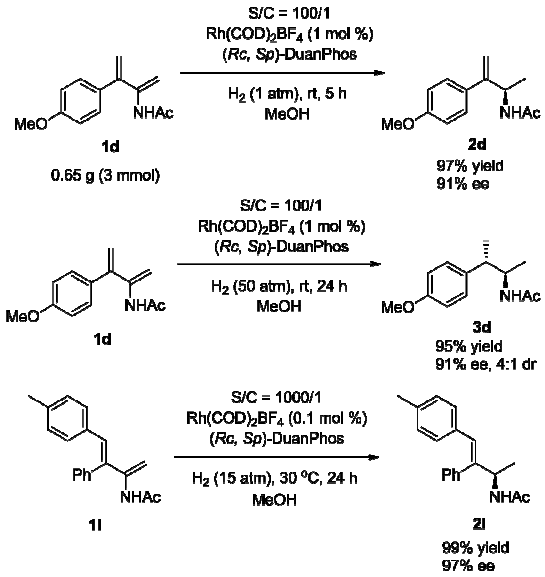


[a]All reactions were carried out with a catalyst/substrate in a ratio of 1:100, in MeOH at rt under 1 atm H_2. [b]The yield of isolated product based on consumed starting material . [c]Determined by HPLC analysis using a chiral stationary phase. [d]Reaction time under condition a. [e]S/C = 20, 20 atm H_2. [f] **2a**, **2b**, **2c**, **2g** were obtained by using (*Sc,Rp*)-DuanPhos as lignd, **2d-2f, 2h-2m** were obtained by using (*Rc,Sp*)-DuanPhos as ligand. [g] no over-reduction product **3** was observed in all cases.

for 24 hours, the full reduction product **3d** was obtained with high yield and moderate diastereoselectivity. Moreover, asymmetric hydrogenation of **1l** with low catalyst loading was evaluated. We found that there was no effect on the yield and enantioselectivity when the catalyst loading was decreased to 0.1 mol%. (Scheme 3).

In conclusion, we have developed a new strategy to synthesize β-substituted chiral allylic amines by Rh/DuanPhos catalyzed asymmetric hydrogenation under very mild reaction conditions. The protocol exhibited high regioselectivity and good to excellent enantioselectivity with broad substrate scope, which suggests that this approach has potential applications in organic synthesis. Further efforts to expand the substrate scope and applications are underway in our lab.

We are grateful for the financial support by a grant from Wuhan University (203273463), the Youth Chen-Guang Science and Technology Project of Wuhan City (2015071704011640), Natural Science Foundation of Hubei Province (2014CFB181), "111" Project of the Ministry of Education of China and the National Natural Science Foundation of China (Grant No. 21372179, 21432007, 21402145).



Scheme 3 Investigation of potential application of asymmetric mono-hydrogenation of 2-acetamido-1,3-dienes.

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14 Absolute configuration of compound **2a** has been established by comparison with literature data. **(** for *S*-**2a** in ref. 7**:** $[\alpha]_D^{20}$ = -30 (c = 0.3, $CHCl_3$, 83% ee), our experiment result of **2a**: $[\alpha]_D^{20}$ = -26 (c = 0.5, $CHCl_3$, 95% ee)**)**. All the other configurations are uncertain and based on the assumption that the configuration follows that of **2a**.