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Cobalt-Catalyzed Enantioselective Vinylation of Activated Ketones and Imines

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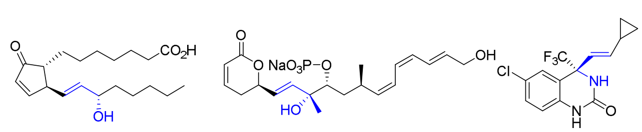
ABSTRACT: We present here an unprecedented cobalt-catalyzed enantioselective vinylation of α-ketoesters, isatins and imines to deliver a range of synthetically useful allylic alcohols and amines in high enantiopurity. This method employs commercially available and easy-to-handle catalysts and reagents, and exhibits a high degree of practicality. The efficiency, selectivity and operational simplicity of this catalytic system coupled with the substrate generality render this method a valuable tool in organic synthesis.

INTRODUCTION

Allylic alcohols and amines are among the most abundant and significant structural motifs in organic synthesis. They are present in numerous biologically active molecules and drugs (**Figure 1**); they can also undergo various selective transformations with high fidelity to afford a range of stereo-defined compounds of value in chemistry and medicine.[1] Consequently, the construction of allylic alcohols and amines in a stereoselective fashion has been a focal point in methodology development for decades. The traditional approaches that have proven to be highly successful include kinetic resolution of allylic alcohols by the Sharpless asymmetric epoxidation,[2] enantioselective reduction of enones[3] as well as vinylation of carbonyls and imines.[4] Other approaches such as metal-catalyzed rearrangement of allylic imidates,[5] allylic oxidation or amination,[6] amination of allenes[7] and organocatalytic tandem reactions[8] have also been documented in recent years.

Figure 1. Chiral Allylic Alcohols/Amines in Natural Products

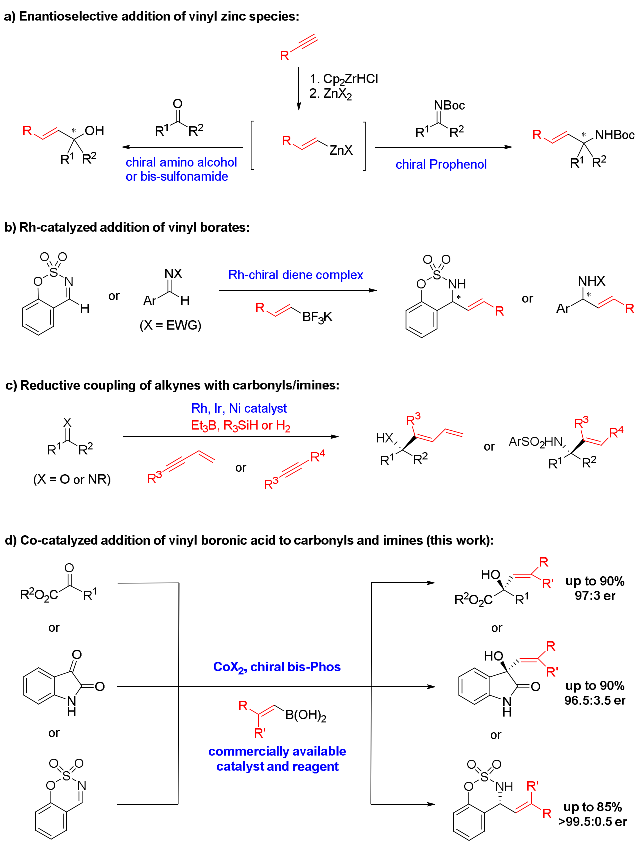


Prostaglandin A_1 (anti-tumor) Fostriecin (anti-tumor) DPC-083(anti-HIV)

Out of the various strategies, the asymmetric vinylation is arguably the most general one to access allylic alcohols and amines of various substitution patterns, including tertiary alcohols and amines (Scheme 1). The catalytic asymmetric addition of preformed vinyl zinc reagents to aldehydes,[9,10] imines[11] and even ketones[12] has been well-established and found wide use in total synthesis of complex molecules (Scheme 1a).[13] This approach, however, involves the tandem hydrometalation-transmetalation of alkynes to afford the organozinc reagents and thus necessitates the use of two stoichiometric metallic reagents. The use of vinyl boron reagents that are more readily available has also been actively investigated and found much success especially in the asymmetric vinylation of imines (Scheme 1b). In addition to examples of organocatalytic asymmetric Petasis reaction,[14] Rh-chiral diene complexes have been almost exclusively used for the metal-catalyzed systems.[15] Another elegant approach that circumvents the use of organometallic reagent is the reductive coupling of alkynes (or conjugated enyne, etc) with carbonyls and imines (Scheme 1c).[16] The Rh/Ir-catalyzed hydrogen-mediated coupling, especially, has been applied to the vinylation of a range of carbonyls and imines in excellent stereoselectivity. However, this approach has been limited to the preparation of dienyl allylic alcohols and certain tri- and tetra-substituted allyl amines to date.

Despite the great advances in this important area of research, a general, practical catalytic system that utilizes readily available catalysts and reagents and works for the asymmetric vinylation of a wide range of substrate types still remains to be developed. The access to tertiary allylic alcohols and amines with different substitution patterns, in particular, is much less established.[12,16e] Also it is noteworthy that precious metal catalysts (such as Rh, Ir, etc) are utilized in most catalytic vinylation reactions. The development of catalytic methods using the more economical and abundant base metals will be highly desired, which has served as a key impetus for the promotion of sustainable chemical synthesis.[17] Based on the recent discovery of hydroallylation of alkenes made in our laboratory,[18] we became particularly interested in cobalt catalysis for carbon-carbon bond forming reactions.[19,20] Herein we present our recent development of an unprecedented cobalt-catalyzed highly efficient and enantioselective vinylation of α-ketoesters, isatins and imines, using commercially available cobalt halides, chiral bisphosphine ligands and vinyl boronic acid reagents.

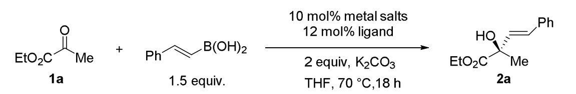
Scheme 1. Strategies for Enantioselective Vinylation



RESULTS AND DISCUSSION

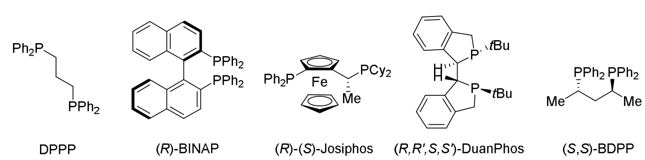
Enantioselective vinylation of α-ketoesters. We initiated our studies by exploring the reaction with α-ketoesters, as asymmetric vinylation of this class of substrate has not been thoroughly explored before,[16e] despite the great utility of the resulting tertiary allylic α-hydroxy esters (Table 1). Emphasis was also put on the use of readily available vinylating agents for practical considerations. After numerous trials, vinyl boronic acids proved to be the most promising and the most convenient choice, as many of them are commercially available and can be used as received. Out of the various catalysts examined initially (entries 1-5), the vinylated product **2a** was obtained only with CoI_2-bis phosphine complex in excellent yield (entry 5). Various chiral bis-phosphine ligands were then screened, the identity of which was found to have a profound effect on the efficiency of the vinylation. While BINAP shut down the vinylation (entry 6), the reactions using Josiphos or Duanphos proceeded in good yield, albeit with only low or moderate enantioselectivity (entries 7-8). To our delight, excellent enantioselectivity of 96:4 er was obtained for **2a** by using BDPP as the ligand (entry 9). Other cobalt salts were also screened, which unfortunately led to no further improvement on reactivity or enantioselectivity (entries 10-12). The desired product **2a** was not obtained at all in the absence of K_2CO_3, suggesting a base-facilitated transmetalation of vinyl boronic acid with cobalt halide. At this point the use of different vinyl boron reagents including styrenyl pinacol boronic esters and trifluoroborate potassium salt was examined again. In contract to the use of boronic acids, these reagents led to no product formation.

Table 1. Optimization of Vinylation of α-Ketoesters



entry	metal	ligand	**2a** yield (%)[a]	**2a** er[b]
1	$FeBr_2$	DPPP	<2	/
2	$NiBr_2$	DPPP	<2	/
3	CuCl	DPPP	<2	/
4	$Co(OAc)_2$	DPPP	<2	/
5	CoI_2	DPPP	90	/
6	CoI_2	(*R*)-BINAP	<2	/
7	CoI_2	(*R*)-(*S*)-Josiphos	60	50:50
8	CoI_2	(*R*,*R*',*S*,*S*')-DuanPhos	50	11:89
9	CoI_2	(*S*,*S*)-BDPP	**60**	**96:4**
10	$CoBr_2$	(*S*,*S*)-BDPP	54	94.5:5.5
11	$CoCl_2$	(*S*,*S*)-BDPP	30	94:8
12	CoF_2	(*S*,*S*)-BDPP	<2	/

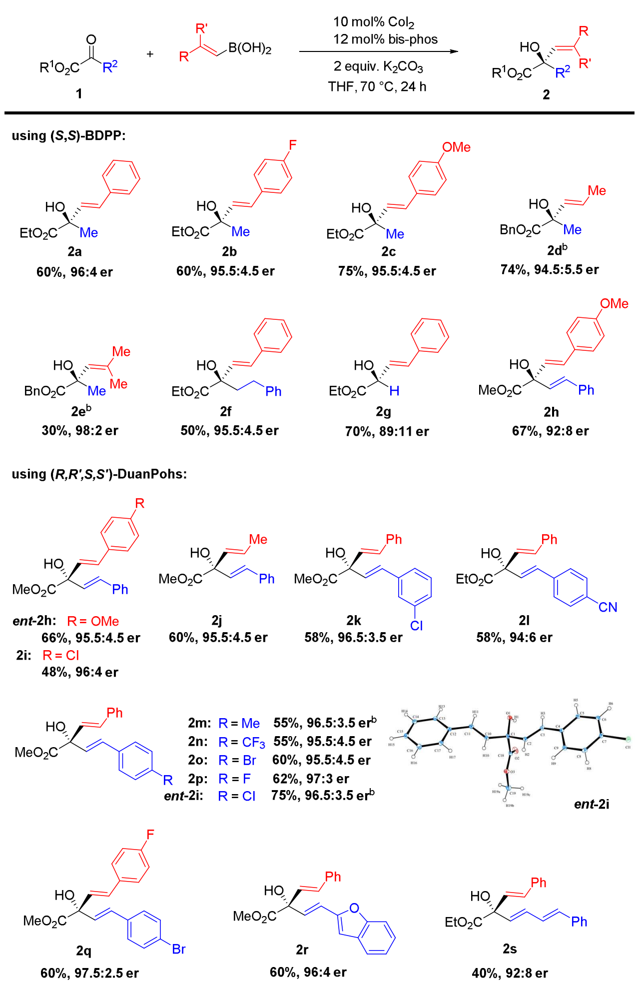
[a]Isolated yields. [b]Determined by chiral HPLC analysis.



The scope of this catalytic system turned out to be broad (Scheme 2). Under the optimal conditions using catalytic CoI_2 and BDPP, various styrenyl boronic acids bearing electron-poor or electron-rich substituents on the arene as well as alkyl-substituted vinyl boronic acids underwent reaction with **1a** smoothly to yield **2a-2d** in uniformly high enantioselectivity. The catalytic activity of this system, however, needs further improvement. In some cases the use of higher catalyst loading was necessary to product the allylic alcohols in good yield (e.g., **2d**). The use of vinyl boronic acids bearing α-substituent failed to yield the product, while the use of β-disubstituted vinylating reagent led to the formation of product in low yield but excellent enantioselectivity (98:2 er for **2e**). For the scope of the substrate, α-Ketoesters bearing other alkyl substituent also worked similarly well (**2e**). Just as a test, glyoxylate also worked under these conditions to yield secondary alcohols (such as **2g**) in good yield but slightly reduced er. We were also intrigued to prepare bis-allylic alcohols by the vinylation of α,β-unsaturated α-ketoesters. However, a decrease in the selectivity was observed for **2h** (92:8 er).[21] Fortunately, DuanPhos was identified to be the optimal choice for this series of substrates, which yielded **2h** in a higher er of 95.5:4.5 (the opposite enantiomer was prepared).

The new set of conditions worked uniformly well for the preparation of a range of bis-allylic α-hydroxy esters. Different vinylating reagents including 2-methyl-vinyl boronic acid underwent reactions with the same level of enantioselectivity to yield **2h**-**2j**. Various substituents at the aryl unit in the substrates could be well-tolerated to yield **2k**-**2q** with high enantioselectivity as well. Heterocycle- and diene-containing substrates also worked out smoothly (**2r**-**2s**). The relative and absolute configuration of ent-**2i** was unambiguously assigned by single crystal x-ray analysis. The configurations of the other products were assigned by analogy.

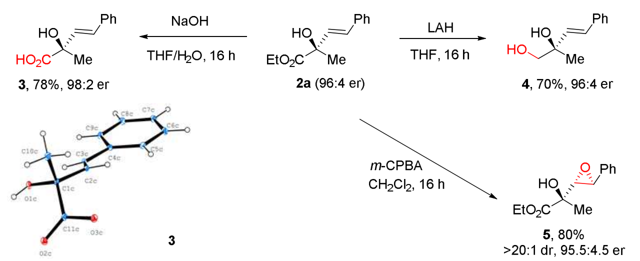
Scheme 2. Scope of Vinylation of α-Ketoesters[a]



[a]See SI for the detailed procedure. [b]20 mol% catalyst was used to produce the product in reasonable yield.

This series of enantioenriched vinylation products are synthetically versatile and representative derivatizations of them are shown in **Scheme 3**. Hydrolysis of the ester moiety in **2a** produced the allylic α-hydroxy acid **3** in 78% yield with 98:2 er (after recrystallization). The relative and absolute configuration of **3** was also assigned by single crystal x-ray analysis. Alternatively, reduction of the ester using LAH produced the primary-tertiary diol **4** in good yield, which would be difficult to access using other method. The alkene moiety in **2a** could also be functionalized in different ways. For example, epoxidation of the alkene using *m*-CPBA produced the corresponding epoxide **5** in a good 80% yield and perfect diastereoselectivity (>20:1 dr) without any erosion of the enantioselectivity (96:4 er).

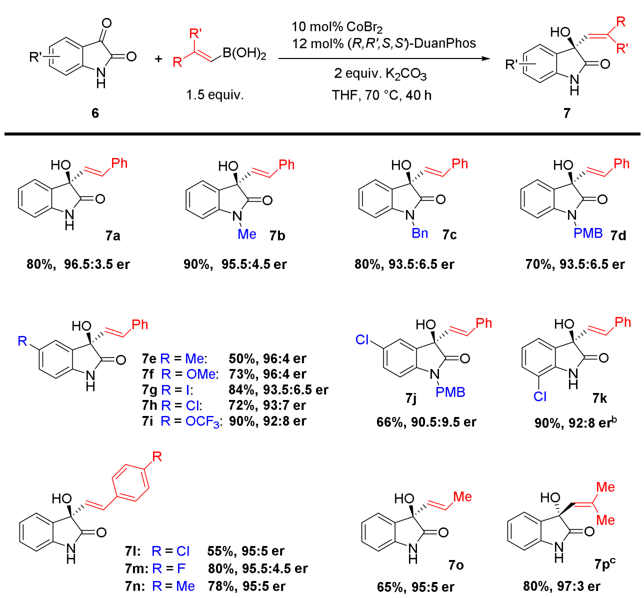
Scheme 3. Derivatization of α-Ketoesters



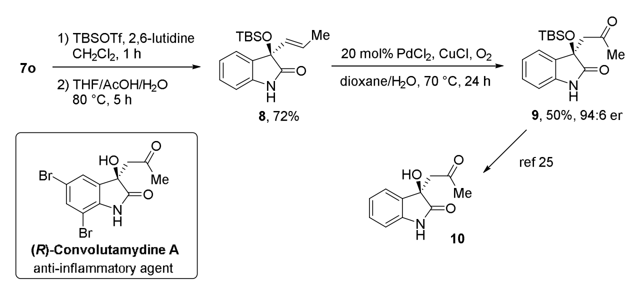
Enantioselective vinylation of oxindoles. With the simple and highly efficient procedure in hand, we became insterested in applying this cobalt-catalyzed system to the enantioselective vinylation of isatins, since chiral 3-alkenyl-3-hydroxy oxindoles represent the core structure of a large number of biologically active entities.[22] A number of successful methods have been reported for the addition of aryl boronic acid to isatins catalyzed by Rh, Pd, Ru and Ir complexes.[23, 24] The extension to asymmetric vinylation, however, was only disclosed by Hayashi and co-workers as part of their Rh-catalyzed additions of phenyl/alkenyl boronic acids to PMB-protected isatins.[23a]

The addition of 2-phenyl vinyl boronic acid to unprotected isatin was chosen for the reaction condition optimization. The combination of DuanPhos and $CoBr_2$ was identified as the best choice in term of reactivity and enantioselectivity. Under the optimal conditions, tertiary allylic alcohol **7a** was obtained in 80% yield with an excellent 96.5:3.5 er (Scheme 4). The efficiency and enantioselectivity of this system turned to be very robust for this class of substrate. Firstly, different isatin substrates bearing methyl-, benzyl-, PMB-substituents on the nitrogen underwent reaction with 2-phenyl vinylboronic acid with similar efficiency and selectivity (**7a**-**7d**). Further experiments then focused on the use of unprotected isatins. The vinylatin of various substituted isatins led to the vinylation products **7e**-**7k** in uniformly high selectivity. The absolute configuration of **7j** was assigned by comparing the optical rotation to the previous report.[23a] A variety of vinyl boronic acids bearing electron-neutral, electron-withdraw and electron-donating substituents on the aryl structure are well tolerated to produce **7l**-**7n** in good to excellent er. It is also noteworthy that 1-propenyl boronic acid proved to be effective in the addition to isatin similar to α-ketoester to produce **7o** in 95:5 er. The use of β-disubstituted vinyl boronic acid also led to the formation of **7p** in good yield and excellent ee, although the use of BDPP as the ligand proved to be beneficial than Duanphos (only 64:36 er was obtained in this case). With **7o** in hand, an efficient procedure was worked out to yield **10**, an analogue of the *anti*-inflammatory agent Convolutamydine A.[25] The protection of the alcohol in **7o** was found to be necessary for the key Wacker oxidation step, in which one single regio-isomer was obtained to yield the methyl ketone **9** exclusively. Steric effect likely plays an important role in determining the regioselectivity for the oxidation of internal alkene in **8**.

Scheme 4. Enantioselective Vinylation of Oxindoles[a]



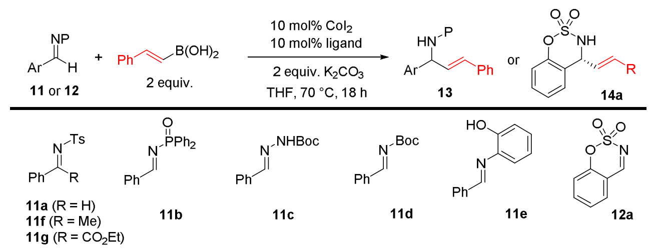
[a-b]See Scheme 3. [c]20 mol% $CoBr_2$ and 20 mol% (*S,S*)-BDPP were used.



Enantioselective vinylation of Imines. Owing to the ubiquitous existence of chiral allylic amine in biologically and pharmacologically active molecules, we were intrigued to find out whether our cobalt system could be applied to the asymmetric vinylation of imines as well. As the varied protecting groups on nitrogen are known to result in drastically different reactivity of imines, we initiated our studies by exploring various imine substrates. As summarized in Table 2, our study initiated with the vinylation of acyclic imines **11a-11e** using 2-phenyl-vinylboronic acid in the presence of CoI_2 and DPPP. While these imines have proven to be effective substrates for Rh- or Pd-catalyzed arylation reaction, the cobalt-bisphosphine system failed to promote an efficient vinylation for **11a-11d** (entries 1-4). In addition, imines **11a**, **11b**, **11d** underwent significant decomposition. While appreciable conversion was observed with **11e** in the presence of DPPP, the enantioselectivity of **13e** was only moderate after screening different types of chiral phosphine ligands (entries 5-8). The best result (60%, 86:14 er) was obtained by the use of BDPP, which was, however, still far from satisfactory.

As these studies pointed out, a more reactive imine substrate that is on the other side more stable at higher temperature should be adopted. Inspired by the previous report on Rh-catalyzed vinylation,[15a] we examined the vinylation of cyclic imine **12a**. To our delight, the desired product **14a** could be obtained in a higher yield of 78% (entry 9). Through the screening of various chiral bisphosphine ligands, DuanPhos proved to be the optimal to yield **14a** in 68% yield with a high er of 96.5:3.5 (entry 11). Further fine-tuning of the reaction parameters showed that the use of $CoBr_2$ was superior, producing **14a** as essentially a single enantiomer in 75% yield (entry 12).

Table 2. Test of Imines for Asymmetric Vinylation



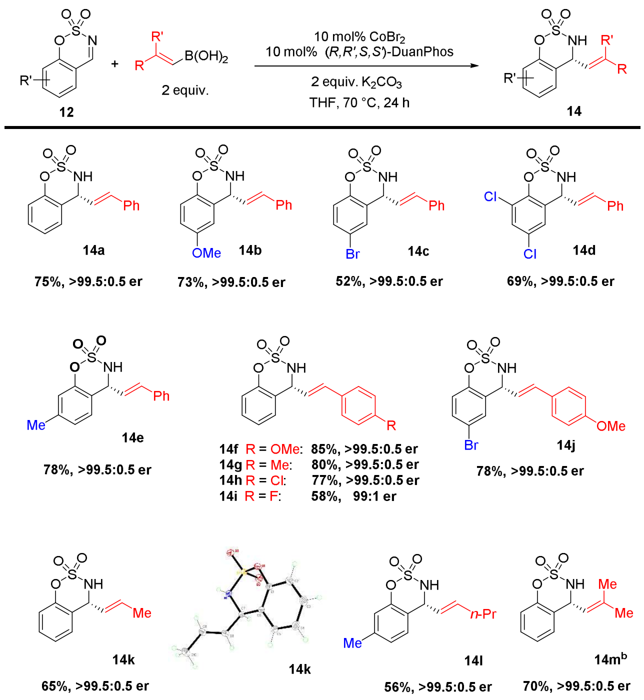
entry	imine	ligand	**13**/**14a** yield (%)[a]	**13**/**14a** er[b]
1	**11a**	DPPP	<2	/
2	**11b**	DPPP	<2	/
3	**11c**	DPPP	<2	/
4	**11d**	DPPP	<2	/
5	**11e**	DPPP	60	/
6	**11e**	(*R*)-(*S*)-Josiphos	18	68:32
7	**11e**	(*R,R',S,S'*)-DuanPhos	25	72:28
8	**11e**	(*S,S*)-BDPP	60	86:14
9	**12a**	DPPP	78	/
10	**12a**	(*S,S*)-BDPP	60	85:15
11	**12a**	(*R,R',S,S'*)-DuanPhos	68	96.5:3.5
12[c]	**12a**	(*R,R',S,S'*)-DuanPhos	**75**	**>99.5:0.5**

[a]Isolated yields. [b]Determined by chiral HPLC analysis. [c]$CoBr_2$ was used and the reaction time was 24 h.

With the optimal reaction condition in hand, a variety of highly substituted benzoxathiazine-2,2-dioxides **12** were examined (scheme 5). Imines containing a range of arene substituents (including chloro, bromo, methyl and methoxy) at various positions underwent reaction smoothly, providing vinylation products **14a-14e** in good yield with uniformly excellent enantioselectivity (>99.5:0.5 er). Various vinyl boronic acids containing aryl and alkyl substituents on the alkene were also well-tolerated to provide **14f-14m** in good yields and again nearly perfect enantioselectivities (>99.5:0.5 er). Single x-ray analysis of **14k** further supported the assignment of the absolute configuration of the products. For this catalytic system, not only the level of enantioselectivity compares favorably with previous report on the vinylation of this type of substrates, but the use of commercially available cobalt salt, ligand and reagents also renders this method a much more economical and convenient choice to access these valuable allylic amines in an enantiopure form.

The corresponding ketoimine substrates bearing a methyl or ester substituent (**11f** and **11g**, Table 2) were also examined under the optimal conditions. Unfortunately, no reactivity was observed, which clearly points to the limitation of the catalytic activity of this cobalt-catalyzed system. Efforts to identify more reactive base-metal catalyzed enantioselective vinylation that hopefully maintains the level of practicality of this system are ongoing in our laboratory.

Scheme 5. Enantioselective Vinylation of Imine



$^{a-b}$See Scheme 3.

CONCLUSIONS

We have demonstrated, for the first time, a cobalt-catalyzed enantioselective vinylation of α-ketoesters, isatins and imines, which greatly expands the scope of cobalt catalysis in asymmetric synthesis. This transformation utilizes a convenient procedure using commercially available catalysts and reagents, and delivers tertiary allylic alcohols and cyclic allylic amines in excellent enantioselectivity. The high efficiency, selectivity and operational simplicity of this transformation, coupled with the wide range of electrophiles are expected to render this method a valuable tool in asymmetric synthesis.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for all the products and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interests.

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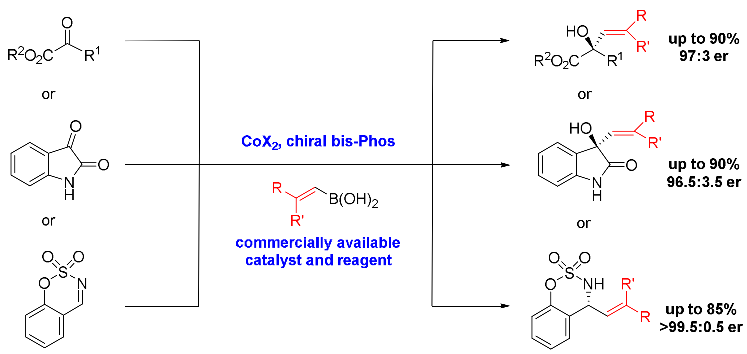
Graphic abstract:



7