Co/Salox Catalyzed Enantioselective C-H Annulation for One Step Elusive Generation of C-N Axial and C Central Chirality

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Abstract: Synthesis of multiple chiral centers with complete selectivity in a single step synthesis remains challenging. A novel strategy for the Co-catalyzed enantioselective annulation of *N*-(quinolin-8-yl) benzamide with the strained bicyclic alkenes has been demonstrated. This catalytic protocol enables double enantio induction to control C-N axis of low rotational barrier and carbon central chirality in one-step synthesis. The developed reaction can be performed with or without (electrooxidation, and photo-redox conditions) metal oxidant.

The complex molecules in nature possess multiple chirality elements in their structure. These multiple stereo elements expand the three-dimensional space of the molecules, [1] which are responsible for several biological activities and other properties of the molecules (Figure 1a). Synthetic design of complex molecules bearing more than one stereo element, with enantiocontrol, is challenging and one of the most fascinating problems in modern organic chemistry.[2] Enantioselective C-H functionalization has been proven to be one of the most dynamic and effective methods for synthesizing optically active molecules with high enantioselectivity. In the last decade, the implementation of C-H activation in enantioselective synthesis has been found to have wider applications.[3] Several synthetic approaches have been developed for the enantioselective C-H activation using transition metal complexes. Hayashi and coworker disclosed rhodium-catalyzed asymmetric 1,4-addition of phenylboronic acids to maleimides, providing *N*-aryl succinimides with a C-N axis and carbon central chirality in high yields with excellent stereoselectivities[4]. Later, this desymmetrization approach has been tested with several metal complexes and organocatalysis for the simultaneous access to C-N axial chirality and point chirality.[5] Recently, a shift towards 3d transition metal complexes offers further sustainability in the enantioselective C-H activation approaches.[6] Among these cobalt complexes act as crucial players as an alternatives to 4d and 5d transition metal complexes in asymmetric C-H activation.[7] Cramer and coworkers have explored high valent chiral cobalt complexes bearing Cp ligand for the enantioselective C-H activation.[8] Despite the vast applications of high valent cobalt complexes, the major drawback associated with these complexes is the tedious synthesis of the chiral backbone of the chiral complexes. To tackle this limitation, Shi group designed *in situ* generated high valent chiral complex *via* a combination of low valent cobalt complex and chiral salox ligand in the presence of stoichiometric metal oxidant for the generation of "*P*" stereogenic centre.[9] Later this approach has also been utilized for enantioselective C-H annulation of benzamides[10].

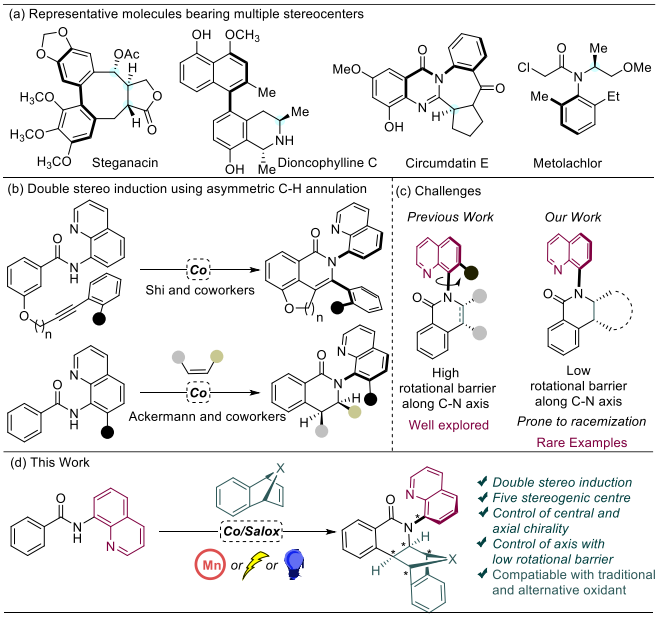
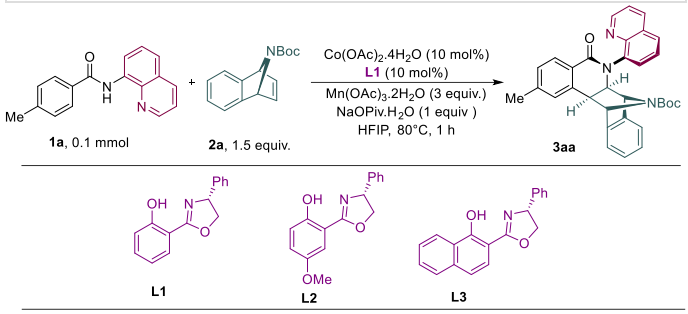


Figure 1: Importance of molecules bearing multi-stereo centers and the synthetic challenge

On the other hand, electro oxidative approaches were also utilized for the *in situ* generation of high valent cobalt complex.[11] Alternatively, molecular oxygen was also used as terminal oxidant in this approach to make process more sustainable.[12] Recently, Shi and sundararaju group utilized photoredox approach for *in situ* generation of the chiral high valent cobalt complexes.[13] Ackermann group achieved the double enantioinduction using *in situ* generated high valent cobalt complexes controlling both point and axial chirality.[14] In this protocol, a bulkier directing group *i.e.* 7-methyl quinoline provides the axial chirality due to the high C-N axis rotational barrier. Shi group[15] utilized a less hindered directing group for intramolecular C-H activation to build up vicinal triaryl motifs with perfect control of two chiral axis vicinal to each

other (Figure 1b). Inspired by this precedent literature and our continuous efforts in asymmetric C-H activation, we assumed multiple stereo genic centers, including both point and axial chirality, can be achieved simultaneously *via* annulation of the *N*-quinolyl benzamides and bridged bicyclic alkene. [16]

Table 1. Initial optimization studies. [a]



Entry	Variation from above condition[a]	% Yield[b]	ee	dr
1	No variation	72%	65%	9:1
2	L2 instead of L1	65%	86%	>20:1
3	L3 instead of L1	85%	89%	>20:1
4[c]	$Co(acac)_2$ instead of $Co(OAc)_2.4H_2O$	82%	89%	13:1
5[c]	$CoCl_2$ instead of $Co(OAc)_2.4H_2O$	70%	90%	11:1
6[c]	$Co(OAc)_2$ instead of $Co(OAc)_2.4H_2O$	79%	86%	9:1
7[c]	$Mn(OAc)_2$ instead of $Mn(OAc)_3.2H_2O$	N.D	-	-
8[c]	MnF_3 instead of $Mn(OAc)_3.2H_2O$	N.D	-	-
9[c]	60°C instead of 80°C	87%	93%	>20:1
10[c]	**TFE instead of HFIP at 60°C**	**98%**	**95%**	**>20:1**
11[c]	MeOH instead of HFIP at 60°C	54%	83%	>20:1
12[c,d]	EOSIN-Y in blue LED instead of $Mn(OAc)_3.2H_2O$ at RT	59%	97%	>20:1
13[c,d]	GF and Pt as electrode in continuous current of 5mA instead of $Mn(OAc)_3.2H_2O$ at RT	22%	97%	>20:1

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (1.5 equiv.), catalyst (10 mol%), Ligand (10 mol%), oxidant (3 equiv), $NaOPiv•H_2O$ (1 equiv), Solvent (0.1 M) [b]isolated yields of 3aa. [c]L3 was used as Ligand

We started our investigation by reacting 4-methyl-*N*-(quinolin-8-yl) benzamide (**1a**) with 7-azabenzonorbornadiene (**2a**) in presence of $Co(OAc)_2.4H_2O$, salicyloxazoline or (*S*)-salox (**L1**), NaOPiv and metal oxidant Mn(III) at 80°C using HFIP as solvent. The desired annulated product (**3aa**) was obtained in 72% yield with 65% ee and 9:1 dr (Table 1, Entry 1). The product **3aa** was confirmed by NMR and HR-ESI(TOF)-MS. Using different substituted salox ligands (**L1-L3**), bulkier salox ligand **L3** found to be the optimum ligand providing **3aa** in 85% yield, 89% ee, and diasteriomeric ratio >20:1 dr (Table 1, Entry 1-3). ^{1}H NMR spectrum of product **3aa** gives rise to a set of peaks suggesting the presence of a diastereomer *i.e.* multiple stereogenic centers in **3aa**. The presence of multiple stereo centers were also confirmed by the crystal structure of two isomers of **3aa,** synthesized by using (*R*)-salox and (*S*)-Salox under the developed reaction condition (Figure 2). Further in screening of various cobalt complexes, $Co(OAc)_2.4H_2O$ was found as a suitable catalyst in this protocol as other cobalt complexes facilitate the formation of product **3aa** with lower diastereoselectivities (Table 1, Entry 4-6). After a systematic investigation of metal oxidant, temperature, and solvents (Table 1, Entry 7-11), we found that the reaction of **1a** with **2a** in the presence of **(*S*)-L3** ligand, $Co(OAc)_2.4H_2O$ as precatalyst and $Mn(OAc)_3.4H_2O$ as oxidant, $NaOPiv.H_2O$ in TFE at 60°C gave the desired product **3aa** in 98% yield with 95% ee and >20:1 dr. Further, we also attempted the alternative oxidant *i.e.* electrooxidative and photoredox approach instead of metal oxidant. Fortunately, our reaction provides **3aa** with excellent enantioselectivity and diastereomeric ratio using photoredox approaches. For photoredox generation of high valent cobalt catalyst, Eosin Y was used under blue light instead of Mn(III) under developed reaction condition, while electrooxidative C-H annulation were carried out using graphite and platinum as electrode in continuous current of 5mA (Table 1, Entry 12-13).

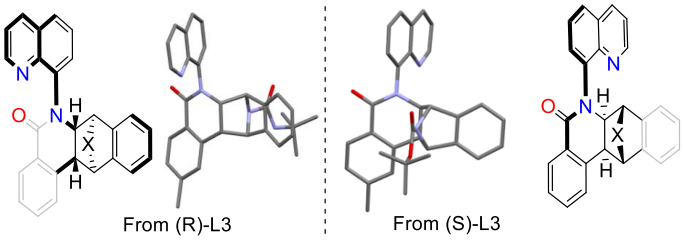
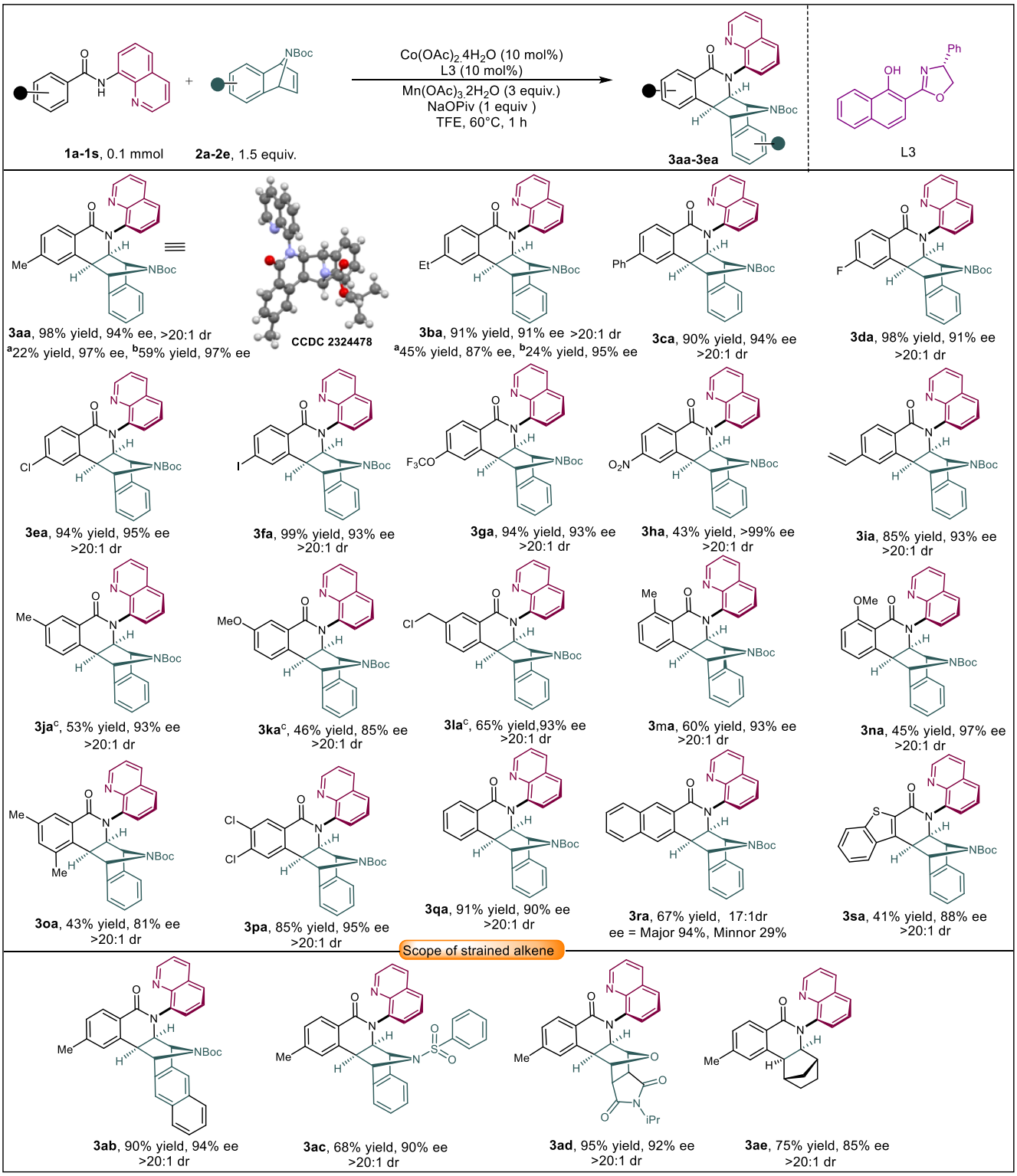


Figure 2: SC-XRD of two isomers of **3aa** (X = -*N*Boc)

With the optimal conditions, we explored the substrate scope of benzamides and strained alkene derivatives (**Scheme 1**). A wide array of *ortho*-, *para*- and *meta*-substituted *N*-quinolyl-benzamides were subjected to the developed reaction conditions. *N*-quinolyl-benzamides substituted with the electron donating and electron withdrawing group at the *para*-position (**1a-1i**) reacted smoothly and provided the corresponding product (**3aa-3ia**) in

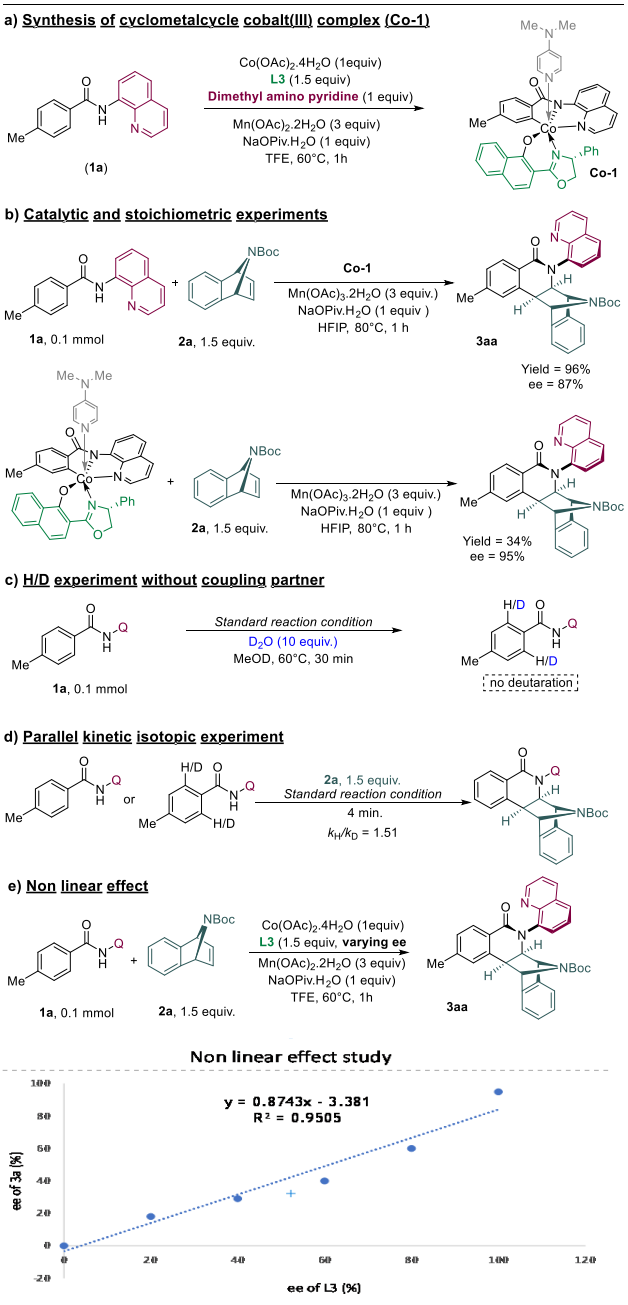
good yields and up to 99% ee along with excellent diastereoselectivities. *Meta*-substituted *N*-quinolyl-benzamides (**1j** -**1l**) did not provide any product under standard reaction condition, however changing the solvent from TFE to HFIP, the regioselective annulated product (**3ja**-**3la**) were obtained in 46% to 65% yield along with good enantioselectivity and diastereoselectivities (ee up to 93% and >20:1 dr). We also observed the effect of the steric hinderance on the developed annulation protocol and found that the *ortho*-substituted *N*-quinolyl-benzamides (**1m** and **1n**) furnished the product (**3ma** and **3na**) in 60% and 45% yield, respectively with excellent enantiomeric excess (93% and 97%, respectively) and diastereomeric ratio (>20:1). Notably, in case of disubstituted *N*-



Scheme-1. Reaction conditions: **1** (0.1 mmol), **2** (0.15mmol), Co-salt (10 mol%), L3 (10mol%), $Mn(OAc)_3 \bullet 2H_2O$ (3 equiv), $NaOPiv \bullet H_2O$ (1 equiv) in TFE (1 mL) under air at 60°C for 1 h; [a]reaction was carried out in electrochemical system using GF/Pt electrode instead of Mn(III) and H_2O as electrolyte. [a]reaction was carried out under photo redox system using eosin-Y instead of Mn(III); [b]HFIP as a solvent.

quinolyl-benzamides electron rich benzamide (**1o**) provided the product in 43% yield and 81% ee, while electron deficient benzamide (**1p**) provided higher yield of the corresponding product, 95% ee and dr upto 20:1. Unsubstituted *N*-quinolyl-benzamide (**1q**) provided the product **3qa** in 91% yield and 90% ee with >20:1 dr. *N*-quinolyl-naphthamide offered the desired product (**3ra**) in 67% yield with a diastereomeric ratio of 17:1 providing major annulated product in 94% ee while minor product in 29% ee. Heterocyclic benzamide (**1p**) reacted smoothly to form **3pa** in 41% yield and 88% ee along with excellent diastereomeric ratio.

Next, strained bicyclic alkenes (**2b-2d**) were also diversified under standard reaction condition. Naphthyl bearing strained alkene reacted well and gave the desired product **3ab** in 90% yield with 94% ee and dr > 20:1. *N*-(phenylsulfonyl)-1,4-dihydro-1,4-epiminonaphthalene (**2c**) and 2-isopropyl-tetrahydro1H-4,7-epoxyisoindole-1,3(2H)-dione (**2d**) were also well tolerated to provide products (**3ac** and **3ad**) with a good control of both enantioselectivity and diastereoselectivity. Interestingly, Bicyclo [2.2.1] hept-2-ene was also found compatible under current reaction conditions and gave 75% yield in 85% ee and dr > 20:1 (**3ae**).



Scheme 2. Mechanistic studies and control experiments.

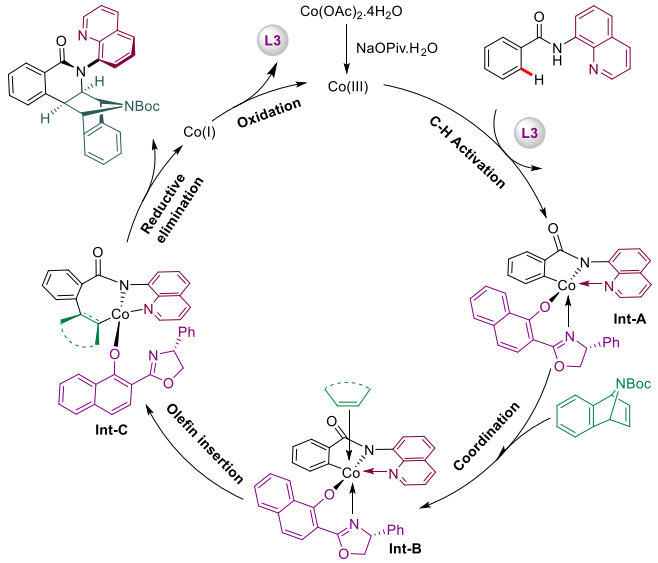
Next the reaction was also explored under electrooxidative and photochemical conditions. For electroxidative reaction conditions, Mn salt was replaced with GF/Pt electrode. Interestingly, the desired product was obtained with 97% ee, albeit with lower yield
(22%). Ethyl group in place of methyl group in the benzamide ring gave the annulated product **3ab** in 45% yield and 87% ee.

Further to explore the photochemical aspect, Eosin Y was used instead of Mn salt and the reaction was carried out under

blue light for 2 hours. The desired annulated product **3a** was obtained in 59% yield and 97% ee. Ethyl- substituted benzamide gave desired product in 24% yield and 95% ee (**3ab**) under photocatalytic condition.

To highlight the practicality of the developed methodology, a gram scale reaction was carried out and 92% of the desired annulated product was obtained in 91% ee and dr >20:1 (See ESI).

In order to investigate the reaction pathway, a brief mechanistic study was carried out. Initially, a stoichiometric reaction was carried out to synthesize possible intermediate **Co-1**, using DMAP as ligand (**Scheme 2a**). To confirm the role of **Co-1** as active intermediate, we carried out the catalytical and stochiometric reaction using the **Co-1** complex and the product **3a** was obtained in 96% and 40% yields with 87% and 95% ee, respectively (**Scheme 2b**). Further, a deuterium labelling experiments signify the irreversible nature of C-H activation step, as no deuteration were observed in the recovered **1a** in absence of **2a** under standard reaction condition (**Scheme 2c**). Next, parallel KIE experiment value was found to be 1.51 which suggested that C-H activation might not the rate-limiting step (**Scheme 2d**). The non-linear experiments were also perfomed with varying degree of **L3** ligand. The results obtained suggested that single chiral salox ligand coordinated with the cobalt atom, which is responsible for the enantiopurity of the annulated product **3a** (**Scheme 2e**).



Scheme 3. Plausible reaction mechanism.

On the basis of these experiments and literature reports [9,10] a plausible reaction mechanism has been proposed (**Scheme 3**). Initially $Co(OAc)_2.4H_2O$ co-ordinated with salox ligand and got oxidized in the presence of Mn(III) to form Co(III) species *in situ*. Co(III) species underwent ligand exchange and reacted with substrate (**1a**) through C-H activation to give **Int-A**. **Int-A** then coordinates with strained alkene **2a** to yield **Int-B** which further underwent olefin insertion to give **Int-C**. **Int-C** undergo reductive elimination to give the product **3aa** and Co(I) species. The oxidation of Co(I) further regenerate the active Co(III) species to continue the catalytic cycle.

In summary, we have disclosed a cobalt-catalyzed C−H annulation for the single-step construction of two stereogenic centers *i.e.* carbon central point chirality with C−N chiral axis of low rotational barrier. Notably, the developed reaction protocol was well compatible with metal oxidant as well as alternative oxidative system *i.e.* photoredox and electrooxidative approaches providing annulated protocol with excellent control of enantioselectivity and diastereoselectivity. Further, optimization of electrochemical and photoredox asymmetric C-H annulation are underway in our laboratory.

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Keywords: •Asymmetric Catalysis •Bicyclic Alkenes •Chirality •Double stereo induction

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