C–H Bond Activation | **Hot Paper**

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Highly Stereoselective Cobalt(III)-Catalyzed Three-Component C–H Bond Addition Cascade

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Dedicated to K. Barry Sharpless on the occasion of his 75th birthday

Abstract: *A highly stereoselective three-component C(sp^2)–H bond addition across alkene and polarized π-bonds is reported for which Co^{III} catalysis was shown to be much more effective than Rh^{III}. The reaction proceeds at ambient temperature with both aryl and alkyl enones employed as efficient coupling partners. Moreover, the reaction exhibits extremely broad scope with respect to the aldehyde input; electron rich and poor aromatic, alkenyl, and branched and unbranched alkyl aldehydes all couple in good yield and with high diastereoselectivity. Multiple directing groups participate in this transformation, including pyrazole, pyridine, and imine functional groups. Both aromatic and alkenyl C(sp^2)–H bonds undergo the three-component addition cascade, and the alkenyl addition product can readily be converted into diastereomerically pure five-membered lactones. Additionally, the first asymmetric reactions with Co^{III}-catalyzed C–H functionalization are demonstrated with three-component C–H bond addition cascades employing N-tert-butanesulfinyl imines. These examples represent the first transition metal catalyzed C–H bond additions to N-tert-butanesulfinyl imines, which are versatile and extensively used intermediates for the asymmetric synthesis of amines.*

C–H functionalization has emerged as a core strategy to access synthetically useful structural motifs, many of which are found in drugs and natural products.[1,2] Of the many transition-metal catalysts that facilitate this process, Rh^{III} catalysts have been demonstrated to be among the most useful because of their unique reactivity and high functional group compatibility.[3] Following the seminal reports of Co^{III}-catalyzed C–H functionalization[4] by Kanai and Matsunaga in 2013,[5ac] a number of groups (including our own) have demonstrated that earth abundant Co^{III} catalysts can provide analogous reactivity to their second row Rh^{III} congeners.[4,5] For some transformations divergent reactivity is displayed between Cp*Co^{III} and Cp*Rh^{III} catalysts,[6] but significant differences in non-annulative redox-neutral couplings have yet to be reported. Recently, we described preliminary results on a three-component C–H functionalization cascade by Rh^{III}-catalysis (Figure 1a).[7] Though the transformation proceeded in good yield, very poor diastereoselectivity was observed. After thorough investigation, only ethyl glyoxylate was reactive in the three-component transformation (Figure 1a,b).

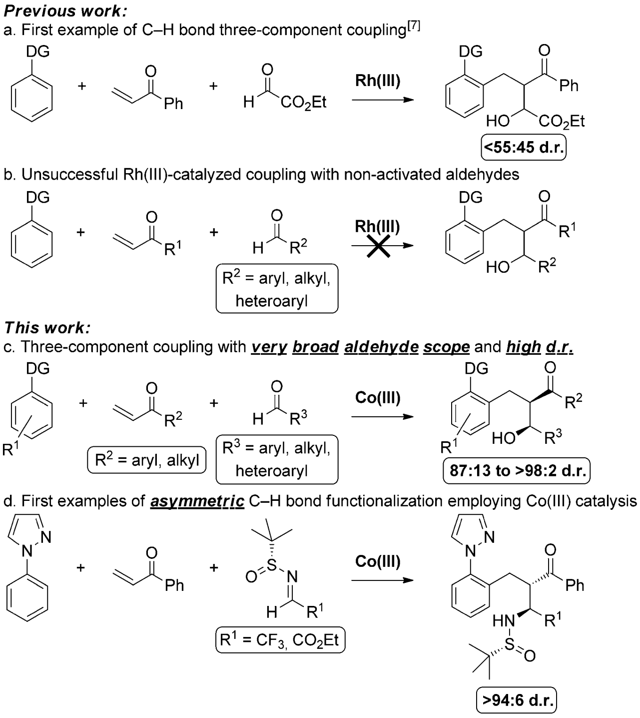

Figure 1. C–H bond enabled three-component coupling.

Herein we report that Cp*Co^{III}-catalysts not only facilitate three-component additions to a wide array of aldehydes, including electron poor and rich aromatic, alkenyl, and branched and unbranched alkyl derivatives, but that the transformation also proceeds with high diastereoselectivities ranging from 87:13 to >98:2 d.r. (Figure 1c).[8,9] Moreover, we disclose the first asymmetric C–H bond functionalization reaction employing Cp*Co^{III} catalysts, with three-component C–H bond addition cascades to *N*-*tert*-butanesulfinyl imines (Figure 1d).

Our initial investigation of non-activated aldehydes in the three-component coupling reaction began with the conditions previously developed for Rh^{III} catalysis using ethyl glyoxylate (Supporting Information, Page S-4).[7] Unfortunately, attempts to obtain desired alcohol products such as **4a** were unsuccessful, leading only to high yields of the two-component product **5a** (Table 1). Subsequently, we

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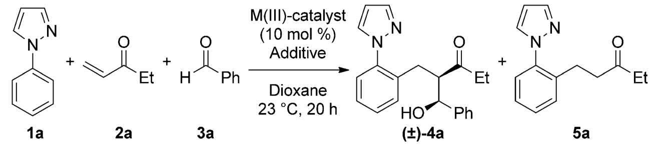
Table 1: Optimization for the three-component transformation.[a,b]



Entry	M^{III}-catalyst	Additive[d]	**3a** [equiv]	Yield **4a** [%][b] (d.r.)	Yield **5a** [%][b]
1[c]	$[Cp^*Co(C_6H_6)][PF_6]_2$	KOAc	5	65 (95:5)	21
2	$[Cp^*Co(C_6H_6)][PF_6]_2$	KOAc	5	<5	<5
3	$[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$	KOAc	5	61 (96:4)	33
4	$[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$	CsOAc	5	57 (96:4)	43
5	$[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$	LiOAc	5	63 (96:4)	37
6	$[Cp^*Co(C_6H_6)][B(C_6F_5)_4]_2$	LiOAc	3	70 (97:3)	27
7[e]	$[Cp^*Co(CO)I_2]/AgB(C_6F_5)_4$	LiOAc	3	63 (97:3)	32
8[e,f]	$[Cp^*RhCl_2]_2/AgB(C_6F_5)_4$	LiOAc	3	<5	77

[a] Conditions: **1a** (1.0 equiv), **2a** (1.2 equiv), and **3a** (3–5 equiv) for 20 h in 1,4-dioxane (2.0 M). [b] Determined by ^1H NMR analysis relative to 1,3,5-trimethoxybenzene as an external standard. [c] Reaction run at 50 °C. [d] Additive (20 mol %). [e] $AgB(C_6F_5)_4$ (20 mol %). [f] $[Cp^*RhCl_2]_2$ dimer (5 mol %).

investigated Co^{III}-catalysis. Kanai and Matsunaga's preformed catalyst $[Cp^*Co(C_6H_6)][PF_6]_2$ was evaluated first because this complex had previously been shown to facilitate C–H bond additions to electron-deficient alkenes.[5ac] The desired product **4a** was formed in 65 % yield and with high diastereoselectivity (95:5 d.r.; entry 1, Table 1). Notably, for ethyl vinyl ketone (**2a**) a single regioisomer of the three-component product was obtained, establishing that equilibration to regioisomeric enolates does not occur after addition to the enone. In an effort to enhance the diastereoselectivity of this transformation we ran the reaction at ambient temperature (23 °C), but noticed minimal conversion (entry 2). In contrast, when we employed the preformed catalyst $[Cp^*Co(C_6H_6)][B(C_6F_5)_4)]_2$ developed in our laboratory for the direct C–H bond addition to aldehydes,[5v] we found that the reaction proceeded at ambient temperature in 61 % yield and with an improved 96:4 d.r. (entry 3). Exploring other acetate salts, such as cesium or lithium acetate, provided similar yields (entries 4–5). Furthermore, upon lowering of the number of equivalents of benzaldehyde (**3a**), with LiOAc as the additive, the yield was maintained along with a slight improvement in diastereoselectivity to 97:3 d.r. (entry 6; see Table 1).

Employing the precatalyst $[Cp^*Co(CO)I_2]$ in conjunction with $AgB(C_6F_5)_4$ under the optimal conditions provided comparable yield and diastereoselectivity to that achieved with the preformed catalyst (entry 7). However, because the preformed catalyst $[Cp^*Co(C_6H_6)][B(C_6F_5)_4)]_2$ simplifies reaction set up and is also prepared without the use of any precious metals,[5v] this preformed catalyst was used in all subsequent experiments. Finally, when the precatalyst $[Cp^*RhCl_2]_2$ with $AgB(C_6F_5)_4$ was used under the optimal reaction conditions for Co^{III}-catalysis, the desired product **4a** was obtained in only trace amounts and high yields of the two-component addition product **5a** were obtained instead (entry 8). This result highlights the vast superiority of Co^{III} over Rh^{III} catalysis for this three-component coupling reaction. When the Co^{III} catalyst was absent no reaction was observed, while removal of the LiOAc additive resulted in some product but with reduced yields and conversion for most substrates (Supporting Information, Page S-4).

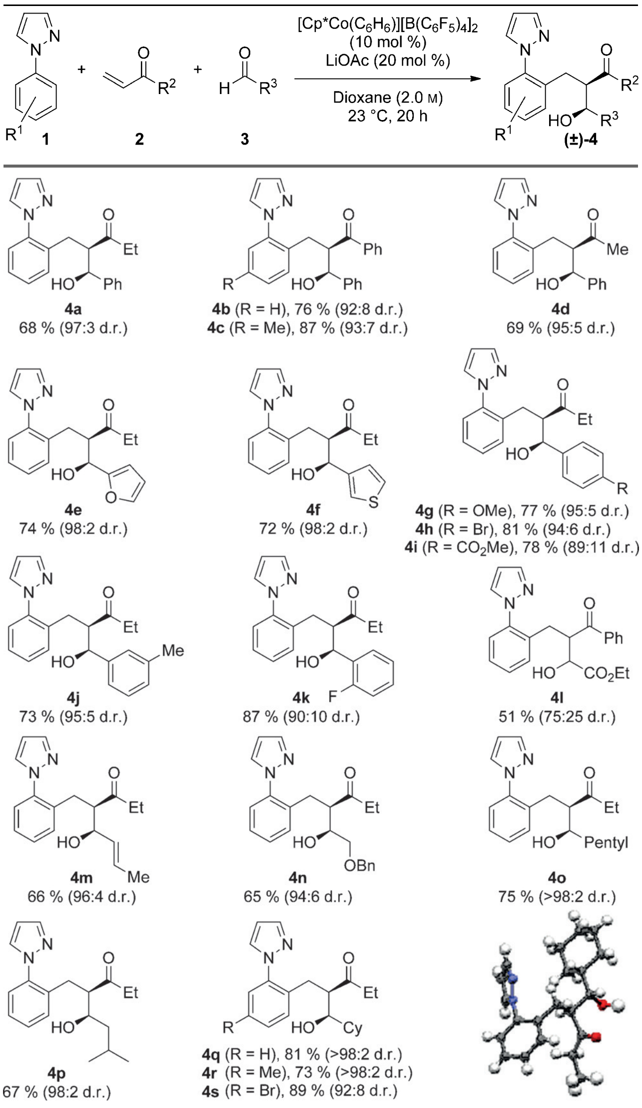
After determining the optimal reaction conditions, we turned our attention to evaluating the scope of the three-component reaction (Table 2). Initially, a variety of enones were investigated.

Phenyl vinyl ketone (**2b**) was an effective coupling partner, leading to high yields of products **4b** and **4c** with good diastereoselectivity. Methyl vinyl ketone also displayed good reactivity, furnishing product **4d** in 69 % yield and a d.r. of 95:5. Subsequently, a series of aldehydes were subjected to the three-component reaction. Electron-rich heteroaryl aldehydes coupled efficiently to give products **4e** and **4f** in good yields and with a d.r. of 98:2. For aryl aldehydes, strongly and weakly donating substituents provided the respective products **4g** and **4j** in good yield and with high diastereoselectivity. Benzaldehydes substituted with weakly and strongly electron deficient groups, such as 4-bromo (**4h**), 4-methyl ester (**4i**), and 2-fluoro (**4k**) groups, also coupled in good yields, though with modestly lower diastereoselectivities. Use of the highly activated ethyl glyoxylate provided product **4l** in 51 % yield and 75:25 d.r.; the lower yield is attributed to a competitive direct arene C–H bond addition to the aldehyde (see the Supporting Information).

Along with aryl and heteroaryl aldehydes, reactions with more challenging alkenyl and alkyl aldehydes also proceeded smoothly. When crotonaldehyde was employed product **4m** was obtained in 66 % yield with a d.r. of 96:4. Importantly, competitive 1,4-addition into crotonaldehyde was not observed. The activated benzyloxy acetaldehyde displayed good reactivity, providing product **4n** in 65 % with a d.r. of 94:6. Linear and branched alkyl aldehydes also underwent successful three-component coupling to give products **4o–s** in high yield and diastereoselectivity. These examples clearly demonstrate that self-condensation side reactions do not compete for enolizable alkyl aldehyde derivatives. Three-component addition product **4q** was isolated as a single diastereomer in 81 % yield. The relative stereochemistry of this product was rigorously determined by X-ray crystallography.[10]

Different directing groups were also explored. As well as pyrazole, pyridine was an effective directing group for the heteroaromatic C–H functionalization of isoquinolinones (Scheme 1). Notably, both aryl and alkyl aldehydes coupled efficiently to furnish products **4t** and **4u** in good yield and selectivity. Ketimine **1c** also directed the three-component C–H bond addition cascade (Scheme 2). Interestingly, the expected alcohol underwent an additional intramolecular

Table 2: Scope for the Co^{III}-catalyzed three-component transformation.[a,b]

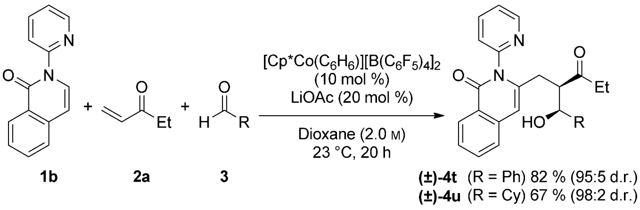


4a 68 % (97:3 d.r.)
4b (R = H), 76 % (92:8 d.r.)
4c (R = Me), 87 % (93:7 d.r.)
4d 69 % (95:5 d.r.)
4e 74 % (98:2 d.r.)
4f 72 % (98:2 d.r.)
4g (R = OMe), 77 % (95:5 d.r.)
4h (R = Br), 81 % (94:6 d.r.)
4i (R = CO$_2$Me), 78 % (89:11 d.r.)
4j 73 % (95:5 d.r.)
4k 87 % (90:10 d.r.)
4l 51 % (75:25 d.r.)
4m 66 % (96:4 d.r.)
4n 65 % (94:6 d.r.)
4o 75 % (>98:2 d.r.)
4p 67 % (98:2 d.r.)
4q (R = H), 81 % (>98:2 d.r.)
4r (R = Me), 73 % (>98:2 d.r.)
4s (R = Br), 89 % (92:8 d.r.)

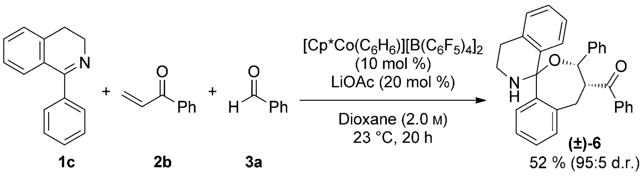
[a] Conditions: **1** (1.0 equiv), **2** (1.2 equiv), and **3** (3.0 equiv) for 20 h in 1,4-dioxane (2.0 M). [b] Yield of isolated products after silica gel chromatography.

cyclization to provide spirohemiaminal ether **6** with a d.r. of 95:5.

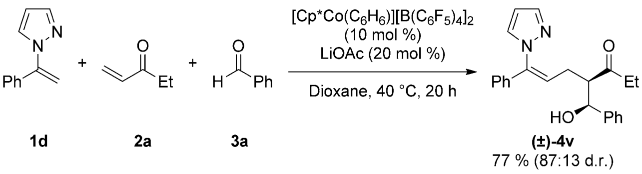
Beyond the functionalization of aryl C(sp^2)-H bonds, participation of alkenyl C(sp^2)-H bonds in the three-component coupling was also demonstrated (Scheme 3).



Scheme 1. Three-component coupling with pyridylisoquinolinone.

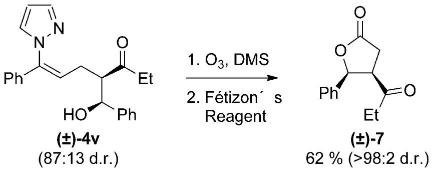


Scheme 2. Use of a ketimine directing group to access a spirohemiaminal ether.

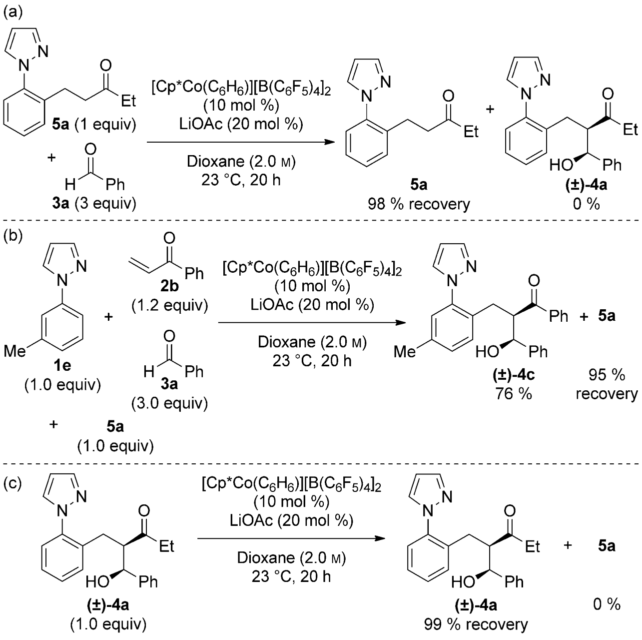


Scheme 3. Alkenyl C–H bond three-component coupling.

Reaction of alkenyl pyrazole **1d** with ethyl vinyl ketone (**2a**) and benzaldehyde (**3a**) gave **4v** in 77% yield and with 87:13 diastereoselectivity. Further elaboration of **4v** was readily accomplished by ozonolysis to afford a lactol intermediate, which was conveniently oxidized with Fétizon's reagent to provide lactone **7** in diastereomerically pure form after chromatography (Scheme 4). This three-component



Scheme 4. Employment of a cleavable directing group for further functionalization.

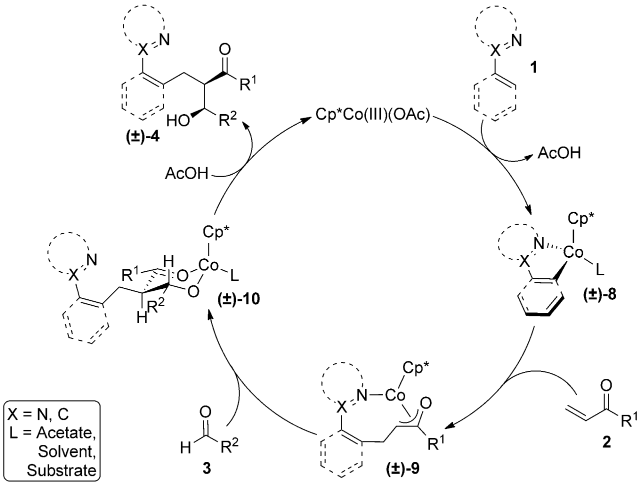


Scheme 5. Mechanistic experiments.

coupling cascade consequently provides rapid access to γ-lactones, which are present in numerous drugs and natural products, including readily available α,β-unsaturated ketones and aldehydes.

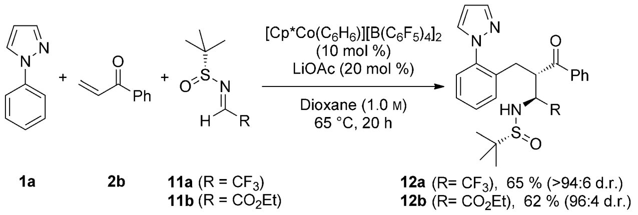
A number of experiments were conducted to provide insight into the mechanism of the Co^{III}-catalyzed three-component reaction (Scheme 5). In the first mechanistic experiment, **5a** was subjected to the optimal reaction conditions in the presence of benzaldehyde (**3a**; Scheme 5a). The alcohol product **4a** resulting from the three-component transformation was not observed. Instead **5a** was recovered quantitatively, suggesting that **5a** does not participate in the catalytic cycle upon release from the catalyst. Subsequently, the three-component coupling of pyrazole **1e** with phenyl vinyl ketone (**2b**) and benzaldehyde (**3a**) was evaluated in the presence of **5a** (Scheme 5b). Under these conditions the expected alcohol product **4c** was formed in only a slightly slower yield than previously observed in the absence of **5a** (Table 2), and **5a** was recovered in 95% yield. This result conclusively indicates that the released conjugate addition product **5a** does not participate in the catalytic cycle, and therefore, the cobalt enolate that reacts with the aldehyde only arises through initial C−H bond addition to enone **2**. To evaluate whether or not alcohol **4a** exists in equilibrium with the conjugate addition product **5a**, alcohol **4a** was subjected to the optimal reaction conditions (Scheme 5c). Complete recovery of **4a** was achieved without any loss in stereochemical purity, thereby establishing irreversible formation of the alcohol.

A plausible mechanism for the reaction is depicted in Scheme 6. Coordination of the directing group to the cationic Co^{III} catalyst, followed by directed C−H bond metalation, provides the active cobaltacycle **8**. Conjugate addition of **8** into the enone coupling partner **2** provides the racemic cobalt enolate **9**.[11] Diastereoselective addition of the cobalt enolate **9** to aldehyde **3** via a chair transition state generates cobalt alkoxide **10**. Release of the product upon proto-demetalation yields the desired alcohol **4** while regenerating the cationic Co^{III} catalyst. The high observed diastereoselectivity of this transformation could alternatively be explained by generation of a *Z*-Co^{III} enolate that reacts with the aldehyde via a boat transition state, with likely coordination of the directing-group nitrogen. Mechanistic studies are planned that should provide better resolution of the reaction pathway and origin of stereoselectivity.



Scheme 6. Proposed mechanism for the Co^{III}-catalyzed three-component transformation.

Following our investigation of aldehydes in the three-component reaction, we subsequently explored additions to imines to provide access to branched amine products **12** (Scheme 7). Given the extensive use of nucleophilic additions to *N-tert*-butanesulfinyl imines for the asymmetric synthesis of amines,[12] we evaluated the viability of using *N-tert*-butanesulfinyl imines in this Co^{III}-catalyzed three-component coupling process. In very promising preliminary results, asymmetric three-component addition to *N*-sulfinyl trifluoroacetaldimine **11a** gave the amine product **12a** with high diastereoslectivity (absolute configuration was rigorously determined by X-Ray crystallography).[10] Furthermore, asymmetric three-component addition to sulfinyl imino ester **11b** proceeded to give α-amino ester **12b**, also with high diastereoselectivity. To our knowledge these are the first asymmetric reactions employing Co^{III}-catalyzed C−H functionalization and are also the first examples of transition metal catalyzed C−H bond addition to *N-tert*-butanesulfinyl imines.



Scheme 7. Three-component coupling with *N-tert*-butanesulfinyl imines.

In summary, we have developed an efficient route for Co^{III}-catalyzed three-component coupling of aromatic and alkenyl $C(sp^2)$−H bonds, enones, and aldehydes, or *N-tert*-butanesulfinyl imines. Significantly, this method highlights major reactivity and stereoselectivity differences between Cp^*Rh^{III} and Cp^*Co^{III} catalyst systems. Herein, we have showcased that Cp^*Co^{III}-three-component coupling is effective for aryl and alkyl enone coupling partners and displays an extremely broad aldehyde scope. The 1-pyrazole, 2-pyridine, and imine directing groups each afforded products in good yield and with high diastereoselectivity. A cleavable alkenyl pyrazole can also be used in the three-component coupling to efficiently provide diastereomerically pure lactones. Additionally, we have provided preliminary data on an asymmetric variant of the reaction with the first C−H bond additions to *N-tert*-butanesulfinyl imines. Broadening of the scope of enone substrates by including β-substitution is currently under investigation as a means of introducing a third stereocenter in diastereoselective fashion. Asymmetric additions to a range of *N*-*tert*-butanesulfinyl imines, as well as chiral aldehydes, are under active investigation, as is the development and evaluation of chiral Co^{III} catalysts for this three-component cascade process.

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Keywords: C–H activation · diastereoselectivity · homogeneous catalysis · multicomponent reactions

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