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Co(I)-catalyzed [3+2] annulation of *o*-haloaryl imines with alkenes for the synthesis of indanamines

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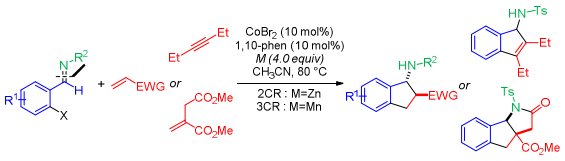
Abstract



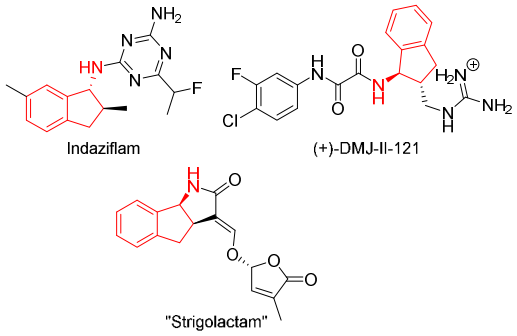
The use of a $CoBr_2$ / 1,10-phenanthroline catalytic system together with Zn as the reductant has been developed to prepare diversely substituted indanamines by a Co(I)-catalyzed [3+2] annulation of *o*-haloaryl imines with electron-deficient alkenes in good yields. The use of Mn as the reductant allowed the elaboration of a three-component version of this reaction. These conditions were also found to be suitable for the activation of various halides and were extended to the preparation of the indenamine and strigolactam scaffolds.

Introduction

The use of first row transition metals in catalysis is of increasing importance thanks to their broad availability, reduced cost and low toxicity.[1] Among them, cobalt is particularly interesting because it can catalyze a large number of reactions, with a great substrate scope

due to a high tolerance to various functional groups. Cobalt complexes are particularly suitable for annulation reactions, and especially [2+2+2] cycloadditions,[2,3] owing to its high affinity to π-systems.[4,5] The crucial field of cross-coupling reactions has also greatly benefited from cobalt catalysis, in traditional reactions between an organometallic species and an electrophile[6,7] and, more recently, in reductive couplings between two electrophiles.[8,9] The merge of cobalt-catalyzed annulation and coupling reactions has been achieved by Cheng in 2003 with the development of the [3+2] annulation reaction between *o*-iodoaryl aldehydes or ketones with carbon-carbon π bonds of alkenes or alkynes in a new synthesis of indenes and indanols.[10,11] The closely related nitrogenated counterpart indanamines are relevant targets in organic synthesis. For instance, this scaffold is a key feature of the broad-spectrum herbicide Indaziflam,[12] HIV-1 entry inhibitors like (+)-DMJ-II-121[13] and strigolactam phytohormones (Figure 1).[14]

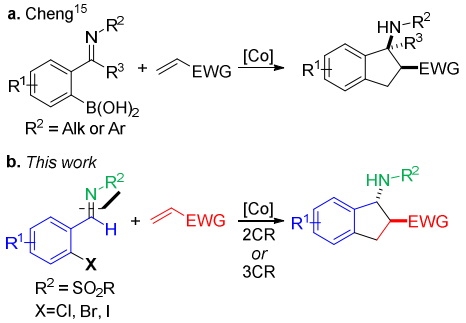
Figure 1. Selected bioactive indanamines.



The first Co-catalyzed preparation of indanamines has been reported by Cheng in 2012.[15] However, these conditions remained limited to the use of *o*-iminoarylboronic acids and Michael acceptors (Scheme 1a). The use of related *o*-halogenated starting materials was only described in multicomponent annulation reactions with alkynes leading to indenamines. In this case, the imine function was formed *in situ* by condensation of a primary aliphatic or aromatic amine on a carbonyl compound[16] However, the process was only exemplified starting from iodinated substrates. In the past few years, our group has developed some

efficient Co(I)-catalyzed transformations based on a halide activation by a Co(II) / reductant catalytic system. These methodologies have been successfully applied to organometallic Mannich reactions involving aryl halides,[17,18] ultimately leading to multicomponent procedures initiated by a Michael addition.[19] More precisely, we recently reported a new synthesis of β[2,3]-aminoesters by multicomponent assembly of aryl halides, Michael acceptors and sulfonated imines.[20,21] Herein, we describe the development of an intramolecular version of this reaction leading to indanamines through a [3+2] annulation of *o*-haloaryl imines with Michael acceptors (Scheme 1b), as well as the elaboration of the corresponding three-component version of the reaction.

Scheme 1. Co-catalyzed syntheses of indanamines.

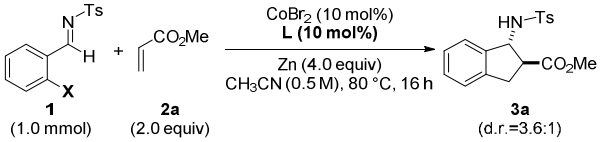


Results and Discussion

We started our investigations of the two-component [3+2] annulation reaction (2CR) from our previously optimized conditions developed for the related multicomponent reaction (MCR) involving aryl halides, imines and Michael acceptors.[21] As a test reaction, we thus submitted a mixture of brominated imine **1a** (1.0 equiv) and methyl acrylate **2a** (2.0 equiv) to the presence of $CoBr_2$ (10 mol%) and activated zinc dust (4.0 equiv) in acetonitrile at 80 °C.[22] The expected indanamine **3a** was gratifyingly isolated in a promising 52% yield (entry 1, Table 1). Having noticed the beneficial influence of ligated cobalt species in similar transformations,[16] we next evaluated the effect of the addition of a ligand (L) to the catalytic system. While the

use of diphenylphosphinoethane (dppe) as disclosed in Cheng's work showed a slight improvement (66%, entry 2), the use of 1,10-phenanthroline (1,10-phen) afforded a good 82% yield (entry 3). It should be noted that the nature of the catalytic system has no influence on the diastereoselectivity of the reaction as **3a** was obtained in a constant 3.6:1 diastereoisomeric ratio, the major product being the trans stereoisomer, determined by NOESY analysis.[23] We also evaluated the influence of the nature of the halogen atom on the reaction outcome. Under the same reaction conditions, iodinated derivative worked equally well (78%, entry 4) and, interestingly, the chlorinated analog of the starting imine allowed the isolation of the product in a reasonable 68% yield (entry 5).

Table 1. Study of the 2CR.[a]



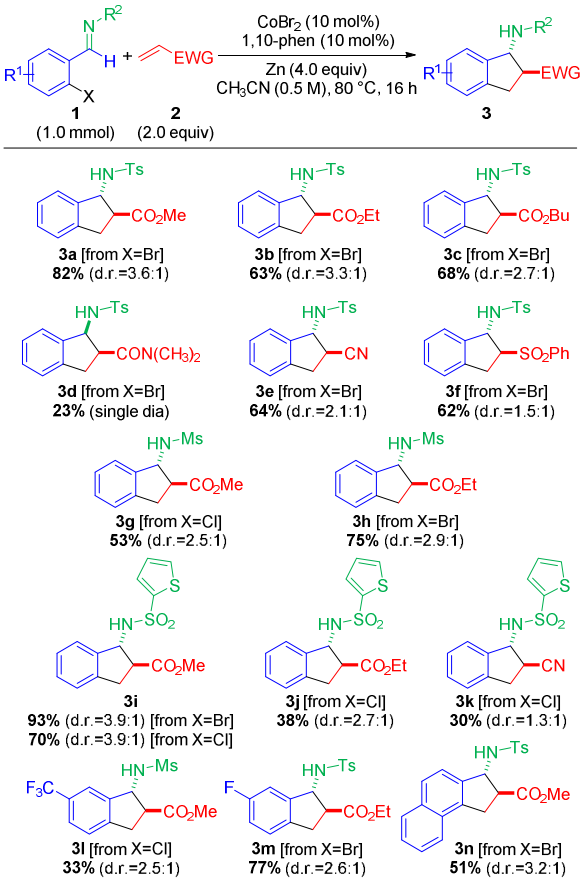
Entry	X	L	Yield
1	Br	-	52%
2	Br	dppe	66%
3	Br	1,10-Phen	82%
4	I	1,10-Phen	78%
5	Cl	1,10-Phen	68%

[a] Yields of isolated products. Reaction conditions: **1** (1.0 mmol), **2a** (2.0 equiv), $CoBr_2$ (10 mol%), L (10 mol%), Zn (4.0 equiv) activated with $BrCH_2CH_2Br$ (10 mol%) and TFA (10 mol%), CH_3CN (C=0.5 M), 80 °C, 16 h.

With these optimized conditions in hands, we next turned our attention to the scope of the 2CR using various *o*-brominated and *o*-chlorinated aromatic imines (Table 2). From a general point of view, bromide derivatives demonstrated higher activities as anticipated. Various Michael acceptors were first evaluated using bromide derivatives as a compromise of

efficiency and availability. While ethyl and butyl acrylates worked efficiently (**3b**: 63% and **3c**: 68%, respectively) with similar diastereoselectivities in favor of the *trans* product, the reaction performed with *N*,*N*-dimethylacrylamide allowed only the isolation of a *cis* diastereoisomer of **3d**, albeit in a modest 23% yield. Other electron-deficient alkenes such as acrylonitrile (64%, **3e**)[24] and phenylvinylsulfone (62%, **3f**) were also efficient partners but showed poorer stereocontrol. However, the use of substituted Michael acceptors was not tolerated in the reaction. The presence of an electron-withdrawing group on the imine function was also required but gave the opportunity to access to the free amine group using a removable substituent. Thus, the use of starting materials bearing a mesyl group or a 2-thiophenesulfonyl group was examined. Mesylated products **3g** and **3h** were obtained in a moderate 53% using a chlorinated substrate and in an improved 75% for the brominated one. In the case of imines bearing a 2-thiophenesulfonyl group (product **3i**), a similar observation could be done. Nevertheless, this group appeared more suitable and allowed the use of chlorinated starting materials with ethyl acrylate (**3j**) and acrylonitrile (**3k**) in useful yields. Substitution of the aromatic ring of **1** was also examined using either chlorinated or brominated starting materials. Therefore, the introduction of a trifluoromethyl group on a chlorinated substrate allowed the synthesis of **3l** in 33%. Once again, bromide derivatives were more efficient and the introduction of a fluorine atom provided similarly good results (**3m**, 77%),[25] whereas the use of a naphthalene-derived substrate allowed the formation of the corresponding tricyclic product **3n** in 51% yield.

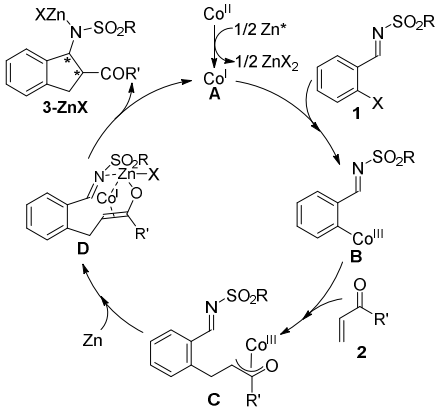
Table 2. Scope of the two-component synthesis of indanamines.[a]



[a] Yields of isolated products. Reaction conditions: **1** (1.0 mmol), **2** (2.0 equiv), $CoBr_2$ (10 mol%), 1,10-phen (10 mol%), Zn (4.0 equiv) activated with $BrCH_2CH_2Br$ (10 mol%) and TMSCl or TFA (10 mol%), CH_3CN (C=0.5 M), 80 °C, 16 h.

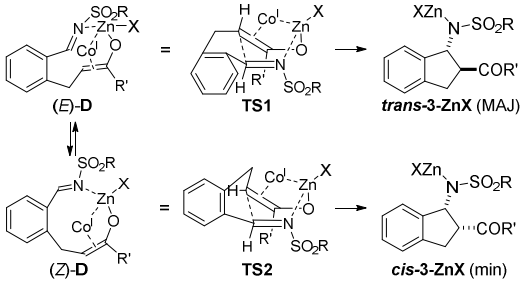
Based on previous studies, the reaction is believed to occur through a classical Co-catalyzed carbometallation followed by an intramolecular addition of the resulting enolate on the imine moiety (Scheme 2). More precisely, a Co(I) complex **A**, generated *in situ* by reduction of $CoBr_2$ with activated Zn dust,[26] underwent an oxidative addition into the C(sp^2)–Br bond to generate the organocobalt species **B**. This latter could perform a carbocobaltation on the Michael acceptor **2**,[27] leading to intermediate **C**. Upon reaction with zinc, Co(III) is reduced to Co(I) concomitantly with the formation of zinc enolate **D**, which evolved by an intramolecular addition on the C=N bond to produce the zinc salt of **3** and release the Co(I) catalyst.

Scheme 2. Plausible reaction mechanism (ligands are omitted for clarity).



The stereo-determinating step should thus be the intramolecular addition of the enolate function onto the imine moiety of **D**. Regarding the particular result obtained in the case of *N*,*N*-dimethylacrylamide, the geometry of the intermediate enolate appeared to be crucial and suggested the intervention of a tethered transition state as in the Zimmerman-Traxler model. However, in the present case, the use of a bimetallic Co / Zn catalytic system should favor an equilibrium between (*E*)- and (*Z*)-enolates and the formation of boat-like conformation,[28] through a cobalt – zinc interaction, as previously proposed by Lam.[29] Therefore, in this hypothesis, the formation of a (*E*)-enolate would lead to **TS1** and thus to the major *trans* product whereas a (*Z*)-enolate would lead to **TS2**, precursor of the minor *cis* product (Scheme 3). The transition state **TS1** should be the predominant form as the substituent of the enolate is in pseudo-equatorial position. As amides are known to produce exclusively (*Z*)-enolates, the present model explained the exclusive formation of the *cis*-product albeit in poor yield due to the formation of the unfavorable intermediate **TS2**.

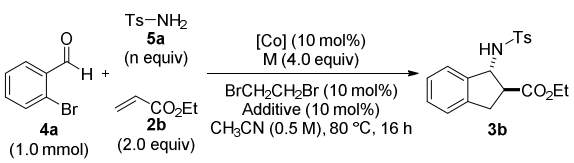
Scheme 3. Diastereoselectivity of the reaction (ligands are omitted for clarity).



As the development of original MCRs is of constant interest,[30] we wondered if a three-component version of this reaction would be feasible. Indeed, the starting imines can be prepared by simple condensation of an aromatic aldehyde with a primary sulfonamide. Such a modification should be possible thanks to the higher electrophilicity of the sulfonated imines in comparison with the corresponding aldehydes[31] and to the low rates of the aza-Michael additions of sulfonamides onto electron-deficient alkenes. We thus started a short optimization of the three-component protocol (Table 3).

Using our previous conditions with a 1:1 mixture of aldehyde **4a** and sulfonamide **5a**, we were pleased to detect the expected product **3a** in an encouraging 19% yield (entry 1). Increasing the amount of sulfonamide **5a** had a negative effect on the reaction (entry 2) presumably due to its Lewis base character. Based on our previous study on the organometallic Mannich reaction involving sulfonamide derivatives,[32] we switched the reductant from Zn to Mn. This modification resulted in an improvement of the reaction (30%, entry 3), even in the absence of the stabilizing ligand (29%, entry 4). The nature of the acidic additive was ultimately evaluated (entry 5) and the use of TFA instead of TMSCl afforded the best 31% isolated yield.

Table 3. Optimization of the three-component synthesis of indanamines.[a]



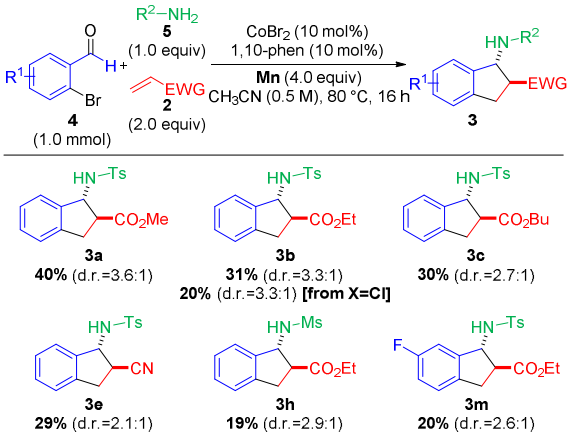
Entry	[Co]	n	M	Additive	Yield[b]

1	$CoBr_2$ + 1,10-phen	1	Zn	TMSCl	19%
2	$CoBr_2$ + 1,10-phen	2	Zn	TMSCl	15%
3	$CoBr_2$ + 1,10-phen	1	Mn	TMSCl	30%
4	$CoBr_2$	1	Mn	TMSCl	29%
5	$CoBr_2$ + 1,10-phen	1	Mn	TFA	31%[c]

[a] Reaction conditions: **4a** (1.0 mmol), **5a** (n equiv), **2b** (2.0 equiv), $CoBr_2$ (10 mol%), L (10 mol%), M (4.0 equiv) activated with $BrCH_2CH_2Br$ (10 mol%) and additive (10 mol%), CH_3CN (C=0.5 M), 80 °C, 16 h. [b] GC yields determined using an internal standard (mesitylene). [c] Isolated yield.

The scope of this new three-component protocol was also briefly examined, and the results are reported in Table 4. In all cases, yields are lower than those observed for 2CRs, due in particular to more complex purifications, but remained useful for the rapid elaboration of a small library of compounds. Remarkably, diastereoselectivities are the same than those observed in 2CRs. All previously used acrylates underwent this reaction, albeit in more moderate yields (**3a-c**, 30–40%). Interestingly, the less expensive *o*-chlorobenzaldehyde was also a suitable substrate and, in this case, **3b** could be isolated in 23% yield. The 3CR also tolerated various reaction partners. The use of acrylonitrile as the Michael acceptor, mesylamide as the nitrogenated partner and 3-fluoro *o*-bromobenzaldehyde as the aldehyde yielded **3e**, **3g** and **3i** in 29%, 19% and 20%, respectively.

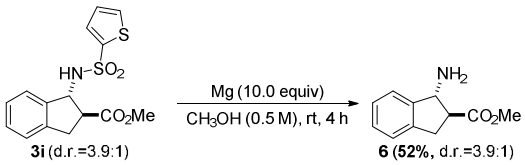
Table 4. Scope of the three-component synthesis of indanamines.[a]



[a] Yields of isolated products. Reaction conditions: **4** (1.0 mmol), **5** (1.0 equiv), **2** (2.0 equiv), $CoBr_2$ (10 mol%), 1,10-phen (10 mol%), Mn (4.0 equiv) activated with $BrCH_2CH_2Br$ (10 mol%) and TFA (10 mol%), CH_3CN (C=0.5 M), 80 °C, 16 h.

As illustrated above, the present annulation reaction led to the substitution of the nitrogen atom by an electron-withdrawing group. This requirement could be advantageously used to recover the free amine derivative **6**. Indeed, by using an excess of magnesium in methanol following Carretero's protocol,[33] the cleavage of the 2-thiophenesulfonyl group of **3i** had been achieved under mild conditions in an unoptimized 52% yield (Scheme 4).[34]

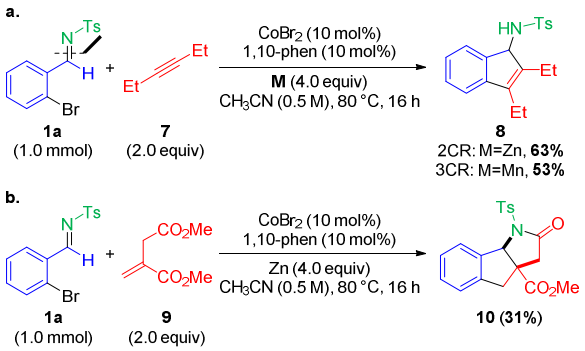
Scheme 4. Removal of the 2-thiophenesulfonyl group.



To further demonstrate the usefulness of these conditions for Co-catalyzed annulation reactions, the procedure was extended to the preparation of other scaffolds. First, the reaction performed using bromoimine **1a** and 3-hexyne **7** afforded the expected indenamine **8** in a fair 64% isolated yield (Scheme 5a). Importantly, the three-component version of this reaction using *o*-bromobenzaldehyde **4a** and *p*-toluenesulfonamide **5a** instead of preformed imine **1a** worked well, affording **8** in 53% with Mn as the reductant. The present method is complementary to those of Cheng as it allowed the use of an imine substituted by an electron-

withdrawing group. On the other hand, the present conditions were also suitable for the synthesis of strigolactam precursors. Indeed, by switching the acrylate for dimethyl itaconate **9**,[35] a domino reaction involving a final intramolecular lactamization took place and led to the expected tricyclic product **10** in 31% yield with an exclusive *cis* ring junction (Scheme 5b).

Scheme 5. Syntheses of an indenamine (a) and a strigolactam precursor (b).



In conclusion, we have developed a general and efficient Co-based catalytic system for the [3+2] annulation of *o*-haloaryl imines with alkenes or alkynes. These conditions were built on the use of cheap and broadly available cobalt complexes and allowed the straightforward preparation of indanamines through two- or three-component reactions. These conditions could additionally be applied to the synthesis of indenamines and strigolactams precursors.

Experimental Section

General considerations: All commercially available reagents were used as received. In particular, cobalt bromide and zinc dust (<10 µm) were purchased from Sigma-Aldrich and manganese powder from Acros. Imines **1** were prepared by condensation of the required aldehyde and amine catalyzed by Dowex 50WX4 hydrogen form in refluxing toluene using a Dean-Stark apparatus. Acetonitrile was distilled over calcium hydride prior to use. Unless other precision, reactions were performed under an argon atmosphere in 10 mL microwave tubes sealed with a Teflon-coated stopper under magnetic stirring. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude mixture. Analytical thin-layer chromatography

(TLC) was performed on TLC silica gel plates (0.25 mm) precoated with a fluorescent indicator. Flash chromatography (FC) was performed on 40–63 μm silica gel with mixtures of ethyl acetate (EtOAc) and petroleum ether (PE). Visualization was effected with ultraviolet light and ethanolic $KMnO_4$. Melting points (mp) are uncorrected and were measured on a Büchi B-545 apparatus. Infrared spectra were recorded on a FT-IR spectrometer in ATR mode. Only IR band frequencies of major functional groups are reported in cm^{-1}. NMR spectra were recorded on a Bruker Avance II 400 MHz spectrometer. ^{1}H NMR chemical shifts were referenced to the residual solvent signal; ^{13}C NMR chemical shifts were referenced to the deuterated solvent signal. Multiplicity was defined by DEPT 135 analysis. ^{19}F NMR chemical shifts were referenced to external $CFCl_3$ (0.0 ppm). Data are presented as follows: chemical shift δ (ppm), multiplicity (*s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet, *br* = broad), coupling constant *J* (Hz), integration. High-Resolution Mass Spectra were obtained at the ICOA of the Université of Orléans by electrospray ionization using a Q-TOF analyzer.

General procedure A (2CR): In air, an oven-dried 10 mL reaction tube equipped with a stir bar was charged with Zn (262 mg, 4.0 mmol, 4.0 equiv), closed with a septum and flushed with Ar. CH_3CN (2 mL, C=0.5 M) and $BrCH_2CH_2Br$ (9 μL, 0.1 mmol, 10 mol%) were added and the mixture was heated to reflux using a heat gun and then cooled down to room temperature. TMSCl (13 μL, 0.1 mmol, 10 mol%) or TFA (8 μL, 0.1 mmol, 10 mol%) was added and the mixture was heated to reflux with a heat gun and then cooled down to room temperature. $CoBr_2$ (22 mg, 0.1 mmol, 10 mol%) and 1,10-phenanthroline (18 mg, 0.1 mmol, 10 mol%) were added and the mixture was stirred at room temperature for 2 min. Acrylate **2** (2.0 mmol, 2.0 equiv) and halogenated imine **1** (1.0 mmol, 1.0 equiv) were successively added and the tube was sealed. The reaction was stirred at 80 °C (external temperature) for 16 h. Then, the reaction mixture was poured into sat aq NH_4Cl (50 mL) and the solution was extracted with EtOAc (2x25 mL). The combined organic layers were washed with brine (50

mL), dried (Na_2SO_4) and evaporated. The crude material by FC to afford the desired product **3**.

General procedure B (3CR): In air, an oven-dried 10 mL reaction tube equipped with a stir bar was charged with Mn (220 mg, 4.0 mmol, 4.0 equiv), closed with a septum and flushed with Ar. CH_3CN (2 mL, C=0.5 M) and $BrCH_2CH_2Br$ (9 μL, 0.1 mmol, 10 mol%) were added and the mixture was heated to reflux using a heat gun and then cooled down to room temperature. TFA (8 μL, 0.1 mmol, 10 mol%) was added and the mixture was heated to reflux with a heat gun and then cooled down to room temperature. $CoBr_2$ (22 mg, 0.1 mmol, 10 mol%) and 1,10-phenanthroline (18 mg, 0.1 mmol, 10 mol%) were added and the mixture was stirred at room temperature for 2 min. Acrylate **2** (2.0 mmol, 2.0 equiv), sulphonamide **5** (1.0 mmol, 1.0 equiv) and halogenated aldehyde **4** (1.0 mmol, 1.0 equiv) were successively added and the tube was sealed. The reaction was stirred at 80 °C (external temperature) for 16 h. Then, the reaction mixture was poured into sat aq NH_4Cl (50 mL) and the solution was extracted with EtOAc (2x25 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and evaporated. The crude material by FC to afford the desired product **3**.

Compound 3a: Following the general procedure A, the reaction performed with bromoimine **1a** (338 mg, 1.0 mmol) and methyl acrylate **2a** (180 μL, 2.0 mmol) with TFA (8 μL, 0.1 mmol, 10 mol%) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE:2/8 then 4/6], **3a** (293 mg, d.r.=3.6:1, 82%) as a white solid. Following the general procedure B, the reaction performed with 2-bromobenzaldehyde **4a** (117 μL, 1.0 mmol), *p*-toluenesulfonamide **5a** (171 mg, 1.0 mmol) and methyl acrylate **2a** (180 μL, 2.0 mmol) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE:2/8 then 4/6], **3a** (141 mg, d.r.=3.6:1, 40%) as a white solid. **mp:** 126–130 °C. **R_f (PE/EtOAc:8/2, UV+$KMnO_4$):** 0.21. **IR (neat)** ν: 1702, 1327, 1154. **HRMS (ESI/Q-TOF)** m/z: $[M+H]^+$

Calcd for $C_{18}H_{20}NO_4S$ 346.1107; Found 346.1106. **^{1}H NMR ($CDCl_3$, 400 MHz):** (2 diastereoisomers) δ 7.82–7.77 (m, 4H), 7.31–7.29 (m, 4H), 7.21–7.07 (m, 7H), 6.97 (d, *J*=7.4 Hz, 1H), 5.62 (d, *J*=10.0 Hz, 1H), 5.27 (d, *J*=8.7 Hz, 1H), 5.15–5.11 (m, 1H), 5.11–5.06 (m, 1H), 3.56 (s, 3H), 3.52 (s, 3H), 3.35 (td, *J*=7.3, 4.2 Hz, 1H), 3.23–3.00 (m, 5H), 2.44 (s, 3H), 2.43 (s, 3H). **^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):** (2 diastereoisomers) δ 173.9 (C), 173.3 (C), 143.5 (C), 143.5 (C), 140.7 (C), 140.6 (C), 140.2 (C), 139.9 (C), 138.5 (C), 137.9 (C), 129.8 (2 CH), 129.7 (2 CH), 128.8 (CH), 128.7 (CH), 127.5 (2 CH), 127.4 (3 CH), 127.2 (CH), 124.7 (CH), 124.6 (CH), 124.3 (CH), 124.2 (CH), 61.8 (CH), 59.4 (CH), 52.7 (CH), 52.0 (CH_3), 51.9 (CH_3), 48.0 (CH), 34.6 (CH_2), 34.2 (CH_2), 21.6 (2 CH_3).

Compound 3b: Following the general procedure A, the reaction performed with bromoimine **1a** (338 mg, 1.0 mmol) and ethyl acrylate **2b** (220 µL, 2.0 mmol) with TMSCl (13 µL, 0.1 mmol, 10 mol%) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE:2/8 then 3/7], **3b** (227 mg, d.r.=3.3:1, 63%) as a white solid. Following the general procedure B, the reaction performed with 2-bromobenzaldehyde **4a** (117 µL, 1.0 mmol), *p*-toluenesulfonamide **5a** (171 mg, 1.0 mmol) and ethyl acrylate **2b** (220 µL, 2.0 mmol) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE:2/8 then 3/7], **3a** (113 mg, d.r.=3.3:1, 31%) as a white solid. Following the general procedure B, the reaction performed with 2-chlorobenzaldehyde **4b** (113 µL, 1.0 mmol), *p*-toluenesulfonamide **5a** (171 mg, 1.0 mmol) and ethyl acrylate **2b** (220 µL, 2.0 mmol) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE:2/8 then 3/7], **3a** (74 mg, d.r.=3.3:1, 20%) as a white solid. **mp:** 109–111 °C. **R_f (PE/EtOAc:8/2, UV+$KMnO_4$):** 0.16 & 0.22. **IR (neat)** ν: 1704, 1334, 1184. **HRMS (ESI/Q-TOF)** m/z: $[M+H]^+$ Calcd for $C_{19}H_{22}NO_4S$ 360.1264; Found 360.1265. **^{1}H NMR ($CDCl_3$, 400 MHz):** (2 diastereomers) δ 7.82 (d, *J*=8.3, 2H), 7.79 (d, *J*=8.3 Hz, 2H), 7.31 (d, *J*=8.3 Hz, 4H), 7.22-7.10 (m, 4H), 7.06 (d, *J*=7.5 Hz, 2H), 6.96 (d, *J*=7.5 Hz, 2H), 5.71 (d, *J*=10.0 Hz, 1H), 5.23 (d, *J*=8.7 Hz, 1H), 5.19 (dd, *J*=8.7, 7.1 Hz, 1H),

5.08 (dd, *J*=10.0, 7.5 Hz, 1H), 4.09-4.01 (m, 4H), 3.36-3.31 (m, 1H), 3.28-3.21 (m, 1H), 3.18-3.16 (m, 1H), 3.14-3.09 (m, 2H), 3.07-3.03 (m, 1H), 2.47 (s, 3H), 2.46 (s, 3H), 1.24 (t, *J*=7.1 Hz, 3H), 1.21 (t, *J*=7.1 Hz, 3H). **^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):** (2 diastereomers) δ 173.5 (C), 173.0 (C), 143.6 (C), 143.5 (C), 140.9 (C), 140.6 (C), 140.3 (C), 139.7 (C), 138.5 (C), 137.8 (C), 129.8 (2 CH), 129.8 (2 CH), 128.8 (CH), 128.6 (CH), 127.5 (CH), 127.4 (3 CH), 127.2 (2 CH), 124.7 (CH), 124.6 (CH), 124.3 (CH), 124.1 (CH), 61.8 (CH), 61.1 (2 CH_2), 59.4 (CH), 52.9 (CH), 47.9 (CH), 34.7 (CH_2), 34.5 (CH_2), 21.6 (2 CH_3), 14.2 (CH_3), 14.1 (CH_3).

Compound 3c: Following the general procedure A, the reaction performed with bromoimine **1a** (338 mg, 1.0 mmol) and *n*-butyl acrylate **2c** (287 μL, 2.0 mmol) with TMSCl (13 μL, 0.1 mmol, 10 mol%) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE:1/9 then 2/8], **3c** (263 mg, d.r.=2.7:1, 68%) as a white solid. Following the general procedure B, the reaction performed with 2-bromobenzaldehyde **4a** (117 μL, 1.0 mmol), *p*-toluenesulfonamide **5a** (171 mg, 1.0 mmol) and *n*-butyl acrylate **2c** (287 μL, 2.0 mmol) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE:1/9 then 2/8], **3c** (116 mg, d.r.=2.7:1, 30%) as a white solid. **mp:** 62–67 °C. **R_f (PE/EtOAc:8/2, UV+$KMnO_4$):** 0.15 & 0.21. **IR (neat)** ν: 1703, 1358, 1111. **HRMS (ESI/Q-TOF)** m/z: $[M+H]^+$ Calcd for $C_{21}H_{26}NO_4S$ 388.1577; Found 388.1575. **^{1}H NMR ($CDCl_3$, 400 MHz):** (2 diastereomers) δ 7.82 (d, *J*=8.3 Hz, 2H), 7.79 (d, *J*=8.3 Hz, 2H), 7.31 (d, *J*=8.3 Hz, 4H), 7.23–7.12 (m, 6H), 7.07-7.01 (m, 2H), 5.74 (d, *J*=10.1 Hz, 1H), 5.19–5.15 (m, 1H), 5.11–5.05 (m, 2H), 3.99-3.94 (m, 2H), 3.88–3.82 (m, 2H), 3.31–3.21 (m, 2H), 3.14–3.01 (m, 4H), 2.44 (s, 6H), 1.60–1.49 (m, 4H), 1.38–1.29 (m, 4H), 0.93 (t, *J*=7.4 Hz, 3H), 0.91 (t, *J*=7.4 Hz, 3H). **^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):** (2 diastereomers) δ 173.5 (C), 173.2 (C), 143.5 (C), 143.5 (C), 141.0 (C), 140.6 (C), 140.4 (C), 139.6 (C), 138.5 (C), 137.8 (C), 129.8 (2 CH), 129.8 (2 CH), 128.9 (CH), 128.6 (CH), 127.6 (CH), 127.4 (3 CH), 127.2 (2 CH), 124.7 (2

CH), 124.3 (CH), 124.1 (CH), 65.0 (CH_2), 65.0 (CH_2), 61.8 (CH), 59.4 (CH), 52.9 (CH), 48.0 (CH), 34.8 (CH_2), 34.6 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 21.6 (2 CH_3), 19.2 (CH_2), 19.1 (CH_2), 13.8 (CH_3), 13.8 (CH_3).

Compound 3d: Following the general procedure A, the reaction performed with bromoimine **1a** (338 mg, 1.0 mmol) and *N,N*-dimethylacrylamide **2d** (206 µL, 2.0 mmol) with TMSCl (13 µL, 0.1 mmol, 10 mol%) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE:5/5 then 8/2], **3d** (82 mg, d.r.>25:1, 23%) as a white solid. **mp:** 166–170 °C. **R_f (PE/EtOAc:5/5, UV+$KMnO_4$):** 0.21. **IR (neat)** ν: 1628, 1301, 1150. **HRMS (ESI/Q-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{19}H_{22}N_2NaO_3S$ 381.1243; Found 381.1242. **^{1}H NMR ($CDCl_3$, 400 MHz):** (1 diastereomer) δ 7.78 (d, *J*=8.0 Hz, 2H), 7.31 (d, *J*=8.0 Hz, 2H), 7.17–7.09 (m, 4H), 6.49 (d, *J*=9.8 Hz, 1H), 5.04 (dd, *J*=9.8, 7.4 Hz, 1H), 3.45 (td, *J*=7.4, 6.0 Hz, 1H), 3.06 (d, *J*=6.0 Hz, 2H), 2.76 (s, 3H), 2.75 (s, 3H), 2.43 (s, 3H). **^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):** (1 diastereomer) δ 172.4 (C), 143.2 (C), 141.8 (C), 140.0 (C), 138.8 (C), 129.6 (2 CH), 128.2 (CH), 127.2 (CH), 127.2 (2 CH), 124.5 (CH), 123.9 (CH), 59.4 (CH), 43.9 (CH), 37.2 (CH_3), 35.4 (CH_3), 35.1 (CH_2), 21.5 (CH_3).

Compound 3e: Following the general procedure A, the reaction performed with bromoimine **1a** (338 mg, 1.0 mmol) and acrylonitrile **2e** (133 µL, 2.0 mmol) with TMSCl (13 µL, 0.1 mmol, 10 mol%) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE: 2/8], **3e** (200 mg, d.r.=2.1:1, 64%) as a white solid. Following the general procedure B, the reaction performed with 2-bromobenzaldehyde **4a** (117 µL, 1.0 mmol), *p*-toluenesulfonamide **5a** (171 mg, 1.0 mmol) and acrylonitrile **2e** (133 µL, 2.0 mmol) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE: 2/8], **3e** (92 mg, d.r.=2.1:1, 29%) as a white solid. **mp:** 191–194 °C. **R_f (PE/EtOAc:8/2, UV+$KMnO_4$):** 0.13 & 0.19. **IR (neat)** ν: 2242, 1326, 1092. **HRMS (ESI/Q-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{17}H_{16}N_2NaO_2S$ 335.0824; Found 335.0824. **^{1}H NMR ($CDCl_3$, 400 MHz):** (2 diastereomers)

δ 7.88–7.85 (m, 4H), 7.38–7.36 (m, 4H), 7.30–7.19 (m, 6H), 7.10–7.06 (m, 2H), 5.65 (d, *J*=10.0 Hz, 1H), 5.62 (d, *J*=8.4 Hz, 1H), 5.11 (dd, *J*=10.0, 7.0 Hz, 1H), 5.03 (dd, *J*=8.4, 7.2 Hz, 1H), 3.46 (td, *J*=7.2, 2.9 Hz, 1H), 3.42–3.35 (m, 1H), 3.24 (dd, *J*=16.1, 2.9 Hz, 1H), 3.19–3.09 (m, 3H), 2.48 (s, 6H). **$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz):** (2 diastereomers) δ 144.2 (2 C), 139.0 (C), 138.8 (C), 138.4 (2 C), 137.5 (C), 137.1 (C), 130.1 (2 CH), 130.1 (2 CH), 129.5 (CH), 129.4 (CH), 128.1 (2 CH), 127.4 (2 CH), 127.3 (2 CH), 125.2 (CH), 124.9 (CH), 124.5 (CH), 124.3 (CH), 120.4 (C), 119.5 (C), 62.4 (CH), 59.2 (CH), 37.4 (CH), 36.5 (CH), 35.0 (CH_2), 34.7 (CH_2), 21.7 (2 CH_3).

Compound 3f: Following the general procedure A, the reaction performed with bromoimine **1a** (338 mg, 1.0 mmol) and phenyl vinyl sulfone **2f** (336 mg, 2.0 mmol) with TMSCl (13 μL, 0.1 mmol, 10 mol%) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE: 3/7 then 5/5], **3f** (265 mg, d.r.=1.5:1, 62%) as a yellow solid. **mp:** 100–103 °C. **R_f (PE/EtOAc:5/5, UV+$KMnO_4$):** 0.51 & 0.6. **IR (neat)** ν: 1304, 1289, 1145, 1119. **HRMS (ESI/Q-TOF)** m/z: $[M+H]^+$ Calcd for $C_{22}H_{22}NO_4S_2$ 428.0984; Found 428.0983. **^1H NMR ($CDCl_3$, 400 MHz):** (2 diastereomers) δ 7.79–7.71 (m, 7H), 7.64–7.57 (m, 3H), 7.50–7.45 (m, 3H), 7.29–7.19 (m, 6H), 7.16–7.10 (m, 2H), 7.05–7.00 (m, 3H), 6.89 (d, *J*=7.6 Hz, 2H), 6.27 (d, *J*=9.1 Hz, 1H), 5.76 (d, *J*=7.4 Hz, 1H), 5.23 (dd, *J*=7.4, 3.5 Hz, 1H), 5.18–5.16 (m, 1H), 4.06–3.97 (m, 2H), 3.48 (dd, *J*=17.0, 4.6 Hz, 1H), 3.28–3.26 (m, 2H), 3.07 (dd, *J*=17.0, 7.8 Hz, 1H), 2.43 (s, 3H), 2.41 (s, 3H). **$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz):** (2 diastereomers) δ 143.5 (C), 143.1 (C), 139.7 (C), 139.7 (C), 139.3 (C), 139.1 (C), 138.5 (C), 138.0 (C), 137.6 (C), 137.3 (C), 133.9 (CH), 133.8 (CH), 129.7 (CH), 129.6 (2 CH), 129.5 (2 CH), 129.2 (2 CH), 129.1 (CH), 129.1 (CH), 128.7 (2 CH), 128.4 (2 CH), 127.5 (CH), 127.5 (CH), 127.2 (2 CH), 127.1 (CH), 126.2 (2 CH), 124.9 (CH), 124.4 (CH), 124.4 (CH), 123.9 (CH), 69.0 (CH), 65.7 (CH), 59.0 (CH), 58.4 (CH), 31.8 (CH_2), 30.8 (CH_2), 21.5 (CH_3), 21.5 (CH_3).

Compound 3g: Following the general procedure A, the reaction performed with chloroimine **1b** (218 mg, 1.0 mmol) and methyl acrylate **2a** (180 μL, 2.0 mmol) with TFA (8 μL, 0.1 mmol, 10 mol%) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE: 2/8 then 4/6], **3g** (144 mg, d.r.=2.5:1, 53%) as a white solid. **mp:** 106–107 °C. **R_f (PE/EtOAc:6/4, UV+$KMnO_4$):** 0.47. **IR (neat)** ν: 1727, 1305, 1141. **HRMS (ESI/Q-TOF)** m/z: $[M+H]^+$ Calcd for $C_{12}H_{16}NO_4S$ 270.0794; Found 270.0793. **^{1}H NMR ($CDCl_3$, 400 MHz):** (2 diastereoisomers) δ 7.45–7.42 (m, 2H), 7.28–7.25 (m, 4H), 7.20–7.18 (m, 2H), 5.33–5.25 (m, 2H), 5.21 (dd, *J*=9.5, 7.6 Hz, 1H), 5.02 (d, *J*=9.4 Hz, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.60 (dd, *J* = 13.8, 7.8 Hz, 1H), 3.35–3.26 (m, 2H), 3.22–3.13 (m, 3H), 3.09 (s, 3H), 3.00 (s, 3H). **^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):** (2 diastereoisomers) δ 174.0 (C), 173.2 (C), 140.8 (C), 140.7 (C), 140.4 (C), 139.8 (C), 129.0 (CH), 128.9 (CH), 127.7 (CH), 127.6 (CH), 125.0 (CH), 124.7 (CH), 124.6 (CH), 124.5 (CH), 61.6 (CH), 59.6 (CH), 52.7 (CH_3), 52.4 (CH_3), 52.2 (CH), 48.6 (CH), 42.2 (CH_3), 41.8 (CH_3), 34.1 (CH_2), 33.8 (CH_2).

Compound 3h: Following the general procedure A, the reaction performed with bromoimine **1c** (262 mg, 1.0 mmol) and ethyl acrylate **2b** (220 μL, 2.0 mmol) with TFA (8 μL, 0.1 mmol, 10 mol%) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE: 2/8 then 4/6], **3h** (213 mg, d.r.=2.9:1, 75%) as a white solid. Following the general procedure B, the reaction performed with 2-bromobenzaldehyde **4a** (117 μL, 1.0 mmol), methanesulfonamide **5b** (95 mg, 1.0 mmol) and ethyl acrylate **2b** (220 μL, 2.0 mmol) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE: 2/8 then 4/6], **3h** (54 mg, d.r.=2.9:1, 19%) as a white solid. **mp:** 85–90 °C. **R_f (PE/EtOAc:8/2, UV+$KMnO_4$):** 0.17. **IR (neat)** ν: 1732, 1307, 1145. **HRMS (ESI/Q-TOF)** m/z: $[M+H]^+$ Calcd for $C_{13}H_{18}NO_4S$ 284.0951; Found 284.0952. **^{1}H NMR ($CDCl_3$, 400 MHz):** (2 diastereoisomers) δ 7.39–7.36 (m, 2H), 7.22–7.19 (m, 4H), 7.13–7.11 (m, 2H), 5.46 (d, *J*=9.8 Hz, 1H), 5.31 (d, *J*=9.2 Hz, 1H), 5.19 (t, *J*=8.5 Hz, 1H), 5.15–5.11 (m, 1H), 4.18 (qd, *J*=7.1,

2.0 Hz, 2H), 4.14–4.03 (m, 2H), 3.53–3.47 (m, 1H), 3.29–3.19 (m, 2H), 3.15–3.09 (m, 2H), 3.07–3.02 (m, 1H), 3.00 (s, 3H), 2.92 (s, 3H), 1.27 (t, *J*=7.1 Hz, 3H), 1.23 (t, *J*=7.1 Hz; 3H). **$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz):** (2 diastereoisomers) δ 173.5 (C), 172.7 (C), 141.0 (C), 140.8 (C), 140.4 (C), 139.7 (C), 128.8 (CH), 128.6 (CH), 127.4 (CH), 127.4 (CH), 124.8 (CH), 124.5 (CH), 124.4 (CH), 124.4 (CH), 61.4 (CH), 61.2 (CH_2), 61.1 (CH_2), 59.5 (CH), 52.6 (CH), 48.6 (CH), 42.0 (CH_3), 41.6 (CH_3), 34.0 (CH_2), 33.7 (CH_2), 14.2 (CH_3), 14.1 (CH_3).

Compound 3i: Following the general procedure A, the reaction performed with bromoimine **1d** (388 mg, 1.0 mmol) and methyl acrylate **2a** (180 µL, 2.0 mmol) with TFA (8 µL, 0.1 mmol, 10 mol%) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE: 2/8 then 4/6], **3i** (315 mg, d.r.=3.9:1, 93%) as a white solid. Following the general procedure A, the reaction performed with chloroimine **1e** (286 mg, 1.0 mmol) and methyl acrylate **2a** (180 µL, 2.0 mmol) with TFA (8 µL, 0.1 mmol, 10 mol%) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE: 2/8 then 4/6], **3i** (236 mg, d.r.=3.9:1, 70%) as a white solid. **mp:** 110–112 °C. **R_f (PE/EtOAc:8/2, UV+$KMnO_4$):** 0.16. **IR (neat)** ν: 1739, 1339, 1152. **HRMS (ESI/Q-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{15}H_{15}NNaO_4S_2$ 360.0334; Found 360.0334. **^{1}H NMR ($CDCl_3$, 400 MHz):** (2 diastereoisomers) δ 7.64 (dd, *J*=3.7, 1.2 Hz, 1H), 7.62–7.58 (m, 3H), 7.20–7.15 (m, 2H), 7.13–7.09 (m, 4H), 7.08–7.04 (m, 3H), 6.90 (d, *J*=7.5 Hz, 1H), 5.83 (d, *J*=9.8 Hz, 1H), 5.64 (d, *J*=8.5 Hz, 1H), 5.19 (dd, *J*=7.7, 7.7 Hz, 1H), 5.15–5.11 (m, 1H), 3.58 (s, 3H), 3.56 (s, 3H), 3.41 (td, *J*=8.0, 4.9 Hz, 1H), 3.24–3.20 (m, 1H), 3.18–3.07 (m, 3H), 3.02 (dd, *J*=14.4, 7.3 Hz, 1H). **$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz):** (2 diastereoisomers) δ 173.9 (C), 173.2 (C), 142.2 (C), 141.6 (C), 140.2 (C), 140.2 (C), 140.1 (C), 140.0 (C), 132.6 (2 CH), 132.1 (CH), 132.0 (CH), 128.8 (CH), 128.7 (CH), 127.6 (CH), 127.4 (2 CH), 127.4 (CH), 124.7 (CH), 124.6

(CH), 124.2 (CH), 124.0 (CH), 61.9 (CH), 59.6 (CH), 52.3 (CH), 52.1 (CH_3), 52.1 (CH_3), 47.8 (CH), 34.5 (CH_2), 34.1 (CH_2).

Compound 3j: Following the general procedure A, the reaction performed with chloroimine **1e** (286 mg, 1.0 mmol) and ethyl acrylate **2b** (220 µL, 2.0 mmol) with TFA (8 µL, 0.1 mmol, 10 mol%) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE: 2/8 then 4/6], **3j** (133 mg, d.r.=2.7:1, 38%) as a white paste. **R_f (PE/EtOAc:6/4, UV+$KMnO_4$):** 0.46 & 0.61. **IR (neat)** ν: 1732, 1339, 1152. **HRMS (ESI/Q-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{16}H_{17}NNaO_4S_2$ 374.0491; Found 374.0489. **^{1}H NMR ($CDCl_3$, 400 MHz):** (2 diastereoisomers) δ 7.66 (d, *J* = 3.7, 1.3 Hz, 1H), 7.64–7.59 (m, 3H), 7.22–7.18 (m, 2H), 7.16–7.12 (m, 4H), 7.09–7.07 (m, 2H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 7.4 Hz, 1H), 5.88 (d, *J* = 9.9 Hz, 1H), 5.52 (d, *J* = 8.5 Hz, 1H), 5.23 (dd, *J* = 7.7, 7.7 Hz, 1H), 5.14 (dd, *J* = 9.5, 7.9 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 4.01 (q, *J* = 7.2 Hz, 2H), 3.39 (td, *J* = 7.9, 4.6 Hz, 1H), 3.24 (dd, *J* = 14.9, 8.4 Hz, 1H), 3.18–3.09 (m, 3H), 3.04 (dd, *J* = 15.2, 7.8 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):** (2 diastereoisomers) δ 173.4 (C), 173.0 (C), 142.4 (C), 141.7 (C), 140.4 (C), 140.3 (C), 140.3 (C), 139.9 (C), 132.7 (CH), 132.1 (2 CH), 132.0 (CH), 128.8 (CH), 128.7 (CH), 127.6 (CH), 127.5 (CH), 127.5 (CH), 127.4 (CH), 124.7 (CH), 124.7 (CH), 124.2 (CH), 124.0 (CH), 61.9 (CH), 61.2 (CH_2), 61.2 (CH_2), 59.6 (CH), 52.7 (CH), 47.9 (CH), 34.7 (CH_2), 34.3 (CH_2), 14.2 (CH_3), 14.1 (CH_3).

Compound 3k: Following the general procedure A, the reaction performed with chloroimine **1e** (286 mg, 1.0 mmol) and acrylonitrile **2e** (133 µL, 2.0 mmol) with TFA (8 µL, 0.1 mmol, 10 mol%) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE: 2/8 then 3/7], **3k** (95 mg, d.r.=1.3:1, 30%) as a white solid. **mp:** 162–167 °C. **R_f (PE/EtOAc:7/3, UV+$KMnO_4$):** 0.44.& 0.41. **IR (neat)** ν: 2246, 1338, 1156. **HRMS (ESI/Q-TOF)** m/z: $[M+H]^+$ Calcd for $C_{14}H_{13}N_2O_2S_2$ 305.0412; Found 305.0414. **^{1}H NMR ($(CD_3)_2CO$, 400**

MHz): (2 diastereoisomers) δ 7.94–7.93 (m, 2H), 7.80–7.77 (m, 3H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.29–7.17 (m, 8H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 7.0 Hz, 1H), 5.26–5.20 (m, 2H), 3.86–3.82 (m, 1H), 3.46 (dd, *J* = 14.9, 8.2 Hz, 1H), 3.37–3.25 (m, *J* = 3H), 3.16 (dd, *J* = 14.9, 8.0 Hz, 1H). **^{13}C{^{1}H} NMR ($(CD_3)_2CO$, 100 MHz):** (2 diastereoisomers) δ 143.7 (C), 143.4 (C), 140.5 (2 C), 140.1 (C), 139.9 (C), 133.4 (CH), 133.2 (CH), 133.1 (CH), 132.9 (CH), 129.7 (2 CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 125.7 (CH), 125.5 (CH), 125.0 (CH), 124.9 (CH), 120.8 (C), 120.2 (C), 63.2 (CH), 60.2 (CH), 37.8 (CH), 37.1 (CH), 35.5 (CH_2), 35.3 (CH_2).

Compound 3l: Following the general procedure A, the reaction performed with chloroimine **1f** (286 mg, 1.0 mmol) and methyl acrylate **2a** (180 μL, 2.0 mmol) with TFA (8 μL, 0.1 mmol, 10 mol%) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE: 3/7 then 4/6], **3l** (111 mg, d.r.=2.5:1, 30%) as a white solid. **mp:** 108–110 °C. **R_f (PE/EtOAc:6/4, UV+$KMnO_4$):** 0.36. **IR (neat)** ν: 1736, 1320, 1114. **HRMS (ESI/Q-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{13}H_{14}F_3NNaO_4S$ 360.0487; Found 360.0488. **^{1}H NMR ($CDCl_3$, 400 MHz):** (2 diastereoisomers) δ 7.68–7.65 (m, 2H), 7.53–7.51 (m, 2H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 5.52 (d, *J* = 10.0 Hz, 1H), 5.31–5.21 (m, 3H), 3.78 (s, 3H), 3.71 (s, 3H), 3.64 (dd, *J* = 12.7, 8.0 Hz, 1H), 3.35–3.29 (m, 2H), 3.26–3.20 (m, 2H), 3.16–3.12 (m, 1H), 3.09 (s, 3H), 3.02 (s, 3H). **^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):** (2 diastereoisomers) δ 173.4 (C), 172.9 (C), 144.3 (C), 143.8 (C), 141.9 (C), 141.8 (C), 130.4 (q, *J* = 32.3 Hz, C), 130.3 (q, *J* = 32.5 Hz, C), 126.1 (q, *J* = 3.9 Hz, CH), 126.0 (q, *J* = 3.8 Hz, CH), 125.4 (CH), 125.2 (CH), 124.2 (q, *J* = 272.3 Hz, 2C), 121.7 (q, *J* = 3.7 Hz, CH), 121.5 (q, *J* = 3.8 Hz, CH), 61.2 (CH), 59.2 (CH), 52.7 (CH_3), 52.6 (CH_3), 52.4 (CH), 48.7 (CH), 42.3 (CH_3), 41.8 (CH_3), 34.0 (CH_2), 33.9 (CH_2). **^{19}F NMR ($CDCl_3$, 377 MHz):** -62.0 (s, 3F), -62.0 (s, 3F).

Compound 3m: Following the general procedure A, the reaction performed with bromoimine **1g** (356 mg, 1.0 mmol) and ethyl acrylate **2b** (220 μL, 2.0 mmol) with TMSCl (13 μL, 0.1

mmol, 10 molafforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE: 2/8 then 3/7], **3m** (294 mg, d.r.=2.6:1, 77%) as a yellow solid. Following the general procedure B, the reaction performed with 2-bromo,5-fluorobenzaldehyde **4c** (203 mg, 1.0 mmol), *p*-toluenesulfonamide **5a** (171 mg, 1.0 mmol) and ethyl acrylate **2b** (220 μL, 2.0 mmol) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE: 2/8 then 3/7], **3m** (78 mg, d.r.=2.6:1, 20%) as a yellow solid. **mp:** 106–109 °C. **R_f (PE/EtOAc:8/2, UV+$KMnO_4$):** 0.12 & 0.2. **IR (neat)** ν: 1707, 1330, 1193. **HRMS (ESI/Q-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{19}H_{20}FNNaO_4S$ 400.0989; Found 400.0990. **^{1}H NMR ($CDCl_3$, 400 MHz):** (2 diastereomers) δ 7.79–7.75 (m, 4H), 7.33–7.29 (m, 4H), 7.08–7.03 (m, 2H), 6.88–6.83 (m, 2H), 6.76 (dd, *J*=8.6, 1.6 Hz, 1H), 6.56 (dd, *J*=8.6, 1.6 Hz, 1H), 5.97 (d, *J*=10.0 Hz, 1H), 5.80 (d, *J*=9.0 Hz, 1H), 5.11 (dd, *J*=9.0, 7.7 Hz, 1H), 5.04 (dd, *J*=10.0, 7.7 Hz, 1H), 4.01–3.90 (m, 4H), 3.34–3.29 (m, 1H), 3.19–3.08 (m, 3H), 3.04–2.96 (m, 2H), 2.45 (s, 3H), 2.43 (s, 3H), 1.18 (t, *J*=7.1 Hz, 3H), 1.17 (t, *J*=7.1 Hz, 3H). **^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):** (2 diastereomers) δ 173.1 (C), 172.8 (C), 162.4 (d, *J*=244.8 Hz, C), 162.3 (d, *J*=244.9 Hz, C), 143.7 (C), 143.6 (C), 143.0 (d, *J*=7.9 Hz, C), 142.9 (d, *J*=7.9 Hz, C), 138.2 (C), 137.8 (C), 135.4 (d, *J*=2.5 Hz, C), 135.1 (d, *J*=2.5 Hz, C), 129.9 (2 CH), 129.7 (2 CH), 127.2 (2 CH), 127.0 (2 CH), 125.7 (d, *J*=8.7 Hz, CH), 125.6 (d, *J*=8.7 Hz, CH), 115.8 (d, *J*=22.7 Hz, CH), 115.5 (d, *J*=22.7 Hz, CH), 111.4 (d, *J*=23.1 Hz, CH), 111.1 (d, *J*=23.3 Hz, CH), 61.4 (d, *J*=1.9 Hz, CH), 61.1 (CH_2), 61.1 (CH_2), 59.1 (d, *J*=1.9 Hz, CH), 52.9 (CH), 48.4 (CH), 33.8 (CH_2), 33.5 (CH_2), 21.4 (2 CH_3), 14.0 (CH_3), 13.9 (CH_3). **^{19}F NMR ($CDCl_3$, 377 MHz):** -114.9 (s, 1F), -115.2 (s, 1F).

Compound 3n: Following the general procedure A, the reaction performed with bromoimine **1h** (388 mg, 1.0 mmol) and methyl acrylate **2a** (180 μL, 2.0 mmol) with TFA (8 μL, 0.1 mmol, 10 mol%) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE: 2/8 then 3/7], **3n** (203 mg, d.r.=3.2:1, 51%) as a white solid. **mp:** 173–176 °C. **R_f**

(PE/EtOAc:8/2, UV+KMnO$_4$): 0.20. **IR (neat)** ν: 1729, 1369, 1156. **HRMS (ESI/Q-TOF)** m/z: [M+Na]$^+$ Calcd for $C_{22}H_{21}NNaO_4S$ 418.1083; Found 418.1081. **^{1}H NMR (CDCl$_3$, 400 MHz):** (2 diastereomers) δ 7.84–7.79 (m, 6H), 7.72–7.63 (m, 4H), 7.52–7.44 (m, 4H), 7.33–7.30 (m, 4H), 7.18 (d, *J*=8.4 Hz, 1H), 7.07 (d, *J*=8.4 Hz, 1H), 5.55 (d, *J*=10.1 Hz, 1H), 5.35–5.32 (m, 1H), 5.32–5.27 (m, 1H), 5.17 (d, *J*=8.9 Hz, 1H), 3.60 (s, 3H), 3.54 (s, 3H), 3.39–3.34 (m, 1H), 3.31–3.27 (m, 2H), 3.25–3.19 (m, 3H), 2.46 (s, 3H), 2.44 (s, 3H). **^{13}C{^{1}H} NMR (CDCl$_3$, 100 MHz):** (2 diastereomers) δ 174.1 (C), 173.3 (C), 143.6 (C), 143.6 (C), 138.5 (C), 137.9 (C), 137.5 (C), 137.1 (C), 136.7 (C), 136.6 (C), 133.8 (C), 133.8 (C), 129.9 (2 CH), 129.8 (2 CH), 129.8 (2 C), 128.7 (CH), 128.6 (CH), 128.6 (CH), 128.5 (CH), 127.5 (2 CH), 127.2 (2 CH), 126.7 (CH), 126.7 (CH), 126.3 (CH), 126.3 (CH), 124.2 (CH), 124.2 (CH), 121.9 (CH), 121.9 (CH), 62.6 (CH), 60.4 (CH), 52.3 (CH), 52.2 (CH_3), 52.1 (CH_3), 47.6 (CH), 33.3 (CH_2), 32.8 (CH_2), 21.7 (2 CH_3).

Synthesis of the free indanamine 6: In air, a 25 mL RBF equipped with a stir bar was charged with **3i** (127 mg, 0.38 mmol), CH_3OH (8 mL, C = 0.05 M) and magnesium turnings (91 mg, 3.8 mmol, 10.0 equiv). The flask was closed with a septum and the reaction was stirred at room temperature for 4 h. Then, the reaction mixture was poured into sat aq NH_4Cl (50 mL) and the solution was extracted with EtOAc (2x25 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and evaporated. The crude material by flash chromatography [50 mL SiO_2, EtOAc/PE: 5/5 then 10/0] to afford the desired product **6** (38 mg, single *trans* diastereomer, 52%) as a brown solid. **mp:** 50–54 °C. **R$_f$ (EtOAc, UV+KMnO$_4$):** 0.17. **IR (neat)** ν: 3351, 1726. **HRMS (ESI/Q-TOF)** m/z: [M+Na]$^+$ Calcd for $C_{11}H_{13}NNaO_2$ 214.0838; Found 214.0839. **^{1}H NMR (CDCl$_3$, 400 MHz):** (major diastereomer) δ 7.27 (d, *J* = 6.3 Hz, 1H), 7.18–7.13 (m, 3H), 4.51 (d, *J* = 8.5 Hz, 1H), 3.71 (s, 3H), 3.08 (t, *J* = 8.4 Hz, 2H), 2.88–2.81 (m, 1H), 1.86 (br s, 2H). **^{13}C{^{1}H} NMR (CDCl$_3$, 100**

MHz): (major diastereomer) δ 174.7 (C), 144.8 (C), 140.2 (C), 127.8 (CH), 127.1 (CH), 124.5 (CH), 123.5 (CH), 60.8 (CH), 56.3 (CH), 52.1 (CH_3), 33.7 (CH_2).

Synthesis of indenamine 8: Following the general procedure A, the reaction performed with bromoimine **1a** (338 mg, 1.0 mmol) and 3-hexyne **7** (230 µL, 2.0 mmol) with TMSCl (13 µL, 0.1 mmol, 10 mol%) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE: 1/9 then 2/8], **7** (217 mg, 63%) as a yellow solid. Following the general procedure B, the reaction performed with 2-bromobenzaldehyde **4a** (117 mg, 1.0 mmol), *p*-toluenesulfonamide **5a** (171 mg, 1.0 mmol) and 3-hexyne **7** (230 µL, 2.0 mmol) afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE: 1/9 then 2/8], **8** (183 mg, 53%) as a yellow solid. **mp:** 133–140 °C. **R_f (PE/EtOAc:9/1, UV+KMnO$_4$):** 0.22. **IR (neat)** ν: 1324, 1163. **HRMS (ESI/Q-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{20}H_{23}NNaO_2S$ 364.1341; Found 364.1342. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.88 (d, *J*=8.2 Hz, 2H), 7.36 (dd, *J*=8.5, 0.6 Hz, 2H), 7.20 (td, *J*=7.5, 0.6 Hz, 1H), 7.12 (d, *J*=7.2 Hz, 1H), 6.97 (td, *J*=7.4, 1.1 Hz, 1H), 6.82 (dd, *J*=7.3, 0.6 Hz, 1H), 4.82 (d, *J*=9.7 Hz, 1H), 4.51 (d, *J*=9.7 Hz, 1H), 2.48 (s, 3H), 2.43 (q, *J*=7.5 Hz, 2H), 2.36-2.29 (m, 1H), 2.24-2.16 (m, 1H), 1.11 (t, *J*=7.6 Hz, 3H), 0.93 (t, *J*=7.5 Hz, 3H). **^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz):** δ 144.2 (C), 143.6 (C), 143.5 (C), 143.4 (C), 139.8 (C), 138.8 (C), 129.9 (2 CH), 128.3 (C), 127.4 (2 CH), 125.1 (CH), 123.5 (CH), 118.7 (CH), 60.2 (CH), 21.7 (CH_3), 18.6 (CH_2), 18.5 (CH_2), 14.5 (CH_3), 13.5 (CH_3).

Synthesis of a strigolactam 10: Following the general procedure A, the reaction performed with bromoimine **1a** (338 mg, 1.0 mmol) and dimethyl itaconate **9** (280 µL, 2.0 mmol) with TFA (8 µL, 0.1 mmol, 10 mol%)afforded, after purification by flash chromatography [50 mL SiO_2, EtOAc/PE: 2/8 then 4/6], **10** (120 mg, 31%) as a white solid. **mp:** 170 °C (dec). **R_f (PE/EtOAc:8/2, UV+KMnO$_4$):** 0.19. **IR (neat)** ν: 1736, 1342, 1154. **HRMS (ESI/Q-TOF)** m/z: $[M+Na]^+$ Calcd for $C_{20}H_{19}NNaO_5S$ 408.0876; Found 408.0875. **^{1}H NMR ($CDCl_3$, 400 MHz):** (1 diastereoisomer) δ 7.87 (d, *J*=8.2 Hz, 2H), 7.84–7.78 (m, 1H), 7.28–7.25 (m, 4H),

7.18–7.15 (m, 1H), 5.80 (s, 1H), 3.47 (d, *J*=16.4 Hz, 1H), 3.46 (s, 3H), 2.95 (d, *J*=16.4 Hz, 1H), 2.80 (d, *J*=17.5 Hz, 1H), 2.47 (d, *J*=17.5 Hz, 1H), 2.36 (s, 3H). **$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz):** (1 diastereoisomer) δ 173.5 (C), 171.1 (C), 145.3 (C), 139.4 (C), 138.4 (C), 135.5 (C), 129.7 (CH), 129.5 (2 CH), 128.6 (2 CH), 128.4 (CH), 127.0 (CH), 125.3 (CH), 71.5 (CH), 53.2 (C), 52.9 (CH_3), 41.5 (CH_2), 39.5 (CH_2), 21.8 (CH_3).

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Supporting Information

Copies of NMR spectra for all products.

References

[1] *Catalysis without Precious Metals*; Bullock, R. M., Ed.; Wiley-VCH: Weinheim, Germany, **2010**.

[2] Gandon, V.; Aubert, C.; Malacria, M. Recent Progress in Cobalt-Mediated [2+2+2] Cycloaddition Reactions. *Chem. Commun.* **2006**, 2209–2217.

[3] Broere, D. L. J.; Ruijter, E. Recent Advances in Transition-Metal-Catalyzed [2+2+2]-Cyclo(co)trimerization Reactions. *Synthesis* **2012**, *44*, 2639–2672.

[4] Pellissier, H.; Clavier, H. Enantioselective Cobalt-Catalyzed Transformations. *Chem. Rev.* **2014**, *114*, 2775–2823.

[5] Gandeepan, P.; Cheng, C.–H. Cobalt Catalysis Involving π Components in Organic Synthesis. *Acc. Chem. Res.* **2015**, *48*, 1194–1206.

[6] Gosmini, C.; Bégouin, J.-M.; Moncomble, A. Cobalt-Catalyzed Cross-Coupling Reactions. *Chem. Commun.* **2008**, 3221−3233.

[7] Cahiez, G.; Moyeux, A. Cobalt-Catalyzed Cross-Coupling Reactions. *Chem. Rev.* **2010**, *110*, 1435−1462.

[8] Knappke, C. E. I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; Jacobi von Wangelin, A. Reductive Cross-Coupling Reactions between Two Electrophiles. *Chem.–Eur. J.* **2014**, *20*, 6828–6842.

[9] Everson, D. A.; Weix, D. J. Cross-Electrophile Coupling: Principles of Reactivity and Selectivity. *J. Org. Chem.* **2014**, *79*, 4793–4798.

[10] Chang, K.-J.; Rayabarapu, D. K.; Cheng, C.-H. Cobalt-Catalyzed Carbocyclization of *o*-Iodobenzaldehydes and *o*-Iodophenylketones with Alkynes. *Org. Lett.* **2003**, *5*, 3963−3966.

[11] Chang, K.-J.; Rayabarapu, D. K.; Cheng, C.-H. Cobalt-Catalyzed Regioselective Carbocyclization Reaction of *o*-Iodophenyl Ketones and Aldehydes with Alkynes, Acrylates, and Acrylonitrile: A Facile Route to Indenols and Indenes. *J. Org. Chem.* **2004**, *69*, 4781−4787.

[12] Ahrens, H. Indaziflam: An Innovative Broad Spectrum Herbicide. *ACS Symposium Series* 2015, *1204*, 233–245.

[13] Courter, J. R.; Madani, N.; Sodroski, J.; Schön, A.; Freire, E.; Kwong, P. D.; Hendrickson, W. A.; Chaiken, I. M.; LaLonde, J. M.; Smith, A. B., III Structure-Based Design, Synthesis and Validation of CD4-Mimetic Small Molecule Inhibitors of HIV‐1 Entry: Conversion of a Viral Entry Agonist to an Antagonist. *Acc. Chem. Res.* **2014**, *47*, 1228−1237.

[14] Lachia, M.; Wolf, H. C.; Jung, P. J. M.; Screpanti, C.; De Mesmaeker, A. Strigolactam: New potent strigolactone analogues for the germination of *Orobanche Cumana*. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2184–2188.

[15] Chen, M.-H.; Mannathan, S.; Lin, P.-S.; Cheng, C.-H. Cobalt(II)-Catalyzed 1,4-Addition of Organoboronic Acids to Activated Alkenes: An Application to Highly *cis*-Stereoselective Synthesis of Aminoindane Carboxylic Acid Derivatives. *Chem.–Eur. J.* **2012**, *18*, 14918−14922.

[16] Liu, C.-C.; Korivi, R. P.; Cheng, C.-H. Cobalt-Catalyzed Regioselective Synthesis of Indenamine from *o*-Iodobenzaldimine and Alkyne: Intriguing Difference to the Nickel-Catalyzed Reaction. *Chem.–Eur. J.* **2008**, *14*, 9503−9506.

[17] Paul, J.; Presset, M.; Le Gall, E. Multicomponent Mannich-like Reactions of Organometallic Species. *Eur. J. Org. Chem.* **2017**, 2386–2406.

[18] Le Gall, E.; Haurena, C.; Sengmany, S.; Martens, T.; Troupel, M. Three-Component Synthesis of α-Branched Amines under Barbier-like Conditions. *J. Org. Chem.* **2009**, *74*, 7970−7973.

[19] Le Gall, E.; Léonel, E. A Four-Component Reaction Involving In Situ Generated Organometallic Reagents: Straightforward Access to β-Amino Esters. *Chem.–Eur. J.* **2013**, *19*, 5238−5241.

[20] Le Gall, E.; Sengmany, S.; Samb, I.; Benakrour, S.; Colin, C.; Pignon, A.; Léonel, E. A multicomponent approach to the synthesis of *N*-sulfonyl $\beta^{2,3}$-amino esters. *Org. Biomol. Chem.* **2014**, *12*, 3423–3426.

[21] Paul, J.; Presset, M.; Cantagrel, F.; Le Gall, E.; Léonel, E. Cobalt-Catalyzed Reductive Multicomponent Synthesis of β-Hydroxy- and β-Aminocarbonyl Compounds under Mild Conditions. *Chem.–Eur. J.* **2017**, *23*, 402−406.

[22] The use of both $EtBr_2$ and TMSCl or TFA as activators for zinc dust allowed a better reproducibility than TMSCl alone.

[23] For more details, see the Supporting Information.

[24] Contrary to Cheng's work (ref 11), no noticeable decyanation was observed in the present reaction conditions.

[25] The introduction of electron-donating methoxy groups on the aryl moiety was not tolerated.

[26] Seka, S.; Buriez, O.; Périchon, J. Stabilization of Co^{I} by Zn^{II} in Pure Acetonitrile and its Reaction with Aryl Halides. *Chem.–Eur. J.* **2003**, *9*, 3597–3603.

[27] Amatore, M.; Gosmini, C.; Périchon, J. $CoBr_2$(Bpy): An Efficient Catalyst for the Direct Conjugate Addition of Aryl Halides or Triflates onto Activated Olefins. *J. Org. Chem.* **2006**, *71*, 6130–6134.

[28] Silveira, C. C.; Vieira, A. S.; Braga, A. L.; Russowsky, D. Stereoselective Mannich-type Reaction of Chlorotitanium α-Phenylseleno Esters Enolates with Aromatic Aldimines. *Tetrahedron* **2005**, *61*, 9312–9318.

[29] Lumby, R. J. R.; Joensuu, P. M.; Lam, H. W. Racemic and Asymmetric Cobalt-Catalysed Reductive Aldol Couplings of α,β-Unsaturated Amides with Ketones. *Tetrahedron* **2008**, *64*, 7729–7740.

[30] *Multicomponent Reaction in Organic Synthesis*; Zhu, J.; Wang, Q.; Wang, M.-X., Eds.; Wiley-VCH: Weinheim, **2015**.

[31] Appel, R.; Chelli, S.; Tokuyasu, T.; Troshin, K.; Mayr, H. Electrophilicities of Benzaldehyde-Derived Iminium Ions: Quantification of the Electrophilic Activation of Aldehydes by Iminium Formation. *J. Am. Chem. Soc.* **2013**, *135*, 6579–6587.

[32] Pignon, A.; Le Gall, E.; Martens, T. A New Manganese-Mediated, Cobalt-Catalyzed Three-Component Synthesis of (Diarylmethyl)sulfonamides. *Belstein J. Org. Chem.* **2014**, *10*, 425–431.

[33] González, A. S.; Arrayás, R. G.; Carretero, J. C. Copper(I)-Fesulphos Lewis Acid Catalysts for Enantioselective Mannich-Type Reaction of *N*-Sulfonyl Imines. *Org. Lett.* **2008**, *8*, 2977–2980.

[34] While both diastereomers were detected by analysis of the crude reaction mixture, only the major *trans* diastereomer was isolated after purification by flash chromatography.

[35] Le Floch, C.; Laymand, K.; Le Gall, E.; Léonel, E. A Cobalt-Catalyzed Domino Route to the ABC Tricyclic Core of Strigolactones and Analogues. *Adv. Synth. Catal.* **2012**, *354*, 823–827.