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Controlled Synthesis of Enantioselective 1-Aminoindenes via Cobalt-Catalyzed [3+2] Annulation Reaction

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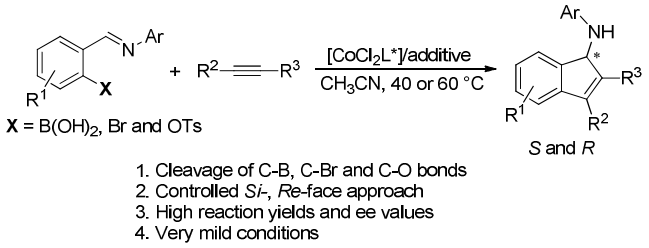
Supporting Information Placeholder

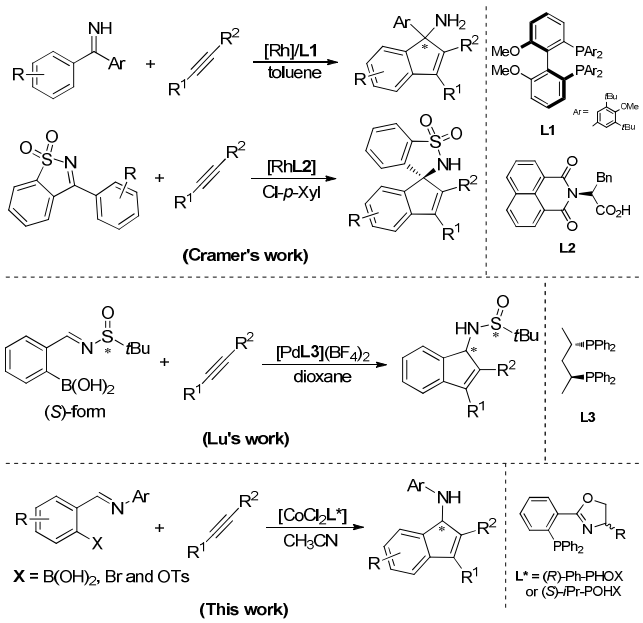


ABSTRACT: A cobalt-catalyzed synthesis of 1-aminoindenes via enantioselective [3+2] annulation is described. In this reaction, the desired products can be selectively prepared in either (*R*)- or (*S*)-form by the ligand controlled synthesis, which is initiated by the cleavage of C-B, C-Br or C-O bonds under very mild reaction conditions. In addition, this enantioselective cobalt catalysis provides high regioselectivity for both internal and terminal alkynes, and affords products generally in high yields and ee values.

KEYWORDS: *enantioselective synthesis, [3+2] annulation, 1-aminoindene, cobalt, chiral PHOX ligand.*

Aminoindene and its analogues are important fragments; they are frequently found in natural alkaloids[1] and known as an important structural motif in many pharmaceutical products. For example, the traditional herbs used as antipyretic,[2] the depression medicines,[3] the potential drugs of atrial fibrillation[4] and antidiabetic[5] have been reported to contain aminoindene core structures. Apart from the pharmaceutical compounds, aminoindenes are also applied in material chemistry[6] and used as ligands for metal complexes.[7] These applications attract attention from many organic chemists and result in continuous exploration of new synthetic strategy.

The transition-metal-catalyzed [3+2] annulation reaction is a facile and often selected method to synthesize aminoindenes and their derivatives. Most of the methods involving this concept were carried out by the cyclization of *o*-functionalized arylimines with alkynes or alkenes. In this respect, a variety of catalysts based on Re,[8] Rh,[9] Pd,[10] Ru,[11] Co[12] and Ir[13] have been reported for this transformation. However, the enantioselective version of the [3+2] annulation reaction is quite limited. Up to now, only few literatures have described the enantioselective synthesis of aminoindenes (Scheme 1). In 2011, Cramer first reported the catalytically enantioselective [3+2] annulation to afford chiral 1-aminoindenes by using rhodium complex with additional bidentate chiral phosphine ligand as the catalyst,[9d] which is specially applied to create quaternary chiral centers, and has been further extended to synthesize spiro-compounds in very recent years.[9f] The second enantioselective catalysis for the synthesis of chiral 1-aminoindenes was also reported in 2011 by Lu,[10b] which involves the cyclization of (*S*)-2-(*N*-*tert*-butanesulfinylimino)arylboronic acids with alkynes by using pre-prepared chiral cationic palladium complex as the catalyst. In this reaction, the *N*-attached (*S*)-*tert*-butylsulfinyl group is necessary to facilitate its enantioselectivity. And to determine the ee values, a further oxidation to convert the sulfinyl group to the corresponding sulfonyl group is required, which restricts the resulted products possessing a *tert*-butylsulfonyl group on the nitrogen.



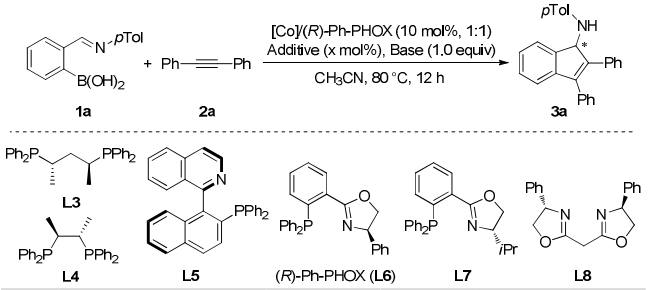
Scheme 1. Enantioselective Synthesis of 1-Aminoindenes

Even though the pioneer works had made a contribution in the enantioselective synthesis of 1-aminoindene, the progress of its synthetic methods is still demanded in response to the requirement of structural diversity. Our continuous interest in

the late-transition-metal catalyzed annulation reactions by utilizing the C-N multiple bonds as the reaction participants[12b, 14] prompted us to develop an asymmetric annulation for chiral 1-aminoindenes through the addition of C-N multiple bond. Herein, we report a controlled synthesis of the cobalt-catalyzed [3+2] enantioselective annulation of *o*-imidoylarylboronic acids (and arylhalides, pseudohalide) with alkynes to afford chiral 1-aminoindenes.

Our initial study started from the survey of chiral ligands (Table 1, entries 1–6; see Table S1 in Supporting Information for the detail of optimization study). By screening a series of chiral ligands, we found P,N-type bidentate chiral ligands are more effective to proceed this enantioselective catalysis than P,P-type and N,N-type bidentate ligands, and (*R*)-Ph-PHOX (**L6**) provided the highest efficacy in both of the reaction yield and the ee value. Further optimizations of conditions through investigating the effect of bases, additives and temperatures were also undertaken and summarized below (entries 7–15). Carbonate base, especially the K_2CO_3, provided much better yield without obvious loss in its ee value (entry 8). However, we were not able to have any improvement in the ee values by introducing the K_2CO_3 as base in further tuning of the reaction conditions. Decreasing the temperature is helpful for the enantioselectivity but pernicious for the yields (entries 10, 11). Thus, we reduced the reaction temperature from 80 °C to 60 °C for other examinations. We further found that an integrated catalyst can slightly increase both yield and ee value (entry 12), and the Lewis acid is very crucial in this reaction (entries 13–15). Among the Lewis acids that we have surveyed, the zinc halides were found to have the highest improvement on the yields, and a catalytic amount of $ZnCl_2$ dramatically enhanced the yield without loss of the enantioselectivity (entry 14).

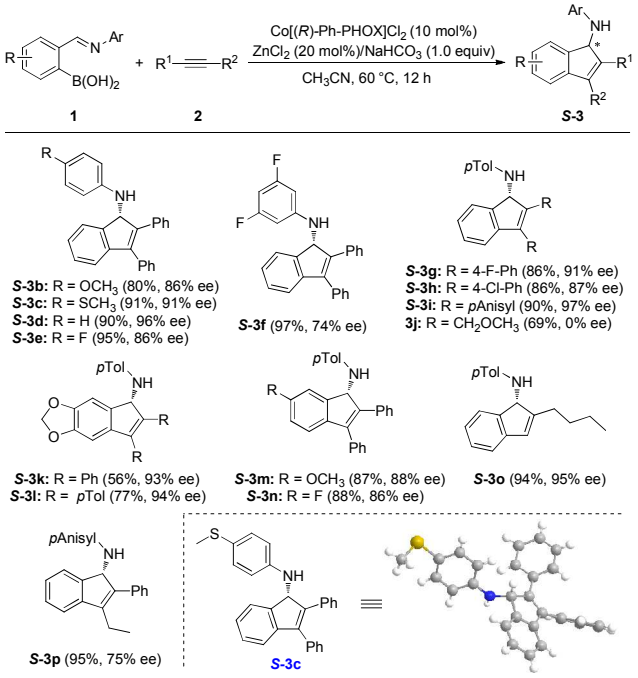
Table 1. Optimization of Reaction Conditions[a]



entry	[Co]/ligand	additive (x)	base	yield (%)[b]	ee (%)[c]
1	$CoCl_2$/L3	none	$NaHCO_3$	66	14
2	$CoCl_2$/L4	none	$NaHCO_3$	73	50
3	$CoCl_2$/L5	none	$NaHCO_3$	77	51
4	$CoCl_2$/L6	none	$NaHCO_3$	52 (66)[d]	85
5	$CoCl_2$/L7	none	$NaHCO_3$	90	77
6	$CoCl_2$/L8	none	$NaHCO_3$	87	3
7	$CoCl_2$/(*R*)-Ph-PHOX	none	Na_2CO_3	54	80
8	$CoCl_2$/(*R*)-Ph-PHOX	none	K_2CO_3	76	83
9	$CoCl_2$/(*R*)-Ph-PHOX	none	K_3PO_4	0	-
10[e]	$CoCl_2$/(*R*)-Ph-PHOX	none	$NaHCO_3$	33	90
11[f]	$CoCl_2$/(*R*)-Ph-PHOX	none	$NaHCO_3$	17	90
12[e]	Co[(*R*)-Ph-PHOX]Cl_2	none	$NaHCO_3$	45	91
13[e]	Co[(*R*)-Ph-PHOX]Cl_2	ZnI_2 (20)	$NaHCO_3$	67	91
14[e]	Co[(*R*)-Ph-PHOX]Cl_2	$ZnCl_2$ (20)	$NaHCO_3$	82	91
15[e]	Co[(*R*)-Ph-PHOX]Cl_2	$ZnCl_2$ (40)	$NaHCO_3$	89	84

[a]Conditions: **1a** (0.2 mmol), **2a** (1.5 equiv), cobalt complex/ligand (10 mol%, 1:1), additive (20–40 mol%), base (1.0 equiv), CH_3CN (1 mL). [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]NMR yield (mesitylene as the internal standard). [e]60 °C. [f]40 °C.

After getting the optimized condition of this Co-catalyzed enantioselective [3+2] annulation, the scope of reaction for various arylboronic acid **1** and alkyne **2** was then examined (Scheme 2). In general, the reactions worked well for selected *N*-attached aryl groups. Slightly reduced performances were found in yield for the *para*-anisyl group (***S*-3b**), and in ee value for the difluorophenyl group (***S*-3f**). The product ***S*-3c** has been verified as an (*S*)-isomer by single-crystal X-ray diffraction analysis. All compounds revealed in Scheme 2 have similar trend in their optical rotation and retention time. Substituents on the alkyne are influential in both of the yields and the ee values. The reactions for electron-deficient alkynes slightly depressed the yields and the ee values (***S*-3g** and ***S*-3h**), while the reaction for electron-rich alkyne remained high yield and ee value (***S*-3i**). Alkyne with the bilateral methoxymethyl groups can be tolerated in this cobalt catalytic reaction as well. However, the corresponding product **3j** was provided without any enantioselectivity. The unexpected coordination of oxygen to catalyst might obstruct the function of chiral PHOX ligand. Substituent on the moiety of arylboronic acid does not have significant affect in the yield and the enantioselectivity. Both of electron-donating groups and electron-withdrawing groups can be tolerated to afford the desired products in moderate to good yields with high ee values (***S*-3k** to ***S*-3n**). Notably, the enantioselective cobalt catalysis also demonstrates excellent stereoselectivity in the step of 1,2-insertion of alkyne. When unsymmetrical alkynes were introduced to the reaction, the corresponding products (***S*-3o** and ***S*-3p**) were afforded in single stereoisomer with high yields and good ee values (see the NOE data of product ***S*-3p** in Supporting Information).

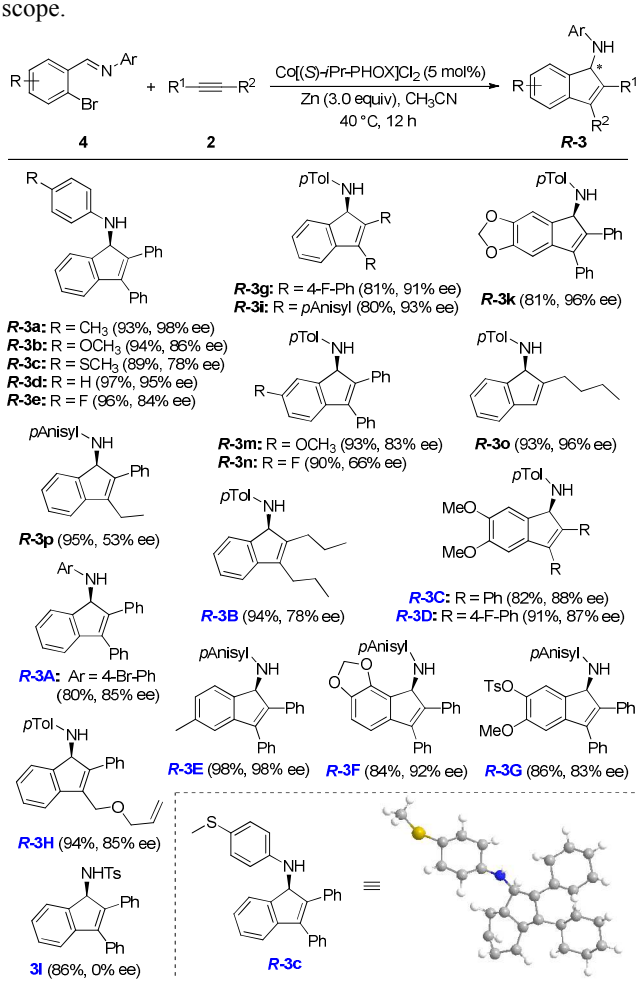


Scheme 2. Reaction Scope of 1 with 2[a]

[a]Condition: **1** (0.2 mmol), **2** (0.3 mmol), Co[(*R*)-Ph-PHOX]Cl_2 (0.02 mmol), $ZnCl_2$ (0.04 mmol), $NaHCO_3$ (0.2 mmol), CH_3CN (1 mL) at 60 °C for 12 h. The yields refer to isolated yield. The ee values were determined by chiral HPLC analysis.

The present Co-catalyzed enantioselective [3+2] annulation can also proceed smoothly by replacing arylboronic acids **1** with arylbromides **4** (Scheme 3). With fine tuning of reaction conditions, the (*R*)-isomers were provided in good yields with high ee values by using Co[(*S*)-*i*Pr-PHOX]Cl_2 as the catalyst

with zinc as the reducing agent to activate the cobalt species (see Table S2 for the optimization study and Scheme 5 for the proposed mechanism). For contradistinction, we confirmed the product ***R*-3c** for its absolute configuration by single-crystal X-ray diffraction analysis. Including ***R*-3c**, all enantiomers illustrated in Scheme 3 (***R*-3a** to ***R*-3p**) and Scheme 2 possess opposite trend in their optical rotation and retention time. Not only the enantiomers of Scheme 2, but we also exhibit some additional structures (***R*-3A** to ***R*-3H**) to evaluate the reaction scope.

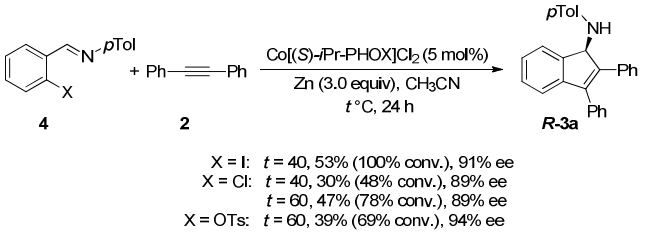


Scheme 3. Reaction Scope of 4 with 2[a]

[a]Condition: **4** (0.2 mmol), **2** (0.24 mmol), Co[(*S*)-*i*Pr-PHOX]Cl_2 (0.01 mmol), Zn (0.6 mmol), undistilled CH_3CN (1 mL) at 40 °C for 12 h. The yields refer to isolated yield. The ee values were determined by chiral HPLC analysis.

Comparing with the reactions in Scheme 2, the reactions for arylbromides **4** require lower temperature and additional H_2O as the proton source (see Table S3).[15] Generally, products ***R*-3a** to ***R*-3p** were afforded in similar yields and ee values with their enantiomers in Scheme 2 except ***R*-3c**, **3j**, ***R*-3n** and ***R*-3p**. Products ***R*-3c**, ***R*-3n** and ***R*-3p** were provided in similar yields with their enantiomers, but in significantly lower ee values. A big difference for **3j** in this protocol was shown in that **3j** is even not able to be obtained from this reaction. The unsymmetrical products ***R*-3o** and ***R*-3p** were furnished in single stereoisomer as well. ***R*-3A** to ***R*-3H** were generated in 80 to 98% yields with 78 to 98% ee. Product **3I** with an *N*-attached tosyl group was collected as racemic mixture in 86% yield. Comparing with the reactions in Scheme 2, reactions by using the arylbromides **4** as substrates are more sensitive in their structural subunit for the enantioselectivity. Every slight change of the substituent obviously affects the ee values (***R*-3B** vs ***R*-3o**, ***R*-3C** vs ***R*-3k** and ***R*-3E** to ***R*-3G**). An additionally unsymmetrical product ***R*-3H** generated from a long chain internal alkyne was also afforded in single isomer (see NOE data).

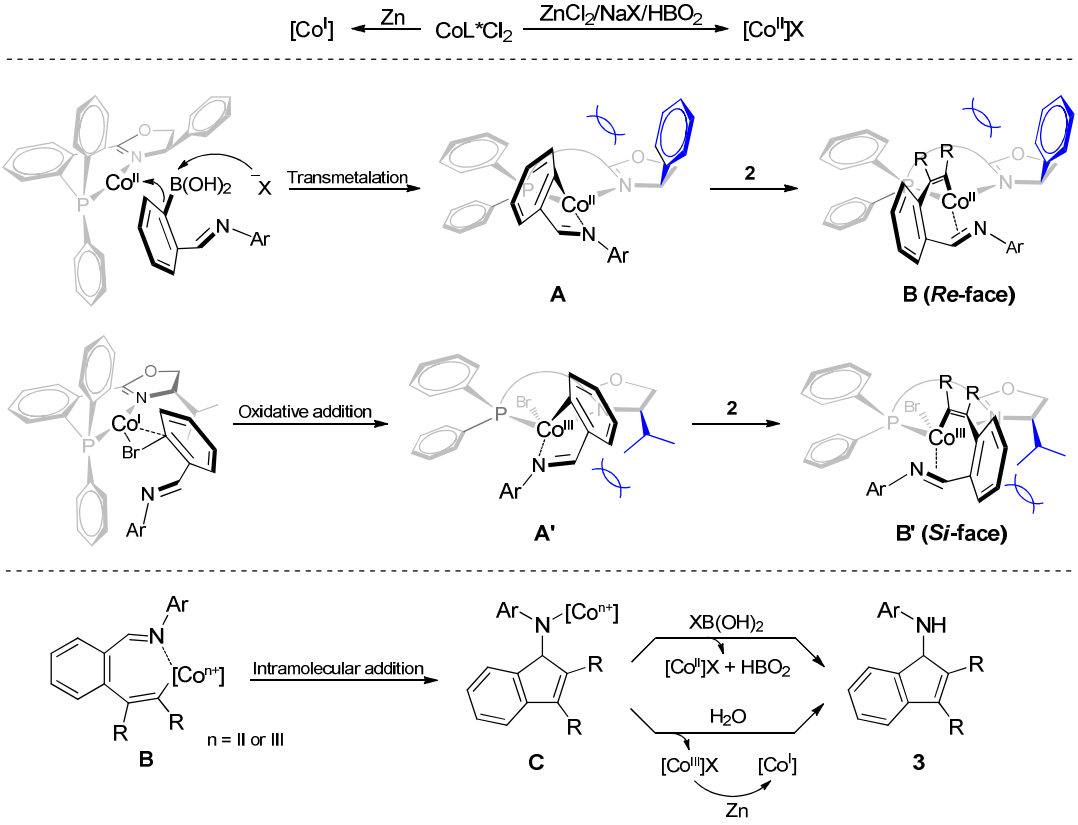
Under a similar protocol, the reaction can be initiated from the cleavage of other carbon-halide or carbon-oxygen bonds as well. Herein, reactions to approach ***R*-3a** from different halo-substrates and pseudohalo-substrate **4** have been examined to understand their properties (Scheme 4). As indicated, when we employed the iodo-substrate, ***R*-3a** could be obtained in 53% yield with 91% ee at 40 °C with complete consumption of the substrate. The low yield was caused by unclear side reactions. However, the chloro-substrate cannot be fully consumed even with longer reaction time or at higher temperature. The best performance was achieved at 60 °C to give ***R*-3a** in 47% yield with 89% ee. Higher temperature significantly caused lower enantioselectivity, while lower temperature reduced reactivity. We further tested the tosylate and found it is also able to be a leaving group; the best enantioselectivity was provided at 60 °C in 39% yield with 94% ee.



Scheme 4. Tolerance of Halides and Pseudohalide

According to the above results and the previous reports,[16] a proposed reaction mechanism accounting for the Co-catalyzed enantioselective synthesis of *N*-arylinden-1-amine **3** is shown in Scheme 5. The reactions are likely initiated from generation of active cobalt complexes. The initial Co(II) complex can be either reduced to a Co(I) complex by zinc powder (Scheme 3), or just converted to the corresponding Co(II) species by $ZnCl_2$, *in situ* generated sodium salt, and metaboric acid (Scheme 2). The key intermediates and pathway for entire reaction start from **A** to **B,** and then convert to **C**. Protonation of the resulted complex **C** via the respective proton sources (boronic acid and H_2O) provides the desired product **3** and regenerates the active cobalt complexes.

For the reaction by using arylboronic acid **1** as substrate, the formation of complex **A** occurs through the transmetalation of substrate **1** to the active Co(II) species. Whereas the formation of complex **A'** is caused by the oxidative addition of aryl bromide **4** to Co(I). A subsequent 1,2-insertion of alkyne **2** transforms **A** (or **A'**) to **B** (or **B'**). The chiral PHOX ligand plays an important role in both complexes **A** (or **A'**) and **B** (or **B'**).[17] The steric hindrance, which dominates the configuration of desired product, is controlled by the substituent attached to the nitrogen-adjacent carbon on the oxazole. As illustrated, the phenyl group of complex **B** makes R group far away from the oxazole moiety and leads the subsequent intramolecular addition of imine from the *Re*-face, while the isopropyl group of complex **B'** leads to the *Si*-face insertion.



Scheme 5. Proposed Mechanism

In conclusion, we have developed the controlled synthesis of chiral 1-aminoindenes in either (*S*)- or (*R*)-form through the Co-catalyzed enantioselective [3+2] annulation reactions. This cobalt catalysis proceeded under very mild reaction conditions, which can be initiated from the cleavage of C-B, C-Br or C-O bonds. In addition, the reaction scope has been found in wide diversity with high yields and good to excellent ee values. The regioselectivity is well performed for unsymmetrical alkynes. Further extension of the reactions with various π components is currently underway.

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ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization, spectral data, X-ray structure, NMR spectra and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Controlled Synthesis of Enantioselective 1-Aminoindenes via Cobalt-Catalyzed [3+2] Annulation Reaction

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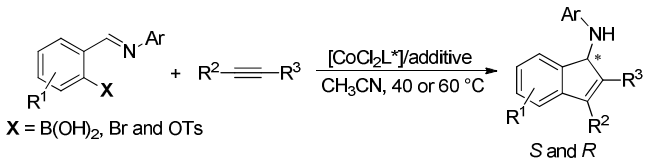

1. Cleavage of C-B, C-Br and C-O bonds
2. Controlled *Si*-, *Re*-face approach
3. High reaction yields and ee values
4. Very mild conditions