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Cobalt-catalyzed 1,4-aryl migration/desulfonylation cascade: synthesis of α-aryl amides.

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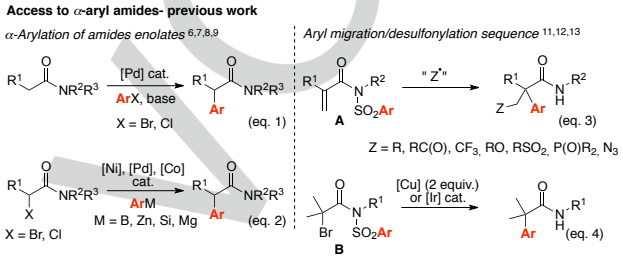
Abstract: A cobalt-catalyzed 1,4-aryl migration/desulfonylation cascade applied to α-bromo *N*-sulfonyl amides is described. The reaction is highly chemoselective allowing the preparation of α-aryl amides possessing a variety of functional groups. The method was used as the key step to synthesize an alkaloid, (±)-deoxyeseroline. Mechanistic investigations suggest a radical process.

As ubiquitous pharmacophores, α-aryl amides constitute a class of attractive compounds in medicinal chemistry.[1] They are present in a range of marketed drugs such as atenolol,[2] which is used in the treatment of cardiovascular diseases, or in many β-lactam antibiotics such as amoxicilline,[3] which is the most frequently employed antibiotic for children. α-Aryl amides are also analogs of α-aryl carboxylic acids that are key motifs in several non-steroidal anti-inflammatory agents.[4] In addition, they can be easily reduced to β-aryl amines that can be found in a variety of biologically active molecules.[5] As a consequence of their outstanding importance, several methods have been developed to access α-aryl amides, the most popular one being the metal-catalyzed arylation of amides enolates (Scheme 1, eq. 1).[6] Since its discovery by Hartwig *et al.* in 1998,[7] this reaction has known numerous developments but still suffers from some drawbacks such as the need for a strong base to generate the amide enolate.[8] As an alternative, metal-catalyzed cross-couplings between α-halo amides and organometallics have been studied, most of them relying on Ni-, Pd- or Co- catalysts (Scheme 1, eq. 2).[9] A third way to access α-aryl amides is based on an aryl migration/desulfonylation process applied to *N*-sulfonyl amides of type **A** or **B** (Scheme 1, eq. 3 and 4).[10,11] In both cases, a radical generated in the α position of the amide moiety is able to perform a 5-*ipso* cyclization triggering, after a desulfonylation step, a 1,4-aryl migration. Numerous radical addition/aryl migration cascade applied to acrylamides have been reported, resulting in α-aryl amides that incorporate a Z group in their final structure coming from the radical precursor (Scheme 1, eq. 3).[12] To avoid this first intermolecular addition of a Z$^{\bullet}$ radical on **A** derivatives, radicals can be generated from α-halo sulfonamides (Scheme 1, eq. 4).[13] However, examples of such rearrangements are scarce in the literature. All of them require the use of tertiary bromides and either stoichiometric amount of copper complexes or expensive iridium photocatalyst.



Scheme 1. Access to α-aryl amides: previous work.

During the course of our studies in sustainable metal-catalyzed reactions, we developed a cobalt-catalyzed cross-coupling of α-halo amides with Grignard reagents.[9i] While using sulfonamide **1.1** under our optimized conditions, we observed the formation of α-tolyl amides **1.2** as the major product instead of the expected α-phenyl amide. We hypothesized that this product could arise from a low-valent cobalt-catalyzed 1,4-aryl migration/desulfonylation process initiated by the formation of a radical in the α position of the amide moiety. Intrigued by this result, the conditions were optimized, particularly with the objective of avoiding the use of Grignard reagent as the reducing agent. Herein, we report a cobalt-catalyzed, manganese-mediated intramolecular aryl migration/desulfonylation sequence applied to the arylation of α-bromo *N*-sulfonyl amides (Scheme 2). As it is not restricted to tertiary bromides, this chemoselective transformation allows the access to a great diversity of α-aryl amides. The rearrangement was used as the key step in the synthesis of (±)-deoxyeseroline and mechanistic investigations have been conducted.

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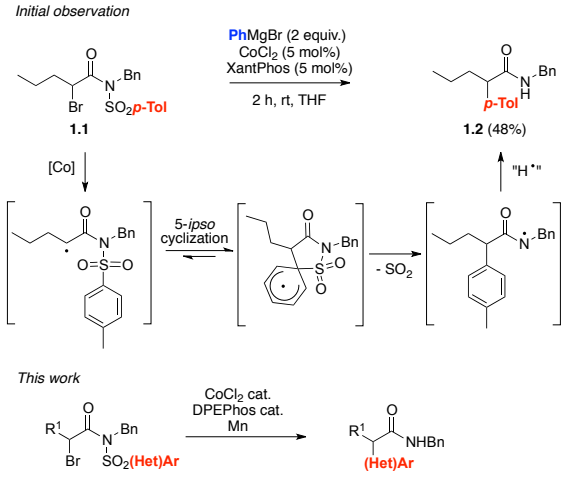
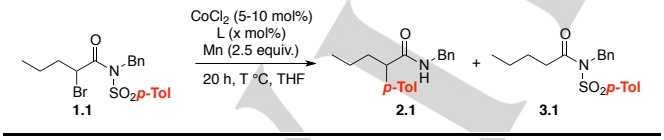


Scheme 2. Access to α-aryl amides through cobalt-catalyzed 1,4-aryl migration/desulfonylation cascade. XantPhos= 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene.

The first objective of our optimization study consisted of finding an alternative reductive agent preventing the waste of the Grignard reagent.[14] The same catalytic system [$CoCl_2$, XantPhos] was used and, among the reductive metals tested (Mg, Zn, Mn), the most promising one was Mn powder (2.5 equiv.). Under these conditions, the starting bromo *N*-sulfonyl amide was fully consumed to give a mixture of the desired α-aryl amide **2.1** together with the dehalogenated compound **3.1** (**2.1**/**3.1** = 32:68), allowing the isolation of the targeted molecule with a moderate yield of 31% (Table 1, entry 1) but this reaction revealed hardly reproducible. However, increasing the temperature to 100 °C revealed to be the key feature to address this issue and also to significantly improve the selectivity in favor of the α-aryl amide (Table 1, entry 2). A range of amine, phosphine and phosphite ligands has then been screened and the best result was obtained with 10 mol% of the bidentate DPEPhos (Table 1, entry 3). Several solvents were examined but moderate conversion of the starting bromo amide and/or formation of the dehalogenated compound as the major product were observed in all cases. Among the commercially available cobalt complexes tested, $CoCl_2$ was the most powerful one to provide α-aryl amide **2.1**.[15,16]

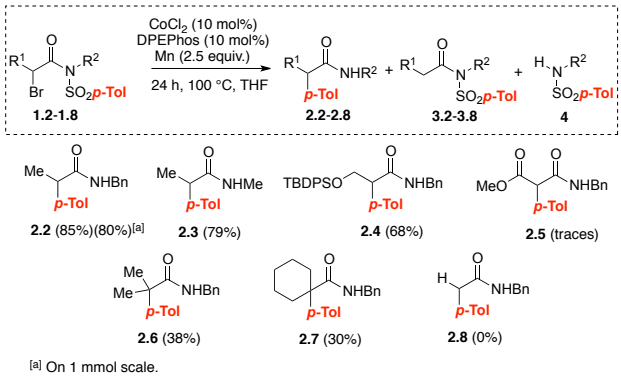


entry	L (x mol%)	T °C	τ_c (%)[a]	**2.1**/**3.1**	**2.1**, yield[b]
1[c],[d]	XantPhos (5)	rt	> 95	32:68	31%
2[c]	XantPhos (5)	100	58	90:10	45%
3[e]	DPEPhos (10)	100	> 95	90:10	80%

[a] Ratio (**2.1**+**3.1**)/(**1.1**+**2.1**+**3.1**) calculated from ^{1}H NMR spectra of the crude. [b] Isolated yield. [c] 5 mol% of $CoCl_2$ was used. [d] The reaction was not reproducible. [e] 10 mol% of $CoCl_2$ was used. XantPhos= 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene. DPEPhos= (Oxydi-2,1-phenylene)bis(diphenylphosphine).

Table 1. Optimization of the reaction conditions.

With the optimized conditions in hand, the scope of the reaction was investigated, first focusing on the influence of α-substituent of the amide (R^1) and nitrogen substituent (R^2). The reaction outcome was not affected when the *n*-propyl group was changed for a methyl substituent as the corresponding α-aryl amide was isolated in an excellent yield of 85%. The reaction was scalable under the optimized conditions as 1 mmol of **1.2** were efficiently transformed in **2.2** with a good yield (80%). Interestingly, the reaction could be performed on an α-chloro *N*-sulfonyl amide and, after 48 h, the desired α-tolyl amide was isolated in an excellent yield (87%).[17] Changing the *N*-Bn substituent for a *N*-Me did not modify the reactivity and the corresponding *N*-Me amide was obtained selectively (79%). The presence of a silyl ether was well tolerated and α-aryl amide **2.4** was formed with a good yield of 68%. However, when α-bromo β-amido ester **1.5** was involved in the reaction, a mixture composed of the desired compound, the dehalogenated product and the primary sulfonamide **4** was obtained and **2.5** could not be isolated.[18,19,20] This result can be obtained by the presence of the electron-withdrawing group which could stabilize the putative radical intermediate, favoring the formation of a cobalt enolate (*vide infra*). This cobalt enolate could provide a transient ketene upon elimination of the observed sulfonamide.[21,22] When tertiary bromides were used, moderate yields in the rearranged product **2.6** and **2.7** (38% and 30% respectively) were obtained, due to the formation of a substantial amount of the non-desired dehalogenated compound. We hypothesized that the stabilization of the radical may favor an hydrogen abstraction to THF over the 5-*ipso* cyclization. Even disappointing, this result highlights the difference of our method with the existing aryl migration/desulfonylation cascades that generally required tertiary bromides. Primary bromide cannot be used in this rearrangement as a mixture of starting bromide and sulfonamide **4** was obtained (Scheme 3).

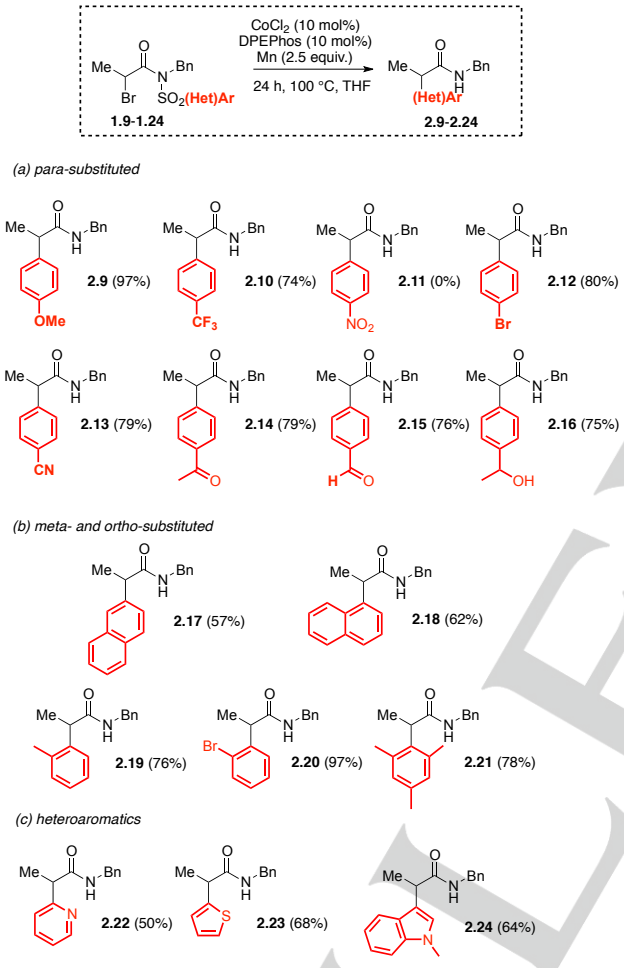


[a] On 1 mmol scale.

Scheme 3. Variation of the R^1 side chain and R^2 nitrogen substituent. DPEPhos= (Oxydi-2,1-phenylene)bis(diphenylphosphine).

N-sulfonyl amides bearing various *para*-substituents on the aryl ring was then evaluated in this cobalt-catalyzed aryl migration/desulfonylation cascade. Pleasingly, the reaction was not sensitive to electronic effects as the migration of aryl rings displaying both *p*-OMe and *p*-CF_3 substituents was efficient. These results differentiate our method from the reported iridium-catalyzed aryl migration,[13d] which does not tolerate the presence of strong electron-rich or electron-

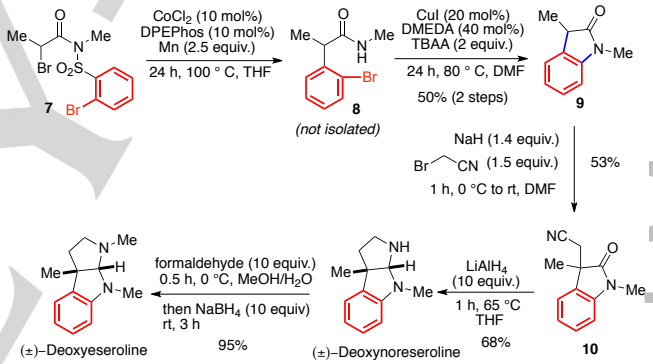
withdrawing groups on the migrating aryl ring. A limitation was noticed in the presence of a nitro substituted aryl as no traces of the rearranged product could be detected. The poisoning of the cobalt catalyst upon coordination to the nitro substituent as well as the undesired reduction of the nitro group could explain this result. Interestingly, the reaction revealed to be highly chemoselective in the presence of an aryl bromide or electrophilic substituents including nitrile, ketone and highly reactive aldehyde moiety. In addition, the presence of a free hydroxyl group did not interfere with the catalytic system. Thus, this aryl migration process appeared as an attractive mild alternative to metal-catalyzed cross-coupling between α-bromo amides and nucleophilic reactive organometallics (Scheme 4a).



Scheme 4. Migration of *para*-, *meta*-, *ortho*-substituted aryl groups and heteroaromatics. DPEPhos= (Oxydi-2,1-phenylene)bis(diphenylphosphine).

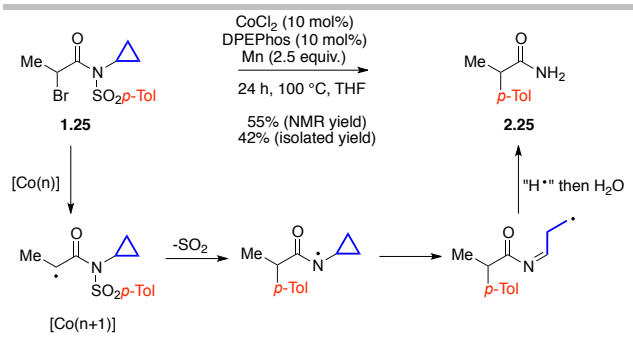
α-Aryl amides incorporating a 1- or 2-naphthyl susbtituents were efficiently synthesized from the starting α-bromo amides (62% and 57% yields respectively). More interestingly, the reaction proved to be not sensitive to steric hindrance as an *ortho*-methyl or *ortho*-bromide aryl rings efficiently migrated to give the corresponding α-aryl amides with good yields (76% and 97% respectively). Even the migration of a sterically hindered mesityl group successfully delivered the α-arylated product with a good yield (78%). These results are highly valuable as only few methods allow the easy preparation of such hindered α-aryl amides (Scheme 4b). Gratifyingly, several heteroaromatics such as pyridine, thiophene and indole successfully migrated to furnish the α-heteroaryl amides, which are challenging to obtain by using other methods (Scheme 4c).

The developed rearrangement could be used as a key step in the synthesis of the (±)-deoxyeseroline, a pyrrolidino-indoline alkaloid featuring a benzylic all carbon quaternary center.[23] The aryl migration was performed on α-bromo *N*-sulfonyl amide **7**[24] under our optimized conditions and the resulting crude α-aryl amide was directly engaged in an Ullmann coupling [CuI (10 mol%), 1,2-dimethylethylenediamine (DMEDA, 40 mol%), *t*-butyl acetoacetate (TBAA, 2 equiv)] affording oxindole **9** with a decent 50% yield for the two consecutive steps. Treatment of oxindole **9** with a base followed by addition of bromoacetonitrile allowed the construction of the quaternary center. Concomitant reduction of the nitrile and amide moieties ($LiAlH_4$, THF, 65 °C) was then performed delivering (±)-deoxynorseroline, which was readily transformed into (±)-deoxyeseroline through a reductive amination. Overall, the alkaloid was prepared in 7 steps from 2-bromobenzenesulfonyl chloride with an overall yield of 16%. Given the chemical tolerance of the developed method, a panel of substituents on the aryl ring could be envisioned, leading to the possible synthesis of various pyrrolidino-indoline analogs.



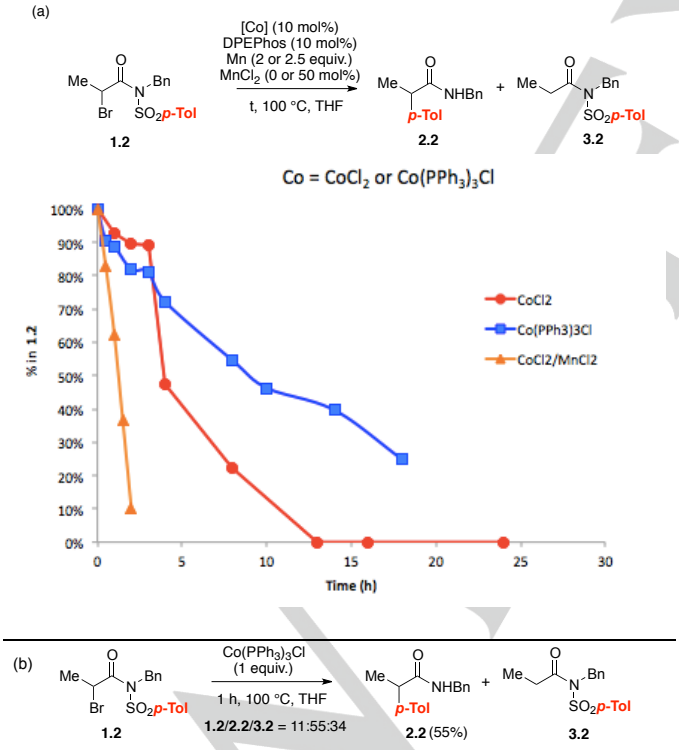
Scheme 5. Synthesis of (±)-deoxyeseroline. DPEPhos= (Oxydi-2,1-phenylene)bis(diphenylphosphine). DMEDA= *N*,*N*'-dimethylethylene-diamine. TBAA= Bis(tetrabutylammonium) adipate.

To get some insights into the mechanism of the transformation, some experiments were conducted. At first, with the objective of confirming the formation of a transient radical species, α-bromo *N*-sulfonyl amide **1.25** featuring a *N*-cyclopropyl ring was treated under the optimized conditions. After 48 h, primary α-aryl amide **2.25** was isolated with a yield of 42% (55% NMR yield). The absence of the cyclopropyl ring in the final product may confirm the formation of an amidyl radical producing a ring-opening of the strained 3-membered ring leading to an unstable imine that finally delivered **2.25**.



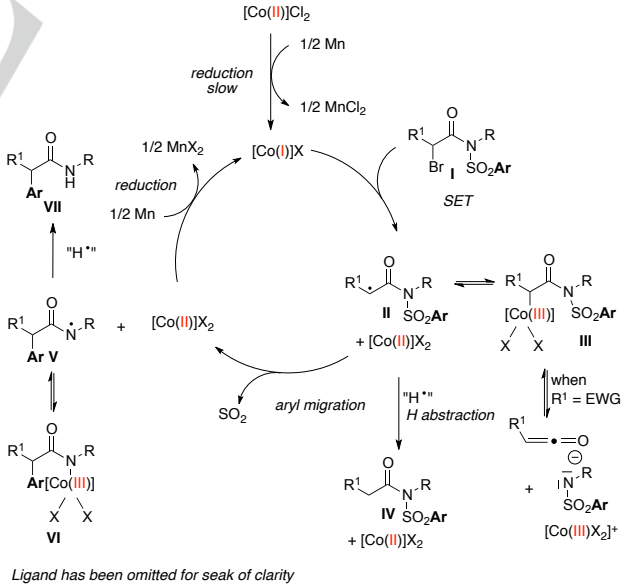
Scheme 6. Rearrangement of radical clock **1.25**.

Kinetic studies were then conducted and the consumption of α-bromo *N*-sulfonyl amide **1.2** was measured at different reaction times. Interestingly, an induction period of ca. 3 h was observed followed by an acceleration of the reaction. (Scheme 7a). The combination of a Co(II) pre-catalyst with Mn has been described in the literature,[25] particularly for the catalysis of reductive cross-coupling between two electrophiles. A reduction of Co(II) pre-catalyst using Mn into a Co(I) is generally proposed as the initiation step to generate the active catalyst. Once formed, the Co(I) catalyst is able to react with halides, generally through a single electron transfer (SET). We hypothesized that the induction period may be due to a slow reduction of $CoCl_2$ into a Co(I) active catalyst that then would be able to transfer one electron to the α-bromo *N*-sulfonyl amide.



Scheme 7. Mechanistic investigations: (a) Kinetic studies: comparison of $CoCl_2$, $Co(PPh_3)_3Cl$ and $CoCl_2/MnCl_2$ catalytic activity. (b) Experiment with stoichiometric amount of $Co(I)(PPh_3)_3Cl$. DPEPhos= (Oxydi-2,1-phenylene)bis(diphenylphosphine).

To confirm the ability of Co(I) catalyst in activating the C-Br bond of **1.2**, the stable $Co(I)(PPh_3)_3Cl$ was prepared and a stoichiometric amount was added to **1.2** in the absence of Mn. The reaction was heated at 100 °C and high conversion of **1.2** into the rearranged and dehalogenated products was obtained, thus confirming the reactivity of Co(I) complex towards C-Br bond (Scheme 7b). In addition, when a kinetic study was conducted in the presence of a catalytic amount of $Co(I)(PPh_3)_3Cl$, no clear induction period was observed compared to the one observed using $CoCl_2$. This observation could be due to the absence of required preliminary reduction step when a Co(I) complex is involved in the reaction (Scheme 7a). Several factors may explain the observed acceleration, such as the progressive activation of Mn or the non-innocent role of generated MnX_2 salts. Indeed, no induction period was observed when the reaction was conducted in the presence of $CoCl_2$ (10 mol%) and 50 mol% of $MnCl_2$ (Scheme 7a).[26] From these experiments and based on literature reports, the following mechanism was hypothesized (Scheme 8). At first, a slow reduction of $CoCl_2$ by Mn into a Co(I) complex would occur delivering the active catalyst of the reaction.[27] In the presence of an α-bromo *N*-sulfonyl amide, a fast single electron transfer (SET) would provide alkyl radical **II** and a Co(II) complex in equilibrium with Co(III) complex **III**. This latter could be favored in the presence of a R^1 electron-withdrawing group leading to a ketene and a sulfonamide. Alkyl radical **II** could undergo a 5-*ipso* cyclization followed by SO_2 extrusion to give the α-aryl amidyl radical that could then abstract an hydrogen to the solvent. Alternatively, radical **II** could abstract directly a hydrogen to the solvent providing the dehalogenated product. In both cases, the Co(II) complex would be reduced by Mn to regenerate the active catalyst.



Scheme 8. Hypothetical mechanism.

In summary, we have developed a cobalt-catalyzed 1,4-aryl migration/desulfonylation cascade allowing the synthesis of a wide variety of α-aryl amides from α-bromo *N*-sulfonyl amides. The reaction is highly chemoselective and appears as a flexible strategy to prepare α-aryl amides. The efficient

synthesis of the alkaloid (±)-deoxyeseroline using the aryl migration as a key step illustrates the potential of the developed reaction. Mechanistic studies suggest the formation of a radical through a SET from a Co(I) complex to α-bromo *N*-sulfonyl amide. To the best of our knowledge, it is the first cobalt-catalyzed aryl migration with SO_2 extrusion and this reactivity pave the way to numerous further developments.

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The authors declare no conflict of interests.

Keywords: cobalt • α-aryl amide • aryl migration • *N*-sulfonyl amide

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[14] See the supporting information for a detailed optimization study.

[15] The robustness of the reaction was assessed by the addition of 1 equiv of water to the reaction mixture. Under these modified conditions, the α-aryl amide was isolated with a correct yield of 54%, see SI for details.

[16] Using $NiCl_2$ (10 mol%) associated to DPEPhos (10 mol%) also led to **2.1** in good yield (78%).

[17] This result is of importance as α-bromo amides can sometimes be prepared as mixtures of α-bromo and α-chloro derivatives when using acyl chloride precursors due to halogen exchange. The rearrangement is compatible with the use of such mixtures as starting materials.

[18] A **2.5**/**3.5**/**4** ratio of 15:21:64 was determined on the ^{1}H NMR spectrum of the crude material.

[19] When a diethylphosphonate was present instead of the ester group, the exclusive formation of sulfonamide **4** was observed.

[20] For R^1= Ph, a mixture of expected, dehalogenated products and sulfonamide was obtained preventing the isolation of the α-aryl amide.

[19] Unfortunately, we were not able to isolate by-products resulting from a nucleophilic attack on the hypothesized ketene intermediate.

[22] An insertion of a low-valent cobalt complex into the C-N bond cannot be excluded, see: Y. Bourne-Branchu, C. Gosmini, G. Danoun *Chem. Eur. J.* **2017**, *23*, 10043.

[23] a) U. Anthony, C. Christophersen, P. H. Nielsen, in Alkaloids: Chemical and Biological Perspectives; S. W. Pelletier, Ed.; Wiley: New-York, 1999; Vol. 13, 163. b) H. J. Lim, T. V. RajanBabu, *Org. Lett.* **2011**, *13*, 6596. c) G. Özüduru, T. Schubach, M. M. K. Boysen, *Org. Lett.* **2012**, *14*, 4990. d) N. Kumar, V. R. Gavit, A. Maity, A. Bisai, *J. Org. Chem.* **2018**, *83*, 10709.

[24] Prepared from the corresponding sulfonamide and α-bromo propionyl bromide (94%, 2 steps, see SI for details).

[25] Selected articles: a) M. Amatore, C. Gosmini, J. Périchon, *Eur. J. Org. Chem.* **2005**, 989. b) M. Amatore, C. Gosmini, *Angew. Chem. Int. Ed.* **2008**, *47*, 2089. c) A. Moncomble, P. L. Le Floch, C. Gosmini, *Chem. Eur. J.* **2009**, *15*, 4770. d) M. Amatore, C. Gosmini, *Chem. Eur. J.* **2010**, *16*, 5848. e) A. Moncomble, P. L. Floch, A. Lledos, C. Gosmini, *J. Org. Chem.* **2012**, *77*, 5056.

[26] In that experiment 50 mol % of $MnCl_2$ were added to the classical conditions and only 2 equiv of Mn were used. The conversion of **1.2** was fast but led to a mixture of **2.2** and **3.2** (**1.2**/**2.2**/**3.2** = 10:37:53 after 5 h). Very low conversion of **1.2** was observed using $MnCl_2$ (10 mol %) in the absence of cobalt catalyst. See SI for details.

[27] Reduction to a Co(0) complex cannot be fully excluded.

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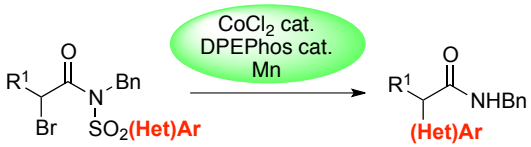

The synthesis of α-aryl amides through a cobalt-catalyzed 1,4-aryl migration/desulfonylation cascade applied to α-bromo *N*-sulfonyl amides is reported. The combination of a cobalt catalyst together with a phosphine ligand and a metal reductive agent results in soft conditions that proved to be compatible with a wide range of functional groups. The cascade reaction was used as a key step in a flexible synthesis of (±)-deoxyeseroline, a pyrrolidino-indoline alkaloid. Mechanistic investigations suggest the formation of a transient radical.

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