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Stereoselective Pincer-Complex Catalyzed C-H Functionalization of Benzyl Nitriles under Mild Conditions. An Efficient Route to β-Aminonitriles

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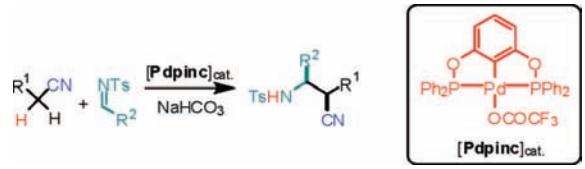
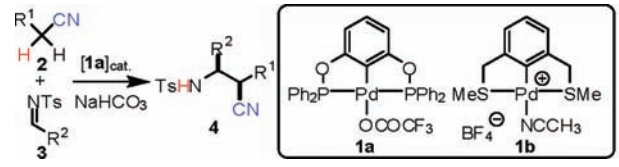
ABSTRACT



An efficient palladium pincer-complex catalyzed reaction has been developed for α-C-H bond functionalization of benzyl nitriles. The studied coupling reaction with sulfonylimines affords β-aminonitriles with usually high levels of stereoselectivity. The stereoselectivity of the process is highly dependent on the electronic effects of the *ortho* substituents of the benzyl moiety. Promising levels of enantiomeric excess are obtained using chiral pincer complexes as catalysts.

Transition metal catalyzed α-C-H functionalization of organonitriles with aldehydes and imines offers an attractive synthetic route[1] to β-amino and hydroxy nitriles, which are important drug intermediates.[2] The transition metal catalyzed pathways usually take advantage of the cooperative interaction[1c−f] of the catalyst and the employed weak base. This interaction leads to enhancement of the acidity of the coordinated organonitrile substrate, which easily undergoes deprotonation generating a metal-bound carbon nucleophile.[1c−f]

The nucleophile generated in this process is usually coupled with aldehyde or imine reagents under mild reaction conditions. α-Cyano carbanions can also be generated without assistance of transition metal catalysts.[3] However, the deprotonation of alkyl[1c] ($pK_a = 31.3$) and benzyl[1c] nitriles ($pK_a = 21.9$) requires very strong bases, such as LDA[3c] and proazaphosphatranes,[3a,b] which may trigger undesired side reactions, such as dehydration[3a,b] or epimerization of the product.[3c]



(1)

Many excellent applications have appeared in the literature using the above-mentioned cooperative catalytic concept for coupling of organonitriles with imines and aldehydes employing ruthenium,[1c,d,f,h] palladium,[1b] rhodium,[1i] copper,[1e] and nickel catalysts.[1j] However, the only literature[3c] proce-

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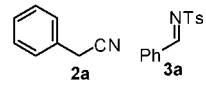
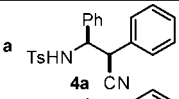
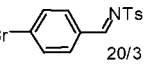
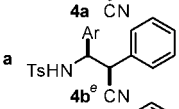
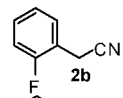
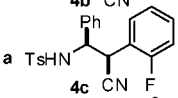
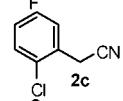
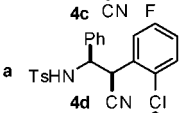
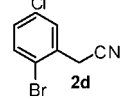
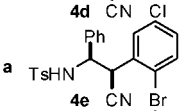
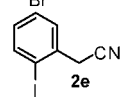
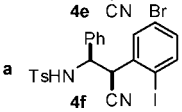
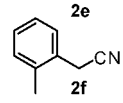
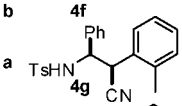
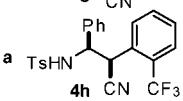
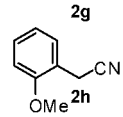
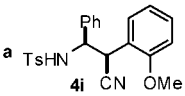
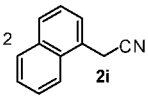
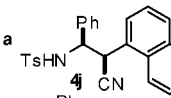
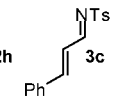
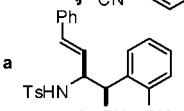
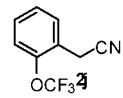
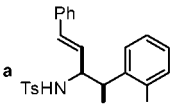
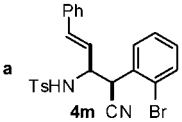
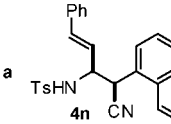
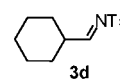
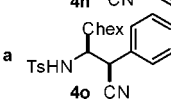
dure that could be found for coupling of benzyl nitriles with imines is based on classical base (LDA) catalysis without application of transition metal catalysts. Application of the very strong base in the absence of transition metal catalysis strongly limits the synthetic scope of this process because of the easy elimination and epimerization of the products under the harsh reaction conditions.[3c]

For the first time, we report here a transition metal catalyzed coupling reaction (eq 1, Table 1) of benzyl nitriles (**2a**−**j**) with sulfonylimines (**3a**−**d**). We have found that palladium pincer-complexes,[4] such as **1a**−**b**,[5] are very powerful catalysts for the benzylic C−H functionalization process. This catalytic transformation can be carried out in the presence of a weak base ($NaHCO_3$) or under completely base-free conditions. The integrity of the pincer-complex catalyst was maintained under the process, as the unchanged catalyst could be detected by ^{31}P NMR spectroscopy in the crude product. The reactions were usually conducted at 20 °C; however, in the presence of electron-donating substituents [such as methyl (**2f**) and methoxy (**2h**) groups] on the aromatic ring of the benzyl nitrile substrate, a higher temperature (up to 40 °C) had to be applied (entries 8 and 11). Interestingly, even deactivated nitriles, such as **2h**, could be reacted (entry 14) without addition of $NaHCO_3$; however, in this case the reaction time had to be extended (cf. entries 13 and 14). In a typical process we have used 1.5 equiv of benzyl nitrile in order to achieve a full conversion of the imine substrate (**3**). On the other hand, in related transformations[1c−f,i] up to a 20-fold excess of organonitriles has commonly been used to complete the coupling reaction. As a result of the mild conditions and the high selectivity of the pincer-complex catalysis, many functional groups are tolerated. Aromatic iodo and bromo substituents (**2d**−**e**) survived the palladium pincer-complex catalyzed coupling without any change, affording **4e**−**f** and **4m**. These products are useful substrates for palladium(0) catalyzed Suzuki−Miyaura and Heck coupling reactions.[6]

The presented reactions usually provide the β-aminonitrile products with a high yield without elimination reactions, which otherwise readily occur using moderate or strong bases

Table 1. Pincer-Complex Catalyzed C−H Functionalization of Benzyl Nitriles with Sulfonylimines[a]

entry	substrates	temp[°C]/time[h]	cat.	product[b]	dr[c]	yield[d]
1	 **2a** **3a**	20/15	**1a**	 **4a**	2:1	99
2	**2a**  **3b**	20/3	**1a**	 **4b**[e]	1.5:1	99
3	 **2b**	**3a** 6/68	**1a**	 **4c**	4.6:1	95
4	 **2c**	**3a** 20/16	**1a**	 **4d**	8.4:1	99
5	 **2d**	**3a** 20/16	**1a**	 **4e**	10:1	83
6	 **2e**	**3a** 20/15	**1a**	 **4f**	10:1	99
7	**2e**	**3a** 20/16	**1b**	**4f**	10:1	70
8	 **2f**	**3a** 40/16	**1a**	 **4g**	4:1	92
9	 **2g**	**3a** 20/16	**1a**	 **4h**	4:1	84
10	**2g**	**3a** 6/68	**1a**	**4h**	8:1	88
11	 **2h**	**3a** 30/65	**1a**	 **4i**	5.6:1	91
12	 **2i**	**3a** 20/24	**1a**	 **4j**	10:1	83
13	**2h**  **3c**	20/16	**1a**	 **4k**	8.4:1	93
14[f]	**2h**	**3c** 20/66	**1a**	**4k**	6:1	92
15	 **2j**	**3c** 20/16	**1a**	 **4l**	3.4:1	74
16	**2d**	**3c** 6/72	**1a**	 **4m**	6.7:1	65
17	**2i**	**3c** 20/16	**1a**	 **4n**	17:1	95
18	**2a**  **3d**	20/18	**1a**	 **4o**	1.4:1	91

[a] Unless otherwise stated, nitrile **2** (0.3 mmol), **3** (0.2 mmol), $NaHCO_3$ (0.2 mmol) and catalyst **1** (5 mol %) in THF (0.3 mL) were stirred for the times and temperatures given. [b] Major diastereomer [c] Diastereomeric ratio (*syn*/*anti*). [d] Isolated yield. [e] Ar = 4-bromo-phenyl. [f] Performed without $NaHCO_3$.

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(6) Tsuji, J. *Palladium Reagents and Catalysts. New Perspectives for the 21st Century*; Wiley: Chichester, 2004.

as catalysts.[1h,3a,b] Using the parent benzyl nitrile **2a** and sulfonylimine **3a**, the reaction proceeds with poor stereoselectivity (entry 1). The reaction is accelerated in the presence of a *p*-bromo substituent (**3b**) in the imine component without a significant change of the stereoselectivity (entry 2) However, in the presence of *ortho* substituents in the benzyl nitrile substrate (**2b**−**j**), the stereoselectivity is considerably increased. The enhancement of the diastereoselectivity is significant for coupling of both the phenyl (**3a**) and vinyl (**3c**) imines. For iodo (**2e**), bromo (**2d**), and naphthyl (**2i**) derivatives (entries 5, 6, 12, and 17), the diastereomeric ratio is 10:1 or better. It is interesting to note that using classical base catalysis (LDA) without transition metal assistance, the α-naphthyl derivative **2i** did not react after 24 h at room temperature,[3c] whereas using pincer-complex catalysis (**1a**) the cooperative deprotonation with $NaHCO_3$ proceeds smoothly, providing the corresponding product in high selectivity and yield (entries 12 and 17). This also demonstrates the strong effect of the palladium-assisted enhancement of the acidity in the case of benzyl nitrile derivatives. As a result of this effect even aliphatic sulfonimines (such as **3d**) react without side reactions, affording the corresponding coupling product with high yield (entry 18).

We have also studied the nature of the substituent effects on the diastereoselectivity of the coupling reaction. As it appears from entries 1−6, the diastereoselectivity increases as one goes from electronegative *ortho* halogenides to electropositive ones (**2b** → **2e**) in the order of $F < Cl < Br \approx I$. As the carbon-halogen bond lengths increases in the same order, this trend suggests that the selectivity is increased with the steric bulkiness of the *ortho* substituent. Indeed, α-naphthyl nitrile **2i** gives about the same selectivity as bromophenyl (**2d**) and iodophenyl (**2e**) derivatives (entries 5, 6, and 12). However, benzyl nitriles with methyl (**2f**) and trifluoromethyl (**2g**) groups [which are apparently bulkier than the bromo (**2d**) and iodo (**2e**) groups] are substituted with lower selectivity (cf., entries 5, 6 with 8, 9). It is particularly interesting to compare the regioselectivity of the coupling reaction of **3c** with methoxy (**2h**) and trifluoromethoxy (**2j**) substituted benzyl nitrile derivatives (entries 13 and 15). Despite the fact that the trifluoromethoxy group is apparently bulkier than the methoxy group, the stereoselectivity is higher for substitution of **2h** than for **2j** (8.4:1 vs 3.4:1). The above findings clearly indicate that high diastereoselectivity can be achieved in the coupling reaction of sulfonylimines (**3a**−**c**) with *ortho*-substituted benzyl nitrile derivatives (such as **2d**−**e**). However, the selectivity is influenced by both the steric and electronic substituent effects.

All substituents generating high stereoselectivity (such as Cl, Br, I, and OMe) have relatively easily accessible lone-pair electrons, suggesting that the effects of the lone pairs are important in the stereo discrimination step of the reaction. This assumption is further supported by the finding (entries 13 and 15) that **2j** reacts with lower diastereoselectivity than **2h**. This can be ascribed to the fact that the electron-withdrawing trifluoromethyl group in **2j** decreases the orbital energy of the lone pairs on the oxygen atom, and thus the lone pairs are energetically less accessible in **2j** than in **2h**.

The high stereoselectivity achieved by the *ortho*-substitution of the benzyl nitrile substrate is a very attractive feature of the presented pincer-complex catalyzed coupling reaction, as in related processes, for example, using classical base (LDA) catalysis, the low diastereoselectivity is a particularly important problem.[3c] The low diastereoselectivity in the LDA catalyzed process is mainly due to the fast base catalyzed epimerization of the product.[3c] As in the present procedure a weak base (if any, e.g., entry 14) is employed, epimerization processes do not decrease the diastereoselectivity of the obtained products. Furthermore, the diastereoselectivity in the presented process is also much higher than in the pincer-complex catalyzed coupling of allyl nitriles and sulfonylimines.[1b] The allylic coupling reactions were also performed under mild conditions. However, the best diastereoselectivity achieved was 2:1 (versus 17:1 in the present benzyl nitrile based process). The higher selectivity can probably be ascribed to the fact that the difference in the size of the stereodiscriminating groups is larger in the case of benzyl nitrile than for allyl nitrile substrates. It was found that SCS pincer-complex **1b** catalyzes the coupling reaction with a lower activity than PCP complex **1a**; however, the diastereoselectivity of the two catalysts are identical (entries 6 and 7).

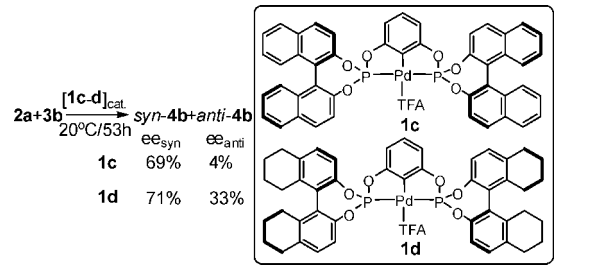

Figure 1. Preliminary studies for coupling of benzyl nitrile **2a** and sulfonylimine **3b** using chiral catalysts (3−5 mol %) **1c** (dr 1:1, yield 32%) and **1d** (dr 1.3:1, yield 99%).

Commonly used palladium(II) sources, such as $Pd(OAc)_2$ and $Pd(OCOCF_3)_2$, proved to be inactive in most of the presented processes. Formation of traces of product (with large amounts of byproducts) could be observed in the coupling reaction of **2e** and **3a** catalyzed by $Pd(OCOCF_3)_2$. Palladium(0) sources, such as $Pd_2(dba)_3$ proved to be completely inefficient as catalyst in the coupling reactions.

Our main interest in application of PCP complexes is also motivated by the fact that recently several chiral analogs[7] of PCP complex **1a** were reported in the literature, stimulat-

(7) (a) Aydin, J.; Kumar, K. S.; Sayah, M. J.; Wallner, O. A.; Szabó, K. J. *J. Org. Chem.* **2007**, *72*, 4689. (b) Wallner, O. A.; Olsson, V. J.; Eriksson, L.; Szabó, K. J. *Inorg. Chim. Acta* **2006**, *359*, 1767. (c) Aydin, J.; Rydén, A.; Szabó, K. J. *Tetrahedron: Asymmetry* **2008**, *19*, 1867. (d) Baber, R. A.; Bedford, R. B.; Betham, M.; Blake, M. E.; Coles, S. J.; Haddow, M. F.; Hurthouse, M. B.; Orpen, A. G.; Pilarski, L. T.; Pringle, P. G.; Wingad, R. L. *Chem. Commun.* **2006**, 3880.

ing the development of the asymmetric version of this process. Our preliminary results (Figure 1) indicate that chiral pincer-complex catalysts have a high potential to create chiral carbon−carbon bonds between benzyl nitriles (such as **2a**) and sulfonylimines (such as **3b**). The bulky chiral catalysts[8] **1c**−**d** showed lower catalytic activity than **1a**, and therefore we employed activated sulfonylimine substrate **3b** in the coupling reaction with **2a**. Complex **1d**[8] displayed somewhat higher selectivity and activity than the BINOL based complex **1c**. The reported (Figure 1) enantioselectivity (up to 71% ee) could be achieved without application of base. When $NaHCO_3$ was employed, the reaction became faster; however, the ee dropped slightly (by 7%). A particular advantage of using pincer-complex catalysis in this process is that the reaction can be conducted under base-free conditions. Without transition metal catalysis the analog coupling reaction requires the use of strong base (LDA), which rapidly racemizes the product,[3c] and thus chiral β-aminonitrile products cannot be obtained in this way.

Based on the mechanistic proposals for the transition metal assisted deprotonation reactions appearing in the literature[1c−f,j] and in our previous studies[1b] on the pincer complex catalyzed allylation reactions, a plausible catalytic cycle (Figure 2) was constructed. Accordingly, the first step of the transformation is coordination of benzyl nitrile **2a** to the palladium atom of **1a** affording complex **5**. The next step is α-deprotonation of **5** to give complex **6**. The deprotonation is facilitated by the coordinated palladium atom, which helps to delocalize the generated negative charge on the pincer complex. This stabilization allows the use of very weak bases (such as $NaHCO_3$) instead[3c] of LDA. Furthermore, spontaneous deprotonation may also occur under base-free conditions (entry 14, Table 1, and the reaction in Figure 1). For complex **6** an alternative mode of coordination can also be considered. Instead of the zwitterionic structure (as in **6**) a direct carbon metal bond may also be formed between the benzyl anion and the palladium atom.[1b,j] The next step is coupling of the palladium coordinated α-cyano carbanion with sulfonylmine to give **7**, which subsequently undergoes protonation and decomplexation to give the final product **4**, regenerating the catalyst **1a**. The stereochemistry of the reaction is determined in the **6** → **7** step of the catalytic cycle.

The presented results (Table 1) indicate that the diastereoselectivity is influenced by both electronic and steric

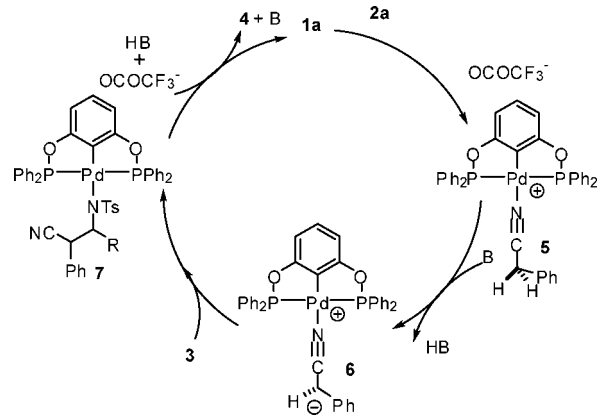

Figure 2. Plausible mechanism of the coupling between benzyl nitriles and sulfonylimines.

effects of the *ortho* substituents. We have previously shown[9] that the stereoselectivity in allylation of sulfonylimines is determined by complicated interactions between the reactant and the pincer-complex catalyst (generating a large number of possible TS structures), and therefore full rationalization of the stereochemistry in the presented procedure requires in-depth DFT modeling studies, which are in progress.

In summary, we have presented the first transition metal catalyzed coupling of benzyl nitriles with sulfonylimines. The reaction has a very broad synthetic scope and it proceeds with high stereoselectivity with *ortho*-substituted substrates. The presented process offers a simple and efficient route for synthesis of functionalized β-aminonitriles, which are useful building blocks for pharmaceuticals and natural products, such as β-amino acids and 1,3-diamines.[2]

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Supporting Information Available: Experimental procedures, NMR data, and ^1H and ^{13}C NMR spectra of products **4a**−**n** and **1d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For synthesis of **1c** see ref 7a–b, while preparation of **1d** is given in the Supporting Information of this paper.

(9) Wallner, O. A.; Szabó, K. J. *Chem. Eur. J.* **2006**, *12*, 6976.