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Copper Acetoacetonate [Cu(acac)$_2$]/BINAP-Promoted Csp^3–N Bond Formation *via* Reductive Coupling of *N*-Tosylhydrazones with Anilines

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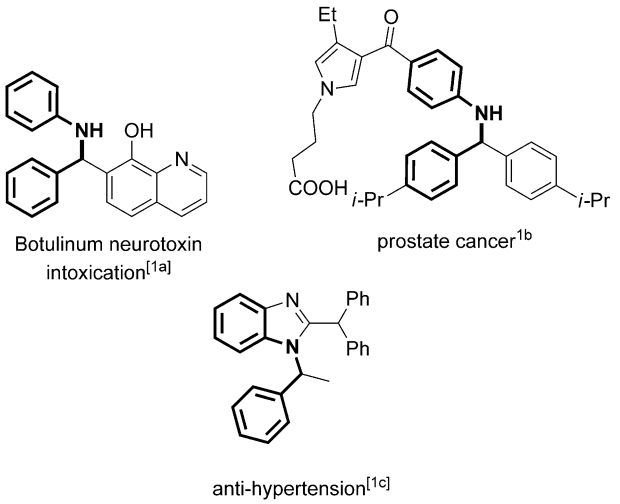
Abstract: We report the the copper(II) acetoacetonate [Cu(acac)$_2$]/BINAP-catalyzed synthesis of arylamines from *N*-tosylhydrazones and anilines. A fine tuning of the reaction conditions was required to accomplish the cross-coupling successfully, including the ligands effect and the addition of small amounts of water. The characteristic feature of this protocol is its functional group compatibility and its chemoselectivity when various aminophenol derivatives were used. Taking into consideration the interest for this copper-reductive coupling in which no stoichiometric metal hydride reagent is employed, this can be considered as an alternative to the conventional reductive amination.

Keywords: carbenoid insertion; copper; Csp^3–N bond formation; *N*-tosylhydrazones; synthetic methods

Introduction

α-Branched arylamines are very important building blocks for drug discovery. Figure 1 shows representative examples of bioactive molecules containing this motif with various pharmacological properties.[1] It is not surprising that numerous synthetic methodologies to access such compounds have been explored in the past decades.[2] The most common method to prepare amines is the reduction of imino C=N bonds.[2a,e,h,i] However, imines are not always easy to synthesize and have limited stability. Tremendous efforts have been devoted to the development of efficient reductive amination reactions. The choice of the reducing agent is very critical to the success of the reaction and the progress is far from satisfactory.[2a,c,d] Transition metal-catalyzed hydrogenation may be incompatible with substrates containing reducible functional groups (e.g., CN, NO_2, C=C).[3] The use of sodium cyanoborohydride as the reductant requires an excess of reagent (up to 5-fold)[4] and produces toxic cyanides as by-products upon work-up.[5] The alternative sodium triacetoxyborohydride has not been successful for aromatic and unsaturated carbonyl compounds.[6] Other reported reductive amination reagents include BH_3-pyridine,[7] $Zn(BH_4)_2$-$ZnCl_2$,[8] $NaBH_4$-$NiCl_2$,[9] $NaBH_3CN$-Ti(O-*i*-Pr)$_4$,[10] Bu_3SnH,[11] or Et_3SiH-TFA.[12] All these methods require stoichiometric or excess of metal hydrides, therefore, the development of alternative and general protocols for the preparation of α-branched arylamines that does not require the use of metal hydrides, is highly desirable.[13]

N-Tosylhydrazones, easily prepared from aldehydes or ketones, have emerged as a new type of cross-coupling partner in organometallic chemistry.[14] They have been extensively employed as a source for the safe generation of diazo compounds and carbenes to

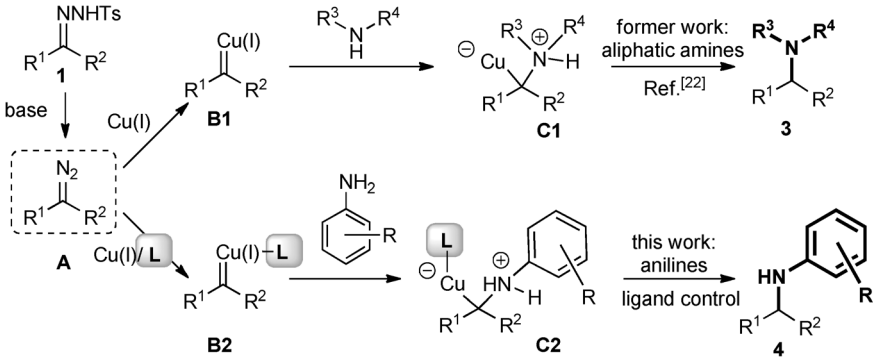


Botulinum neurotoxin intoxication[1a]

prostate cancer[1b]

anti-hypertension[1c]

Figure 1. Representative α-branched arylamines.



Scheme 1. Reductive coupling of *N*-tosylhydrazones with amines.

merge with different types of transition metal-catalyzed transformations. Elegant methods using *N*-tosylhydrazones as a coupling partner in C–C bond formation include their reactions with aryl halides,[15] aryl sulfonates,[16] alkynes,[17] azoles,[18] arylboronic acids,[19] benzylic halides,[20] isocyanides,[21] etc.

Recently, we described a copper-catalyzed C–N bond-forming reaction between *N*-tosylhydrazones **1** and primary or secondary aliphatic amines, giving rise to the reductive coupling products **3** (Scheme 1).[22]

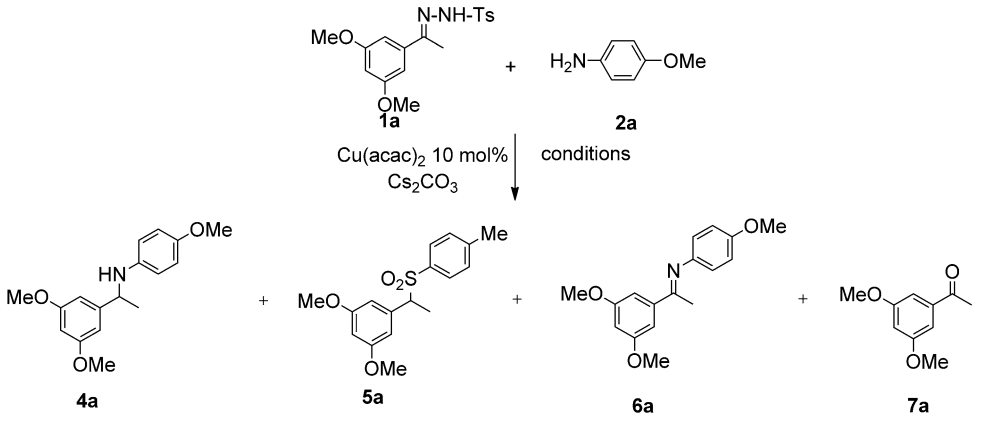
The mechanism proposed for this reaction comprises the following steps: (i) decomposition of the hydrazone **1** under basic and thermal conditions to form *in situ* the diazo compound **A**; (ii) loss of nitrogen then delivers the copper(I)-carbene complex **B1**; (iii) N–H insertion on the carbene center might take place to produce copper ylide species **C1**; and (iv) a subsequent 1,2-proton shift produces the reductive coupling products **3**.

Although this reductive coupling proceeds very efficiently with primary and secondary aliphatic amines, to our disappointment, no reaction occurred between hydrazones and anilines. For instance, when reacting **1a** with **2a** under our previous optimized conditions,[22] the reductive coupling product **4a** was not detected (Table 1, entry 1). Careful analysis by NMR showed the presence of significant amounts of three by-products: (i) the sulfone **5a**,[23] (ii) imine **6a**,[24] and (iii) ketone **7a**. To promote the formation of **4a** from anilines, which are less nucleophilic than aliphatic amines, we postulated that the use of effective ancillary ligands could be a prerequisite in order to control the coordination sphere of the copper catalyst.[25] The electronic interaction between the copper and the ligand should improve the reactivity and selectivity of the copper(I)-carbenoid **B2** in the N–H insertion reaction.[26] A judicious choice of a copper-ligand system to facilitate the formation of ylide **C2** from **B2** is thus required to fit into the narrow requirements of the process. Taking into consideration the interest of this copper-reductive coupling in which no stoichiometric metal hydride reagent is employed, herein, we report a general protocol for the reductive coupling of *N*-tosylhydrazones with anilines using a copper salt/BINAP combination as a versatile catalytic system.

Results and Discussion

In order to test the reactivity of hydrazones **1** and anilines **2**, an extensive screening of copper sources, bases, solvents and ligands was carried for the coupling of hydrazone **1a** with *p*-anisidine **2a** (Table 1).[27] A number of Cu(I) and Cu(II) salts were applied in this reductive coupling reaction, among them, Cu-$(acac)_2$ gave the superior result. The screening was continued with respect to the solvent. Among several solvents tested (toluene, MeCN and THF), PhF revealed to be the best solvent. When the coupling was achieved at 120 °C in PhF the desired product **4a** was obtained in a 40% isolated yield (Table 1, entry 2). In view of the finding that, in transition metal-catalyzed X–H insertions, water can act as an efficient proton-transport catalyst for the ylide 1,2-H shift process,[28] we realized the coupling in the presence of H_2O (25 equiv.) as a protic additive. Under these conditions, the yield of **4a** was strikingly improved to 58%, and formation of imine **6a** was significantly diminished (entry 3).[29] Then, we turned to a combination of the copper catalyst with different ligands. Although diamino type ligands such as DMEDA, TMEDA, and 1,10-phenanthroline did not give any improvement on the yield of the desired product, however, we are delighted to find that the use of phosphine ligands markedly improved the yield of **4a**. The best results were obtained with PPh_3 and *rac.* BINAP offering **4a** in 78% and 85% isolated yields, respectively (entries 4 and 5). A control experiment, under metal-free conditions,[30] shows that no product **4a** was detected. It should be noted that the coupling of hydrazone **1a** with *p*-anisidine **2a** is not limited to a small scale (0.57 mmol) as it could be conveniently performed on

Table 1. Preliminary experiments of reductive coupling of *N*-tosylhydrazone **1a** with *p*-anisidine **2a**.[a]



Entry	Conditions	Ratio [b] **4a/5a/6a/7a**	Yield[c] **4a**
1	dioxane/100 °C	-/50/35/15	-
2	PhF/120 °C	55/10/30/5	40%
3	PhF/H_2O/120 °C	68/17/10/5	58%
4	PPh_3 20 mol%/PhF/H_2O/120 °C	85/5/7/3	78%
5	*rac.* BINAP 10 mol%/PhF/H_2O/120 °C	90/5/5/-	85%[d]

[a] *Reaction conditions: N*-tosylhydrazone **1a** (1 equiv.), amine **2a** (1.5 equiv.), $Cu(acac)_2$ (10 mol%), Cs_2CO_3 (2.5 equiv.), solvent (2.5 mL) in a sealed tube at 120 °C for 2 h.

[b] Ratio was determined by ^1H NMR in the crude reaction mixture, see the Supporting Information.

[c] Yield of isolated product **4a**.

[d] Performing the reaction in the presence of $Cu(acac)_2$ (5 mol%) and *rac.* BINAP (5 mol%) led to 75% of **4a**.

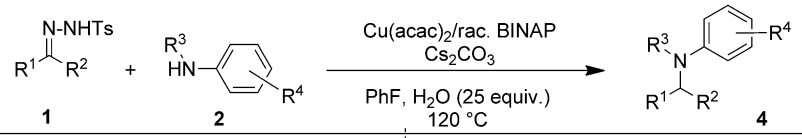
a 2 g scale for **1a** (5.74 mmol), giving rise to an 80% yield of **4a**.

With the optimized reaction conditions in hand (Table 1, entries 4 and 5), the substrate scope was investigated (Table 2). Examples **4a–f** demonstrate the superiority of the bidentate ligand, *rac.* BINAP in comparison to the monodentate PPh_3, especially in the case of electron-poor anilines (compounds **4d–f**). These observations highlight the ability of ligands to dictate the course of the catalytic reactions. Table 2 shows selected examples of anilines insertion products (**4a–y**) which were obtained efficiently by using *rac.* BINAP ligand. The reaction is very general with respect to the structure of anilines and hydrazones. Regardless of the electronic nature of the substituents on the aniline or hydrazone partners (electron-withdrawing or electron-donating group), the reaction proceeded with similar yields (compounds **4a–f** and compounds **4k**, **4l**, **4q**, **4u** and **4v**). The reaction does not display any dependence upon steric hindrance either on the aniline or hydrazone moieties. *ortho*-Anilines and sterically hindered hydrazones reacted completely and effectively in 2 h (compounds **4b** and **4i**). The high functional group tolerance of the reaction must be noted, i.e., it can be carried out in the presence of a nitrile group (**4e**, **4k** and **4l**), and even a hydroxy group (*vide infra*).

Coupling of *N*-alkylanilines, constitutes a challenging issue, since they are an example of poor NH nucleophiles in metal-catalyzed cross-coupling. The problem is not the diminished NH acidity but rather the steric congestion around the nitrogen center. We are pleased to find that under our optimized conditions, satisfactory to good yields were obtained with these secondary amines (compounds **4m–o**).

The present catalytic system was found to be equally successful in the coupling of heterocyclic anilines or hydrazones (compounds **4p** and **4q**). The scope of the coupling reaction can be extended to *N*-tosylhydrazones derived from benzophenones and benzyl ketones (compounds **4r–w**). One can note a slight improvement of the yield of compounds **4s–w** with hydrazones derived from benzophenones in comparison to those derived from acetophenones. To broaden the scope of substrates, we further investigated this coupling reaction with tosylhydrazones derived from aldehydes. We found that the reactions could also be carried out by the same copper/BINAP catalytic

Table 2. Cu/BINAP-catalyzed reaction of *N*-tosylhydrazones with anilines.[a]



1 2 4

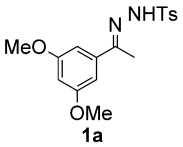
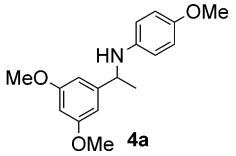
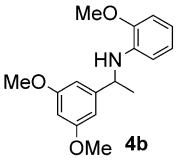
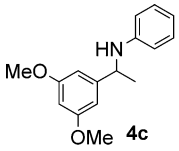
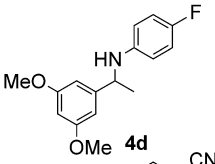
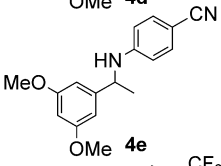
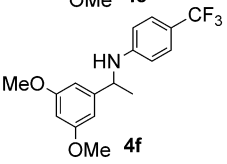
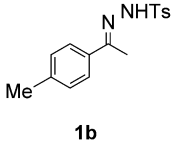
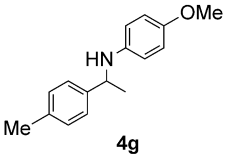
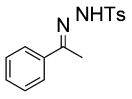
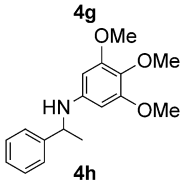
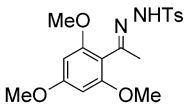
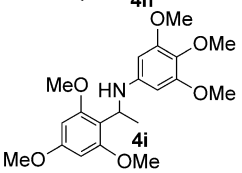
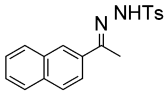
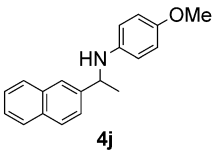
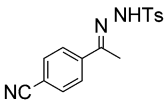
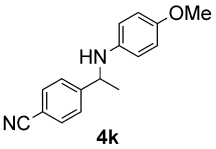
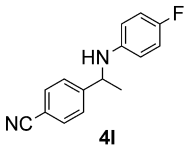
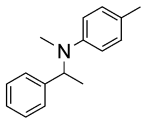
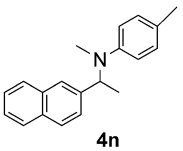
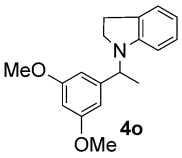
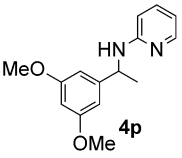
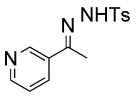
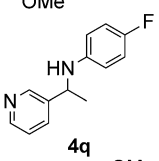
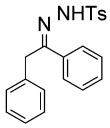
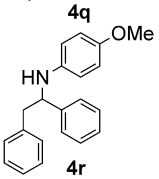
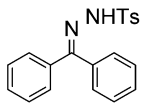
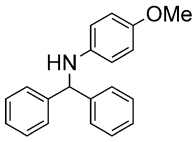
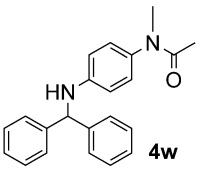
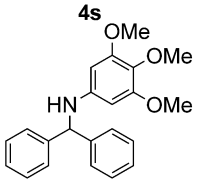
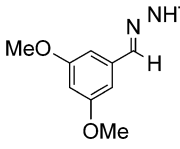
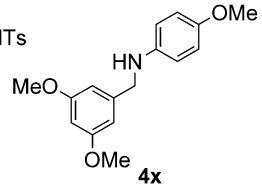
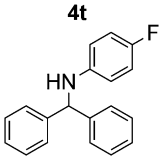
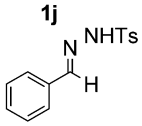
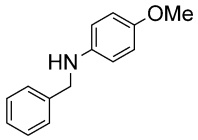
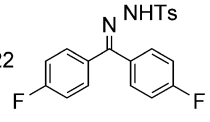
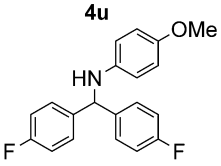
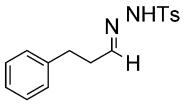
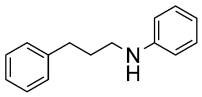
Entry	Hydrazone	Product	Yield[b]
1	 **1a**	 **4a**	85% 78%[c]
2	**1a**	 **4b**	82% 60%[c]
3	**1a**	 **4c**	70% 58%[c]
4	**1a**	 **4d**	85% 30%[c]
5	**1a**	 **4e**	78% 40%[c]
6	**1a**	 **4f**	83% 20%[c]
7	 **1b**	 **4g**	71%
8	 **1c**	 **4h**	86%
9	 **1d**	 **4i**	65%
10	 **1e**	 **4j**	80%
11	 **1f**	 **4k**	84%
12	**1f**	 **4l**	66%
13	**1c**	 **4m**	58%
14	**1e**	 **4n**	78%
15	**1a**	 **4o**	75%
16	**1a**	 **4p**	62%
17	 **1g**	 **4q**	68%
18	 **1h**	 **4r**	74%

Table 2. (Continued)

Entry	Hydrazone	Product	Yield[b]	Entry	Hydrazone	Product	Yield [b]
19	 **1i**	 **4s**	93%	23	**1i**	 **4w**	79%
20	**1i**	 **4t**	91%	24	 **1j**	 **4x**	55%[d]
21	**1i**	 **4u**	82%	25	 **1k**	 **4y**	50%[d]
22	 **1i**	 **4v**	72%	26	 **1l**	 **4z**	-

[a] *Reaction conditions: N*-tosylhydrazones **1** (1 equiv.), amines **2** (1.5 equiv.), Cu(acac)$_2$ (10 mol%), *rac.* BINAP (10 mol%), Cs_2CO_3 (2.5 equiv.), H_2O (25 equiv.), PhF (2.5 mL) in a sealed tube at 120 °C for 2 h.

[b] Isolated yield of compounds **4** after column chromatography.

[c] PPh_3 was used as the ligand instead of BINAP.

[d] Reaction was performed at 80 °C and K_2CO_3 was used as the base instead of Cs_2CO_3.

system, but the use of K_2CO_3 as the base in this case gives a better result compared with Cs_2CO_3; α-branched arylamines (compounds **4x** and **y**) were obtained in moderate yields. Unfortunately, when a tosylhydrazone derived from an aliphatic aldehyde was reacted with aniline, none of the desired product **4z** was detected.

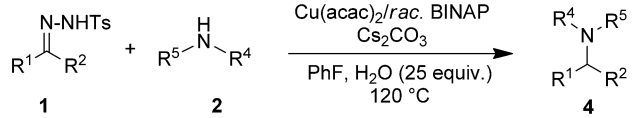
Although we have shown in our previous work that aliphatic amines and azoles[22] reacted with tosylhydrazones in the absence of ligand, we next investigated their reactivity under our novel protocol.

As depicted in Table 3, we demonstrated that the use of our new conditions led to a significant improvement of the yield of the cross-coupling, this was proved with derivatives of the benzylamine-type, but also with other azoles[22,31] (compounds **4aa**–**4ah**).

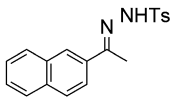
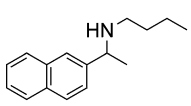
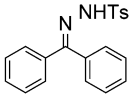
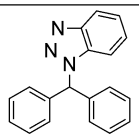
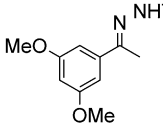
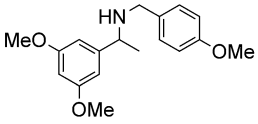
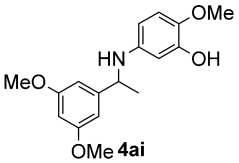
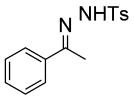
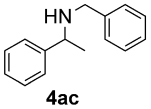
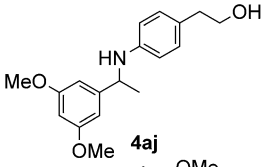
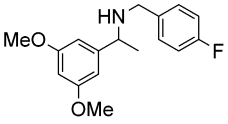
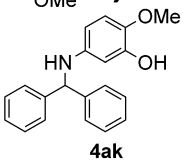
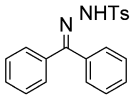
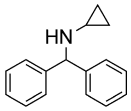
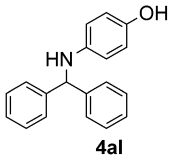
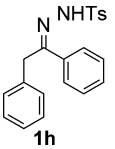
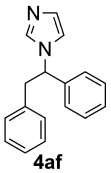
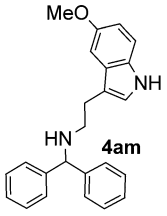
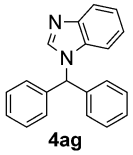
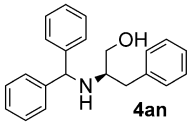
To extend the scope of this protocol, we further investigated the reaction selectivity issue between hydrazones and anilines containing phenol or alcohol group (C–N versus C–O bond forming reaction, Table 3). This study was anticipated to be a potential challenge to overcome, since Barluenga and Valdes group demonstrated that the base-promoted decomposition of tosylhydrazones in the presence of phenols resulted in the O–H bond insertion into the resulting carbene.[30b] When Cu(acac)$_2$/*rac.* BINAP combination as a catalytic system was applied, we observed high selectivity leading exclusively to C–N bond forming reaction; no C–O products were detected by ^{1}H NMR analysis of the crude reaction mixture. Secondary amines **4ai–4an** were obtained in good isolated yields. Next, we examined the selectivity issue between aliphatic amine and N–H azole. As expected, the C–N bond forming reaction took place exclusively at the more nucleophilic and non-steric aliphatic amine of 5-methoxytryptamine (compound **4am**). Then, we turned our attention to the reaction of a hydrazone derived from benzophenone and an amino alcohol containing a chiral center [(*S*)-2-amino-3-phenylpropan-1-ol]. To our delight, we observed in this case, a total regioselectivity in favor of the C–N bond-forming reaction, and the resulting amine product **4an** was obtained with high yield and 98% *ee*; therefore, no erosion of the chirality had occurred (Table 3).

Since this reaction is carried out in the presence of BINAP as the ligand, this opens the way for an enantioselective version of the coupling. Thus, we realized

Table 3. Cu/BINAP catalyzed reaction of *N*-tosylhydrazones with various amines.[a]



1 2 4

Entry	Hydrazone	Product	Yield[b]	Entry	Hydrazone	Product	Yield [b]
1	 **1e**	 **4aa**	82% 50%[c]	8	 **1i**	 **4ah**	55% 40%[c]
2	 **1a**	 **4ab**	75% 42%[c]	9	**1a**	 **4ai**	72%
3	 **1c**	 **4ac**	87% 53%[c]	10	**1a**	 **4aj**	72%
4	**1a**	 **4ad**	60% 35%[c]	11	**1i**	 **4ak**	92%
5	 **1i**	 **4ae**	80%	12	**1i**	 **4al**	85%
6	 **1h**	 **4af**	56% 35%[c]	13	**1i**	 **4am**	77%
7	**1i**	 **4ag**	70% 64%[c]	14	**1i**	 **4an**	84%[d]

[a] *Reactions conditions: N*-tosylhydrazone **1** (1 equiv.), amine **2** (1.5 equiv.), $Cu(acac)_2$ (10 mol%), *rac.* BINAP (10 mol%) Cs_2CO_3 (2.5 equiv.), H_2O (25 equiv.), PhF (2.5 mL) in a sealed tube at 120 °C for 2 h.

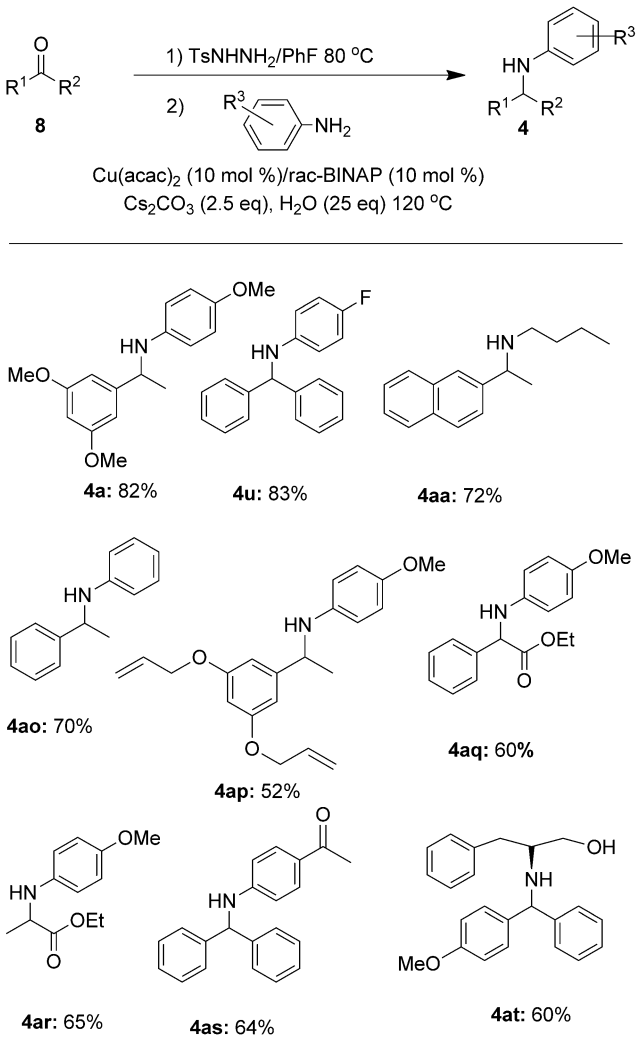
[b] Isolated yield of compounds **4** after column chromatography.

[c] Reaction was performed without ligand in dioxane.

[d] 98% *ee* determined by HPLC on a chiral stationary phase type: Chiralcel Column OD.

the coupling between tosylhydrazone **1a** and amine **2a** in the presence of (*S*)- and (*R*)-BINAP; unfortunately, under our standard conditions, no control of the enantioselectivity was observed. Other chiral bidendate phosphines (JoSPOphos-type ligand) were also tested and a racemic mixture was always obtained.

As sulfonylhydrazones could be simply prepared by mixing the related sulfonylhydrazides and the carbonyl compounds, we investigated whether the reaction could be carried out in a one-pot fashion directly from carbonyl compounds **8**, avoiding the isolation of the tosylhydrazone intermediates **1**.



Scheme 2. Examples of the one-pot procedure.

We were pleased to successfully achieve this one-pot protocol, yields similar to those obtained from hydrazones **1** were achieved (Scheme 2). A compound containing an allyl function was coupled successfully (compound **4ap**). Good results were also obtained with α-keto ester derivatives such as phenyl- or methylglyoxylate ethyl ester (compounds **4aq** and **4ar**). In addition, the optimized conditions allow *para*-carbonyl-substituted aniline to react efficiently giving rise to **4as** in a good 64% isolated yield.

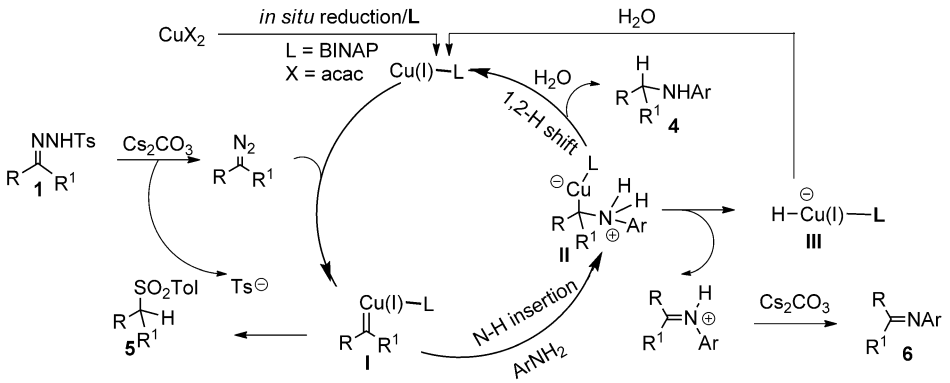
This result clearly demonstrates that this protocol is chemoselective towards a carbenoid N–H insertion rather than the condensation of aniline with the ketone group. Finally, we performed the coupling between an unsymmetrical benzophenone and (*S*)-2-amino-3-phenylpropan-1-ol in order to examine the diastereoselectivity at the new C–N bond. However, no enantiomeric control was observed using our standard conditions. In fact, product **4at** was obtained in an equimolar mixture of the two diastereomers.

A tentative rationale mechanism for the Cu/BINAP catalysis in the reductive coupling of *N*-tosylhydrazones with anilines is depicted in Scheme 3.

Initially, *N*-tosylhydrazone **1** in basic media undergoes thermal decomposition through the Bamford–Stevens reaction to generate a diazo compound. This latter would react with copper(I) species to give the Cu(I) carbene complex **I**. Further copper carbene N–H insertion might proceed with attack of the nitrogen atom on the electrophilic carbene to generate copper species **II**. Ligand BINAP may preclude β-elimination from copper ylide **II** to form hydride species **III** together with iminium intermediate, precursor of imine **6**.[24] In addition, water can act as an efficient proton-transport catalyst for the ylide 1,2-H shift process, as was previously reported.[28]

Conclusions

In conclusion, we have successfully developed the first copper/BINAP-catalyzed reductive coupling of *N*-tosylhydrazones with anilines for the rapid construction of α-branched arylamines. This catalytic system performs well over a broad scope of sub-



Scheme 3. Proposed mechanism for the Cu/BINAP-promoted Csp^3–N bond formation *via* reductive coupling of *N*-tosylhydrazones with anilines.

strates, allowing the coupling to be chemoselective and tolerates a variety of functional groups. This reductive coupling reaction can be envisioned as a new type of amination of carbonyl compounds through tosylhydrazones without the use of any metal hydride. For the reasons above, and taking into consideration the generality of the process, and the ready availability of both types of coupling partners, we believe that these reactions may be very useful in organic synthesis.

Experimental Section

General Procedure for Copper-Catalyzed Reductive Coupling of *N*-Tosylhydrazones Derived from Acetophenones or Benzophenones with Amines

The reactions were carried out in a sealed tube with *N*-tosylhydrazone **1** (200 mg, 1.0 equiv.), $Cu(acac)_2$ (10 mol%), *rac*-BINAP (10 mol%), Cs_2CO_3 (2.5 equiv.), the amine (1.5 equiv.) then 3 mL of fluorobenzene and 25 equiv. H_2O were successively added *via* syringe at room temperature. The tube was sealed and put into a pre-heated oil bath at 120 °C for 2 h. The crude reaction mixture was allowed to cool to room temperature. EtOAc was added to the mixture, which was filtered through celite. The solvents were evaporated under reduced pressure and the crude residue was purified by flash chromatography on neutralized silica gel (2% triethylamine). The chiral column used was Chiralcel OD-H (DAIC, 4.6×250 mm). The solvent used was hexane/isopropanol (98:2) at a flow rate of 1 mL min^{-1} and the absorbance monitored using a PDA detector at 240 nm.

***N*-[1-(3,5-Dimethoxyphenyl)ethyl]-2-methoxyaniline (4b):** Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 90/10) afforded **4b** as a yellow oil; yield: 135 mg (0.47 mmol, 82%); M = 287.35 g mol^{-1}; R_f = 0.54 (cyclohexane/ethyl acetate 80/20); IR (film): ν = 2836, 1593, 1511, 1453, 1427, 1372, 1345, 1311, 1290, 1251, 1222, 1203, 1178, 1152, 1129, 1107, 1066, 1051, 1026, 926 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.77 (ddd, *J* = 15.1, 7.7, 1.5 Hz, 2H), 6.65 (td, *J* = 7.7, 1.5 Hz, 1H), 6.59 (d, *J* = 2.2 Hz, 2H), 6.43 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.37 (t, *J* = 2.2 Hz, 1H), 4.68 (bs, 1H), 4.42 (q, *J* = 6.7 Hz, 1H), 3.91 (s, 3H), 3.80 (s, 6H), 1.58 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.2 (2C), 148.6 (C), 146.7 (C), 137.4 (C), 121.3 (CH), 116.6 (CH), 111.3 (CH), 109.4 (CH), 104.0 (2CH), 98.6 (CH), 55.5 (OCH_3), 55.3 (2OCH_3), 53.9 (CH), 25.1 (CH_3); HR-MS (ESI): *m/z* = 288.1598 $(M+H)^+$, calculated for $C_{17}H_{22}NO_3$: 288.1600.

***N*-[1-(3,5-Dimethoxyphenyl)ethyl]aniline (4c):** Flash chromatography on neutralized silica gel (cyclohexane/ethyle acetat 90/10) afforded **4c** as a white solid; yield: 103 mg (0.40 mmol, 70%); M = 257.33 g mol^{-1}; mp 97–99 °C; R_f = 0.47 (cyclohexane/ethyle acetate 80/20); IR (film): ν = 3408, 2962, 2836, 1596, 1505, 1459, 1428, 1373, 1346, 1320, 1289, 1257, 1203, 1153, 1065, 1052, 1023, 993, 925 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10 (t, *J* = 7.9 Hz, 2H), 6.67 (t, *J* = 7.3 Hz, 1H), 6.54 (m, 4H), 6.34 (t, *J* = 2.2 Hz, 1H), 4.40 (q, *J* = 6.7 Hz, 1H), 3.77 (s, 6H), 1.51 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.2 (2C), 148.2 (C), 147.3 (C), 129.2 (2CH), 117.6 (CH), 113.6 (2CH), 104.1 (2CH), 98.7 (CH), 55.4 (2OCH_3), 54.1 (CH), 25.0 (CH_3); HR-MS (ESI): *m/z* = 258.1493 $(M+H)^+$, calculated for $C_{16}H_{20}NO_2$: 258.1494.

***N*-[1-(3,5-Dimethoxyphenyl)ethyl]-4-fluoroaniline (4d):** Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 90/10) afforded **4d** as a yellow oil; yield:134 mg (0.49 mmol, 85%); M = 275.32 g mol^{-1}; R_f = 0.53 (cyclohexane/ethyle acetate 80/20); IR (film): ν = 2838, 1610, 1594, 1508, 1457, 1428, 1373, 1345, 1309, 1290, 1254, 1221, 1203, 1152, 1125, 1066, 1053, 1024, 908 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.81 (t, *J* = 8.8 Hz, 2H), 6.54 (d, *J* = 2.1 Hz, 2H), 6.45 (dd, *J* = 8.8, 4.4 Hz, 2H), 6.35 (t, *J* = 2.1 Hz, 1H), 4.33 (q, *J* = 6.7 Hz, 1H), 3.78 (s, 6H), 1.50 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.2 (2C), 157.4–154.3 (C, $^1J_{C,F}$ = 234.9 Hz), 148.1 (C), 143.7 (C), 115.7–115.4 (2CH, $^2J_{C,F}$ = 22.3 Hz), 114.3–114.2 (2CH, $^3J_{C,F}$ = 7.6 Hz), 104.0 (2CH), 98.7 (CH), 55.4 (2OCH_3), 54.5 (CH), 25.1 (CH_3); ^{19}F NMR (188 MHz, $CDCl_3$): δ = −128.3; HR-MS (ESI): *m/z* = 276.1402 $(M+H)^+$, calculated for $C_{16}H_{19}FNO_2$: 276.1400.

4-[1-(3,5-Dimethoxyphenyl)ethylamino]benzonitrile (4e): Flash chromatography on neutralized silica gel (cyclohexane/ethyle acetat 90/10) afforded **4e** as a colorless oil; yield: 127 mg (0.45 mmol, 78%); M = 282.34 g mol^{-1}; R_f = 0.7 (cyclohexane/ethyl acetate 50/50); IR (film): ν = 3485, 3378, 3352, 3203, 2835, 2343, 2318, 2212, 2177, 2154, 2070, 2046, 1607, 1522, 1461, 1428, 1336, 1204, 1174, 1155, 1053 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 8.9 Hz, 2H), 6.54–6.40 (m, 4H), 6.35 (t, *J* = 2.2 Hz, 1H), 4.54 (bs, 1H), 4.43 (q, *J* = 6.7 Hz, 1H), 3.77 (s, 6H), 1.53 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.4 (2C), 150.3 (C), 146.6 (C), 133.7 (2CH), 120.5 (2C), 113.2 (2CH), 104.0 (2CH), 98.8 (CH), 55.5 (2OCH_3), 53.6 (CH), 24.7 (CH_3); HR-MS (ESI): *m/z* = 283.1441 $(M+H)^+$, calculated for $C_{17}H_{19}N_2O_2$: 283.1447.

***N*-[1-(3,5-Dimethoxyphenyl)ethyl]-4-(trifluoromethyl)aniline (4f):** Flash chromatography on neutralized silica gel (Ccyclohexane/ethyl acetate 90/10) afforded **4f** as a white solid; yield: 155 mg (0.48 mmol, 83%); M = 325.33 g mol^{-1}; mp 96–98 °C; R_f = 0.56 (cyclohexane/ethyl acetate 70/30); IR (film): ν = 3495, 3425, 3393, 3296, 1617, 1593, 1530, 1458, 1429, 1316, 1265, 1204, 1188, 1152, 1102, 1064, 1051, 1024, 925 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 8.6 Hz, 2H), 6.58–6.48 (m, 4H), 6.36 (t, *J* = 2.2 Hz, 1H), 4.43 (q, *J* = 6.7 Hz, 1H), 3.78 (s, 6H), 1.53 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.3 (2C), 149.6 (C), 147.2 (C), 130.5–126.9–123.3 (t, $^1J_{C,F}$ = 270.41 Hz, C), 126.6 (q, $^3J_{C,F}$ = 3.8 Hz, 2CH), 119.2–118.8 (d, $^2J_{C,F}$ = 32.4 Hz, C), 112.7 (2CH), 104.00 (2CH), 98.7 (CH), 55.4 (2OCH_3), 53.7 (CH), 24.8 (CH_3); ^{19}F NMR (188 MHz, $CDCl_3$): δ = −59.12; HR-MS (ESI): *m/z* = 326.1365 $(M+H)^+$, calculated for $C_{17}H_{19}F_3NO_2$: 326.1368.

4-Methoxy-*N*-[1-(2,4,6-trimethoxyphenyl)ethyl]aniline (4i): Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 90/10) afforded **4i** as a yellow oil; yield: 109 mg (0.34 mmol, 65%); M = 317.38 g mol^{-1}; R_f = 0.53 (cyclohexane/ethyl acetate 70/30); IR (film): ν = 2835, 1608, 1589, 1510, 1467, 1452, 1416, 1369, 1316, 1290, 1234, 1222, 1203, 1180, 1152, 1114, 1082, 1060, 1038, 1018, 951, 909 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.69 (d, *J* = 9.1 Hz, 2H), 6.63 (d, *J* = 9.1 Hz, 2H), 6.09 (s, 2H), 5.11 (q,

J=6.9 Hz, 1H), 3.84 (s, 6H), 3.76 (s, 3H), 3.70 (s, 3H), 1.49 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=159.8 (C), 158.9 (2C), 152.0 (C), 142.4 (C), 115.4 (2CH), 114.6 (2CH), 112.8 (C), 91.1 (2CH), 55.8 (2OCH_3), 55.7 (OCH_3), 55.3 (OCH_3), 45.0 (CH), 20.7 (CH_3); HR-MS (ESI): m/z= 318.1529 $(M+H)^+$, calculated for $C_{18}H_{24}NO_4$: 318.1527.

4-Methoxy-*N*-[1-(naphthalen-2-yl)ethyl]aniline (4j): Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 95/5) afforded **4j** as a yellow oil; yield: 131 mg (0.47 mmol, 80%); M=277.36 g mol^{-1}; R_f=0.69 (cyclohexane/ethyl acetate 70/30); IR (film): ν=3055, 2831, 1732, 1601, 1510, 1465, 1440, 1373, 1326, 1294, 1233, 1178, 1133, 1037 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.83 (dd, J=8.7, 5.0 Hz, 4H), 7.62–7.39 (m, 3H), 6.70 (d, J=9.0 Hz, 2H), 6.54 (d, J=9.0 Hz, 2H), 4.59 (q, J=6.7 Hz, 1H), 3.69 (s, 3H), 1.59 (d, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=153.1 (C), 141.8 (C), 139.7 (C), 133.6 (C), 133.0 (C), 128.6 (CH), 128.0 (CH), 127.8 (CH), 126.1 (CH), 125.7 (CH), 125.0 (CH), 124.7 (CH), 116.2 (2CH), 114.9 (2CH), 56.0 (CH), 55.8 (OCH_3), 24.5 (CH_3); HR-MS (ESI): m/z= 278.1546 $(M+H)^+$, calculated for $C_{19}H_{20}NO$: 278.1545.

4-[1-(4-Fluorophenylamino)ethyl]benzonitrile (4l): Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 90/10) afforded **4l** as a yellow oil; yield: 101 mg (0.42 mmol, 66%); M=240.28 g mol^{-1}; R_f=0.46 (cyclohexane/ethyl acetate 70/30); IR (film): ν=3456, 3436, 3413, 3373, 3082, 2228, 1609, 1505, 1315, 1257, 1221, 1206, 1142, 1018, 839, 818, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.61 (d, J=8.3 Hz, 2H), 7.47 (d, J=8.3 Hz, 2H), 6.80 (t, J= 8.8 Hz, 2H), 6.38 (m, 2H), 4.45 (q, J=6.8 Hz, 1H), 1.51 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=157.64–154.52 (C, $^1J_{C,F}$=235.8 Hz), 150.9 (C), 143.0 (C), 132.7 (2CH), 126.8 (2CH), 119.0 (C), 115.8 (2CH, $^2J_{C,F}$=22.4 Hz), 114.3 (2CH, $^3J_{C,F}$=7.2 Hz), 111.0 (C), 54.2 (CH), 25.0 (CH_3); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−125.5; HR-MS (ESI): m/z=241.1142 $(M+H)^+$, calculated for $C_{15}H_{14}FN_2$: 241.1141.

***N*,4-Dimethyl-*N*-(1-phenylethyl)aniline (4m):** Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 95/5) afforded **4m** as a yellow oil; yield: 91 mg (0.40 mmol, yield 58%); M=225.33 g mol^{-1}; R_f=0.47 (cyclohexane/ethyl acetate 70/30); IR (film): ν=3408, 3340, 3313, 3295, 3271, 3204, 3148, 2363, 2163, 2076, 2042, 2012, 1618, 1516, 1448, 1372, 1303, 1109, 1027, 908 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.34 (m, 5H), 7.08 (d, J=8.4 Hz, 2H), 6.79 (d, J=7.6 Hz, 2H), 5.07 (q, J=6.8 Hz, 1H), 2.66 (s, 3H), 2.28 (s, 3H), 1.54 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=148.4 (C), 143.1 (C), 129.8 (2CH), 128.5 (2CH), 127.1 (2CH), 127.0 (CH), 126.2 (C), 113.8 (2CH), 57.2 (CH), 32.2 (CH_3), 20.4 (CH_3), 16.3 (CH_3); HR-MS (ESI): m/z=226.1598 $(M+H)^+$, calculated for $C_{16}H_{20}N$: 226.1596.

***N*,4-Dimethyl-*N*-[1-(naphthalen-2-yl)ethyl]aniline (4n):** Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 98/2) afforded **4n** as a colorless oil; yield: 127 mg (0.46 mmol, 78%); M=275.39 g mol^{-1}; R_f=0.77 (cyclohexane/ethyl acetate 70/30); IR (film): ν=3473, 3417, 3386, 2219, 2092, 2036, 2012, 1736, 1679, 1616, 1515, 1368, 1237, 1180, 1108, 858 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.88–7.80 (m, 2H), 7.78 (d, J=7.3 Hz, 2H), 7.54–7.42 (m, 3H), 7.10 (d, J=8.4 Hz, 2H), 6.86 (d, J=7.3 Hz, 2H), 5.22 (q, J=6.8 Hz, 1H), 2.69 (s, 3H), 2.30 (s, 3H), 1.65 (d, J= 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=148.4 (C), 140.8 (C), 133.5 (C), 132.7 (C), 132.6 (C), 129.9 (2CH), 128.2 (CH), 128.1 (CH), 127.7 (CH), 126.2 (CH), 126.1 (CH), 125.8 (CH), 125.2 (CH), 113.9 (2CH), 57.3 (CH), 32.3 (CH_3), 20.4 (CH_3), 15.9 (CH_3); HR-MS (ESI): m/z= 276.1739 $(M+H)^+$, calculated for $C_{20}H_{22}N$: 276.1747.

1-[1-(3,5-Dimethoxyphenyl)ethyl]indoline (4o): Flash chromatography on neutralized silica gel (cyclohexane/ethyle acetat 90/10) afforded **4o** as a colorless oil; yield: 122 mg (0.43 mmol, 75%); M=283.36 g mol^{-1}; R_f=0.68 (cyclohexane/ethyl acetate 70/30); IR (film): ν=3406, 3249, 3230, 3095, 2197, 2168, 2052, 1606, 1591, 1487, 1456, 1426, 1344, 1256, 1203, 1151, 1055, 1037, 924 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.14–7.00 (m, 2H), 6.67 (d, J= 7.3 Hz, 1H), 6.64 (d, J=2.1 Hz, 2H), 6.43 (m, 2H), 4.66 (q, J=6.8 Hz, 1H), 3.81 (s, 6H), 3.41 (t, J=8.2 Hz, 2H), 2.99 (t, J=8.2 Hz, 2H), 1.55 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=161.0 (2C), 151.4 (C), 145.7 (C), 130.3 (C), 127.2 (CH), 124.4 (CH), 117.2 (CH), 107.5 (CH), 105.4 (2CH), 98.7 (CH), 55.4 (2OCH_3), 55.0 (CH), 48.2 (CH_2), 28.3 (CH_2), 16.6 (CH_3); HR-MS (ESI): m/z=284.1649 $(M+H)^+$, calculated for $C_{18}H_{22}NO_2$: 284.1651.

***N*-[1-(3,5-Dimethoxyphenyl)ethyl]pyridin-2-amine (4p):** Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 90/10) afforded **4p** as a colorless oil; yield: 92 mg (0.36 mmol, 62%); M=258.32 g mol^{-1}; R_f=0.21 (cyclohexane/ethyl acetate 70/30; IR (film): ν=2836, 1593, 1571, 1528, 1504, 1455, 1427, 1373, 1325, 1290, 1245, 1203, 1151, 1067, 1053, 1027, 987, 925 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.06 (d, J=3.6 Hz, 1H), 7.32 (ddd, J=8.8, 7.3, 1.8 Hz, 1H), 6.54 (m, 3H), 6.33 (t, J=2.3 Hz, 1H), 6.21 (d, J=8.4 Hz, 1H), 5.08 (d, J=5.8 Hz, 1H), 4.61 (p, J=6.8 Hz, 1H), 3.76 (s, 6H), 1.53 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=161.2 (2C), 158.1 (C), 148.1 (CH), 147.6 (C), 137.7 (CH), 113.2 (CH), 106.9 (CH), 104.0 (2CH), 98.9 (CH), 55.4 (2OCH_3), 52.4 (CH), 24.5 (CH_3); HR-MS (ESI): m/z=259.1449 $(M+H)^+$, calculated for $C_{15}H_{19}N_2O_2$: 259.1447.

4-Fluoro-*N*-[1-(pyridin-3-yl)ethyl]aniline (4q): Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 80/20) afforded **4q** as a brown oil; yield: 102 mg (0.47 mmol, 68%); M=216.25 g mol^{-1}; R_f=0.08 (cyclohexane/ethyle acetat 70/30); IR (film): ν=3478, 3383, 3342, 3230, 2489, 2278, 2235, 2203, 2152, 1928, 1509, 1212 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ=(ppm) 8.57 (d, J=52.9 Hz, 2H), 7.78 (d, J=7.8 Hz, 1H), 7.37 (s, 1H), 6.83 (t, J= 9.0 Hz, 2H), 6.49 (dd, J=9.0, 4.6 Hz, 2H), 4.52 (q, J= 6.8 Hz, 1H), 1.43 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, DMSO): δ=155.8 (C), 152.8 (C), 147.7 (CH), 147.4 (CH), 144.2 (C), 133.9 (2CH), 115.1 (2CH, $^2J_{C,F}$=22.0 Hz), 113.6 (2CH, $^3J_{C,F}$=7.2 Hz), 50.2 (CH), 24.2 (CH_3); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−127.5; HR-MS (ESI): m/z= 217.1127 $(M+H)^+$, calculated for $C_{13}H_{14}FN_2$: 217.1136.

***N*-Benzhydryl-3,4,5-trimethoxyaniline (4t):** Flash chromatography on neutralized silica gel (cyclohexane/ethyle acetat 80/20) afforded **4t** as a yellow solid (crystallized in a mixture of diisopropyl ether/ethyle acetat); yield: 182 mg (0.52 mmol, 91%); M=349.42 g mol^{-1}; mp 142–144 °C; R_f= 0.42 (cyclohexane/ethyle acetat 70/30); IR (film): ν=3492, 3453, 3427, 3345, 3262, 3224, 3198, 3060, 2929, 2169, 1963, 1611, 1509, 1451, 1409, 1233, 1206, 1184, 1129, 1010, 912 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.49–7.15 (m,

10H), 5.80 (s, 2H), 5.45 (s, 1H), 4.18 (bs, 1H), 3.74 (s, 3H), 3.66 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=153.9 (3C), 143.0 (3C), 128.9 (4CH), 127.6 (2CH), 127.5 (4CH), 91.5 (2CH), 64.0 (CH), 61.2 (OCH_3), 55.9 (2OCH_3); HR-MS (ESI): m/z=350.1752 $(M+H)^+$, calculated for $C_{22}H_{24}NO_3$: 350.1756.

***N*-Benzhydryl-4-fluoroaniline (4u):** Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 95/5) afforded **4u** as a yellow oil; yield: 130 mg (0.47 mmol, 82%); M=277.34 g mol^{-1}; R_f=0.78 (cyclohexane/ethyle acetat 70/30); IR (film): ν=3028, 1506, 1451, 1399, 1345, 1309, 1264, 1220, 1156, 1111, 1090, 1064, 1028, 908 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.45–7.14 (m, 10H), 6.79 (t, J=8.7 Hz, 2H), 6.45 (dd, J=8.7, 4.4 Hz, 2H), 5.41 (s, 1H), 4.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=157.7–154.5 (C, $^1J_{C,F}$=235.5 Hz), 143.7 (C), 142.8 (2C), 128.9 (4CH), 127.6 (2CH), 127.5 (4CH), 115.8–115.5 (2CH, $^2J_{C,F}$=22.2 Hz), 114.6 (2CH), 63.8 (CH); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−128.0; HR-MS (ESI): m/z=278.1344 $(M+H)^+$, calculated for $C_{19}H_{17}FN$: 278.1345.

***N*-[Bis(4-fluorophenyl)methyl]-4-methoxyaniline (4v):** Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 95/5) afforded **4v** as a yellow oil; yield: 121 mg (0.37 mmol, 72%); M=325.35 g mol^{-1}; R_f=0.77 (cyclohexane/ethyle acetat 70/30); IR (film): ν=3481, 3465, 3442, 3423, 3330, 3215, 3173, 3058, 3034, 2358, 2158, 2136, 2038, 2005, 1601, 1506, 1243, 1223, 1156, 1037, 842 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.31 (m, 4H), 7.01 (t, J=8.5 Hz, 4H), 6.73 (d, J=8.6 Hz, 2H), 6.50 (d, J=8.6 Hz, 2H), 5.39 (s, 1H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=162.2 (2C, J=235.0 Hz), 156.4 (C), 152.7 (C), 138.8 (2C), 129.1 (4CH, J=8.0 Hz), 122.8 (2CH), 115.8 (4CH, J=21.4 Hz), 114.1 (2CH), 62.7 (CH), 55.9 (OCH_3); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−113.2; HR-MS (ESI): m/z=326.1328 $(M+H)^+$, calculated for $C_{20}H_{18}F_2NO$: 326.1325.

***N*-[4-(Benzhydrylamino)phenyl]-*N*-methylacetamide (4w):** Flash chromatography on neutralized silica gel (cyclohexane/ethyle acetat 90/10) afforded **4w** as a yellow solid (crystallized in a mixture of diisopropyl ether/ethyl acetate); yield: 149 mg (0.45 mmol, 79%); M=330.42 g mol^{-1}; mp 152–154 °C; R_f=0.19 (cyclohexane/ethyl acetate 70/30); IR (film): ν=3487, 3460, 3405, 3389, 3296, 3190, 3147, 2510, 2194, 1997, 1973, 1657, 1637, 1517, 1449, 1420, 1381, 1319, 1278, 1177, 1142, 975 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.43–7.23 (m, 10H), 6.90 (d, J=8.6 Hz, 2H), 6.54 (d, J=8.6 Hz, 2H), 5.49 (s, 1H), 3.18 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.4 (C), 146.7 (C), 142.5 (2C), 135.0 (C), 129.0 (4CH), 127.9 (2CH), 127.7 (2CH), 127.5 (4CH), 114.2 (2CH), 63.4 (CH), 37.4 (CH_3), 22.5 (CH_3); HR-MS (ESI): m/z=331.1808, $(M+H)^+$, calculated for $C_{22}H_{23}N_2O$: 331.1810.

***N*-[1-(Naphthalen-2-yl)ethyl]butan-1-amine (4aa):** Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 80/20) afforded **4aa** as a colorless oil; yield: 110 mg (0.48 mmol, 82%); M=227.34 g mol^{-1}; R_f=0.18 (cyclohexane/ethyle acetate 70/30); IR (film): ν=3393, 3253, 2959, 2927, 2017, 1968, 1947, 1730, 1602, 1509, 1381, 1183, 1127, 1077 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.82 (m, 3H), 7.75 (s, 1H), 7.56–7.39 (m, 3H), 3.96 (q, J=6.6 Hz, 1H), 2.64–2.37 (m, 2H), 1.48 (m, 4H), 1.30 (dd, J=15.0, 7.7 Hz, 3H), 0.87 (t, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=142 (C), 133.6 (C), 133.0 (C), 128.4 (CH), 127.9 (CH), 127.8 (CH), 126.1 (CH), 125.6 (CH), 125.4 (CH), 125.0 (CH), 58.7 (CH), 47.7 (CH_2), 32.4 (CH_2), 24.32 (CH_3), 20.62 (CH_2), 14.11 (CH_3); HR-MS (ESI): m/z=228.1738 $(M+H)^+$, calculated for $C_{16}H_{22}N$: 228.1747.

1-(3,5-Dimethoxyphenyl)-*N*-(4-methoxybenzyl)ethanamine (4ab): Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 90/10) afforded **4ab** as a yellow oil; yield: 129 mg (0.43 mmol, 75%); M=301.38 g mol^{-1}; R_f=0.13 (cyclohexane/ethyl acetate 70/30); IR (film): ν=3112, 2836, 1610, 1594, 1512, 1457, 1427, 1346, 1290, 1244, 1203, 1151, 1117, 1055, 1033, 926, 908 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.22 (d, J=8.6 Hz, 2H), 6.86 (d, J=8.6 Hz, 2H), 6.56 (d, J=2.2 Hz, 2H), 6.38 (t, J=2.2 Hz, 1H), 3.81 (s, 6H), 3.79 (s, 3H), 3.72–3.48 (m, 3H), 1.36 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=161.1 (2C), 158.7 (C), 148.5 (C), 132.8 (C), 129.4 (2CH), 113.9 (2CH), 104.7 (2CH), 98.9 (CH), 57.8 (CH), 55.4 (2OCH_3), 55.4 (OCH_3), 51.1 (CH_2), 24.5 (CH_3); HR-MS (ESI): m/z=302.1757 $(M+H)^+$, calculated for $C_{18}H_{24}NO_3$: 302.1756.

1-(3,5-Dimethoxyphenyl)-*N*-(4-fluorobenzyl)ethanamine (4ad): Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 90/10) afforded **4ad** as a yellow oil; yield: 100 mg (0.34 mmol, 60%); M=289.34 g mol^{-1}; R_f=0.13 (cyclohexane/ethyl acetate 70/30); IR (film): ν=2962, 2836, 1976, 1609, 1594, 1509, 1457, 1428, 1345, 1292, 1221, 1203, 1152, 1122, 1054, 907 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.24 (dd, J=8.8, 5.3 Hz, 2H), 6.97 (t, J=8.8 Hz, 2H), 6.51 (d, J=2.3 Hz, 2H), 6.36 (t, J=2.3 Hz, 1H), 3.79 (s, 6H), 3.72 (q, J=13.1, 6.6 Hz, 1H), 3.59 (q, J=13.1 Hz, 2H), 1.34 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=163.6–160.4 (C, $^1J_{C,F}$=244 Hz), 161.1 (2C), 148.3 (C), 136.4 (C, $^4J_{C,F}$=2.7 Hz), 129.8 (2CH, $^3J_{C,F}$=7.9 Hz), 115.2 (2CH, $^2J_{C,F}$=21.2 Hz), 104.7 (2CH), 98.9 (CH), 57.9 (CH), 55.4 (2OCH_3), 51.0 (CH_2), 24.5 (CH_3); ^{19}F NMR (188 MHz, $CDCl_3$): δ=−116.5; HR-MS (ESI): m/z=290.1554 $(M+H)^+$, calculated for $C_{17}H_{21}NO_2F$: 290.1556.

5-[1-(3,5-Dimethoxyphenyl)ethylamino]-2-methoxyphenol (4ai): Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 90/10) afforded **4ai** as a red oil; yield: 125 mg (0.41 mmol, 72%); M=303.35 g mol^{-1}; R_f=0.26 (cyclohexane/ethyl acetate 70/30); IR (film): ν=3402, 3104, 1593, 1511, 1455, 1427, 1345, 1203, 1151, 1065, 1052, 1023, 980 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.63 (d, J=8.6 Hz, 1H), 6.54 (d, J=2.0 Hz, 2H), 6.33 (d, J=2.0 Hz, 1H), 6.28 (d, J=2.4 Hz, 1H), 6.08 (dd, J=8.6, 2.4 Hz, 1H), 4.32 (q, J=6.7 Hz, 1H), 3.77 (s, 9H), 1.51 (d, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=161.2 (2C), 152.8 (C), 147.5 (C), 146.5 (C), 139.9 (C), 112.4 (CH), 105.7 (CH), 104.3 (2CH), 102.2 (CH), 99.0 (CH), 56.9 (CH), 55.4 (3OCH_3), 24.6 (CH_3); HR-MS (ESI): m/z=304.1535 $(M+H)^+$, calculated for $C_{17}H_{22}NO_4$: 304.1543.

2-{4-[(1-{3,5-dimethoxyphenyl}ethyl)amino]phenyl}ethanol (4aj): Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 80/20) afforded **4aj** as a yellow oil; yield: 125 mg (0.41 mmol, 72%); M=301.38 g mol^{-1}; R_f=0.22 (cyclohexane/ethyl acetate 70/30); IR (film): ν=3425, 3242, 2355, 2218, 2203, 2166, 2151, 2088, 2069, 2009, 1609, 1593, 1517, 1427, 1257, 1203, 1151, 1065 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.95 (d, J=8.5 Hz, 2H), 6.55 (d, J=2.3 Hz, 2H), 6.50 (d, J=8.5 Hz, 2H), 6.34 (t, J=2.3 Hz, 1H), 4.37 (q, J=6.7 Hz, 1H), 3.86–3.63 (m, 8H), 2.71 (t, J=6.6 Hz, 2H), 1.50 (d, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$): $\delta = 161.2$ (2C), 148.2 (C), 145.9 (C), 129.8 (2CH), 127.0 (C), 113.8 (2CH), 104.1 (2CH), 98.6 (CH), 63.9 (CH_2), 55.4 ($2OCH_3$), 54.2 (CH), 38.3 (CH_2), 24.9 (CH_3); HR-MS (ESI): $m/z = 302.1743$ $(M+H)^+$, calculated for $C_{18}H_{24}NO_3$: 302.1751.

5-(Benzhydrylamino)-2-methoxyphenol (4ak): Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 90/10) afforded **4ak** as a red oil; yield: 161 mg (0.53 mmol, 92%); $M = 305.37\ g\,mol^{-1}$; $R_f = 0.5$ (cyclohexane/ethyl acetate 70/30); IR (film): $\nu = 3424$, 3261, 2211, 1594, 1512, 1451, 1350, 1291, 1244, 1204, 1153, 1066, 1028, 961 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.27$ (m, 10H), 6.62 (d, $J = 8.6$ Hz, 1H), 6.22 (d, $J = 2.5$ Hz, 1H), 6.00 (dd, $J = 8.6$, 2.5 Hz, 1H), 5.50 (bs, 1H), 5.40 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 146.6$ (C), 143.2 (2C), 142.8 (C), 139.4 (C), 128.8 (4CH), 127.6 (4CH), 127.4 (2CH), 112.4 (CH), 104.7 (CH), 101.5 (CH), 63.8 (CH), 56.9 (OCH_3); HR-MS (ESI): $m/z = 306.1496$ $(M+H)^+$, calculated for $C_{20}H_{20}NO_2$: 306.1494.

4-(Benzhydrylamino)phenol (4al): Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 80/20) afforded **4al** as a yellow oil; yield: 134 mg (0.49 mmol, 85%); $M = 275.34\ g\,mol^{-1}$; $R_f = 0.54$ (cyclohexane/ethyl acetate 70/30); IR (film): $\nu = 3197$, 2341, 2235, 2150, 2013, 1598, 1511, 1491, 1451, 1416, 1343, 1304, 1234, 1119, 1028 cm^{-1}; ^1H NMR (400 MHz, DMSO): $\delta = 8.37$ (bs, 1H), 7.40 (d, $J = 7.3$ Hz, 4H), 7.29 (t, $J = 7.6$ Hz, 4H), 7.19 (t, $J = 7.3$ Hz, 2H), 6.48 (dd, $J = 18.5$, 8.8 Hz, 4H), 5.76 (bs, 1H), 5.49 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 147.8$ (C), 143.3 (2C), 141.9 (C), 128.8 (4CH), 127.5 (4CH), 127.4 (2CH), 116.2 (2CH), 114.9 (2CH), 64.0 (CH); HRMS (ESI): $m/z = 276.1385$ $(M+H)^+$, calculated for $C_{19}H_{18}NO$: 276.1388.

***N*-Benzhydryl-2-(5-methoxy-1*H*-indol-3-yl)ethanamine (4am):** Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 80/20) afforded **4am** as a brown oil; yield: 157 mg (0.44 mmol, 77%); $M = 356.46\ g\,mol^{-1}$; $R_f = 0.26$ (cyclohexane/ethyl acetate 70/30); IR (film): $\nu = 2163$, 1624, 1584, 1485, 1453, 1437, 1293, 1265, 1214, 1171, 1071, 1029, 923, 834, 794, 734, 698, 641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.03$ (bs, 1H), 7.42 (d, $J = 7.3$ Hz, 4H), 7.32 (t, $J = 7.3$ Hz, 4H), 7.22 (dd, $J = 15.8$, 8.2 Hz, 3H), 7.05 (d, $J = 2.4$ Hz, 1H), 6.96–6.78 (m, 2H), 4.91 (s, 1H), 3.86 (s, 3H), 3.00 (dd, $J = 12.3$, 5.3 Hz, 4H), 1.84 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 153.9$ (C), 144.3 (2C), 131.6 (C), 128.5 (4CH), 127.9 (C), 127.4 (4CH), 127.0 (2CH), 122.9 (CH), 113.8 (C), 112.3 (CH), 112.0 (CH), 100.8 (CH), 67.4 (CH), 56.0 (OCH_3), 48.1 (CH_2), 26.0 (CH_2); HR-MS (ESI): $m/z = 357.1960$ $(M+H)^+$, calculated for $C_{24}H_{25}N_2O$: 357.1961.

(*R*)-2-(Benzhydrylamino)-3-phenylpropan-1-ol (4an): Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 90/10) afforded **4an** as a yellow oil; yield: 152 mg (0.48 mmol, 84%); $M = 317.42\ g\,mol^{-1}$; $R_f = 0.44$ (cyclohexane/ethyl acetate 70/30); IR (film): $\nu = 3270$, 3228, 3180, 3148, 3088, 2326, 2235, 1493, 1452, 1086, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.54$–6.77 (m, 15H), 4.91 (s, 1H), 3.57 (dd, $J = 10.8$, 3.4 Hz, 1H), 3.32 (dd, $J = 10.8$, 4.6 Hz, 1H), 2.96–2.63 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 143.6$ (2C), 138.6 (C), 129.4 (2CH), 128.6 (6CH), 127.5 (2CH), 127.3 (2CH), 127.2 (2CH), 126.5 (CH), 64.2 (CH), 63.1 (CH_2), 57.6 (CH), 38.4 (CH_2); HR-MS (ESI): $m/z = 318.1860$ $(M+H)^+$, calculated for $C_{22}H_{24}NO$: 318.1858.

General Procedure for Copper-Catalyzed Reductive Coupling of *N*-Tosylhydrazones Derived from Benzaldehydes with Amines

The reactions were carried out in a sealed tube with *N*-tosylhydrazone (200 mg, 1.0 equiv.), $Cu(acac)_2$ (10 mol%), racemic BINAP (10 mol%), K_2CO_3 (2.5 equiv.), the amine (1.5 equiv.) then 3 mL of fluorobenzene and 25 equiv. H_2O were successively added *via* syringe at room temperature. The tube was sealed and put into a pre-heated oil bath at 80 °C for 2 h. The crude reaction mixture was allowed to cool to room temperature. EtOAc was added to the mixture, which was filtered through celite. The solvents were evaporated under reduced pressure and the crude residue was purified by flash chromatography on neutralized silica gel (2% triethylamine).

***N*-(3,5-Dimethoxybenzyl)-4-methoxyaniline (4x):** Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 90/10) afforded **4x** as a yellow oil; yield: 90 mg (0.33 mmol, 55%); $M = 273.33\ g\,mol^{-1}$; $R_f = 0.55$ (cyclohexane/ethyl acetate 70/30); IR (film): $\nu = 3476$, 3443, 3334, 3277, 3261, 3202, 3099, 3000, 2600, 2315, 2186, 2169, 2124, 2094, 2038, 2007, 1983, 1596, 1512, 1429, 1234, 1204, 1155, 1064, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.76$ (s, 4H), 6.55 (s, 2H), 6.36 (s, 1H), 4.22 (s, 2H), 3.77 (s, 6H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.1$ (2C), 154.0 (C), 140.2 (C), 139.3 (C), 116.5 (2CH), 115.0 (2CH), 106.1 (2CH), 99.8 (CH), 55.9 (OCH_3), 55.5 ($2OCH_3$), 51.0 (CH_2); HR-MS (ESI): $m/z = 274.1438$ $(M+H)^+$, calculated for $C_{16}H_{20}NO_3$: 274.1443.

***N*-Benzyl-4-methoxyaniline (4y):** Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 90/10) afforded **4y** as a yellow oil; yield: 78 mg (0.37 mmol, 50%); $M = 213.28\ g\,mol^{-1}$; $R_f = 0.68$ (cyclohexane/ethyl acetate 70/30); IR (film): $\nu = 3471$, 3431, 3351, 3334, 3313, 3215, 3174, 3053, 2181, 2122, 2061, 2016, 1512, 1233, 1036, 903 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.43$–7.24 (m, 5H), 6.80 (d, $J = 9.0$ Hz, 2H), 6.62 (d, $J = 9.0$ Hz, 2H), 4.30 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 152.35$ (C), 142.60 (C), 139.84 (C), 128.72 (2CH), 127.67 (2CH), 127.29 (CH), 115.07 (2CH), 114.25 (2CH), 55.94 (OCH_3), 49.39 (CH_2); HR-MS (ESI): $m/z = 214.1227$ $(M+H)^+$, calculated for $C_{14}H_{16}NO$: 214.1232.

General Procedure for the One-Pot Copper-Catalyzed Reductive Coupling of *N*-Tosylhydrazones with Amines

The reactions were carried out in a sealed tube with the carbonyl compound (100 mg), tosylhydrazide (1 equiv.) and 2 mL PhF. The vessel was sealed with a septum and put in a heated oil bath at 80 °C until completion (1–2 h). Then, $Cu(acac)_2$ (10 mol%), *rac*-BINAP (10 mol%), Cs_2CO_3 (2.5 equiv.), the amine (1.5 equiv.) and 25 equiv. H_2O were successively added to the resulting reaction mixture. Again, the vessel was sealed with a septum and placed into a pre-heated oil bath at 120 °C for 2 h. The crude reaction mixture was allowed to cool to room temperature. EtOAc was added to the mixture, which was filtered through celite. The

solvents were evaporated under reduced pressure and the crude residue was purified by flash chromatography on neutralized silica gel (2% triethylamine).

***N*-{1-[3,5-Bis(allyloxy)phenyl]ethyl}-4-methoxyaniline (4ap):** Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 95/5) afforded **4ap** as a yellow oil; yield: 76 mg (0.22 mmol, 52%); $M = 339.43\ g\,mol^{-1}$; $R_f = 0.64$ (cyclohexane/ethyl acetate 70/30); IR (film): n = 3412, 3376, 3236, 3151, 2361, 2158, 1594, 1512, 1442, 1423, 1286, 1234, 1166, 1148, 1038, 928, 818, 762, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.70$ (d, $J = 8.9$ Hz, 2H), 6.56 (d, $J = 2.2$ Hz, 2H), 6.47 (d, $J = 8.9$ Hz, 2H), 6.36 (t, $J = 2.2$ Hz, 1H), 6.03 (m, 2H), 5.53–5.18 (m, 4H), 4.49 (dt, $J = 5.3$, 1.3 Hz, 4H), 4.31 (q, $J = 6.7$ Hz, 1H), 3.70 (s, 3H), 1.47 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 160.1$ (2C), 152.1 (C), 148.5 (C), 141.8 (C), 133.4 (2CH), 117.8 ($2CH_2$), 114.9 (2CH), 114.7 (2CH), 105.1 (2CH), 100.1 (CH), 69.0 ($2CH_2$), 55.9 (CH), 54.7 (OCH_3), 25.1 (CH_3); HR-MS (ESI): $m/z = 340.1910$ $(M+H)^+$, calculated for $C_{21}H_{26}NO_3$: 340.1913.

1-[(4-Benzhydrylamino)phenyl]ethanone (4as): Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 95/5) afforded **4as** as a white oil; yield: 110 mg (0.37 mmol, 64%); $M = 301.38\ g\,mol^{-1}$; $R_f = 0.48$ (cyclohexane/ethyl acetate 70/30); IR (film): n = 3489, 3456, 3431, 3392, 3334, 3317, 3300, 3277, 3120, 2569, 2111, 2055, 2006, 1988, 1938, 1596, 1521, 1272, 1180 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.77$ (d, $J = 8.8$ Hz, 2H), 7.42–7.21 (m, 10H), 6.54 (d, $J = 8.8$ Hz, 2H), 5.62 (d, $J = 4.6$ Hz, 1H), 4.79 (d, $J = 4.6$ Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 196.5$ (C), 151.2 (C), 141.9 (2C), 130.7 (2CH), 129.0 (4CH), 127.8 (2CH), 127.5 (4CH), 127.3 (C), 112.5 (2CH), 62.5 (CH), 26.1 (CH_3); HR-MS (ESI): $m/z = 302.1542$ $(M+H)^+$, calculated for $C_{21}H_{20}NO$: 302.1545.

(2*R*)-2-[(4-methoxyphenyl)-(phenyl)methylamino]-3-phenylpropan-1-ol (4at): Flash chromatography on neutralized silica gel (cyclohexane/ethyl acetate 90/10) afforded **4at** as a yellow oil; yield: 95 mg (0.28 mmol, 60%); $M = 347.45\ g\,mol^{-1}$; $R_f = 0.39$ (cyclohexane/ethyl acetate 70/30); IR (film): n = 3487, 3458, 3401, 3317, 3252, 3215, 3052, 2188, 2133, 1965, 1610, 1510, 1453, 1303, 1247, 1175, 1030, 908 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.54$–7.17 (m, 8H), 7.19–6.99 (m, 4H), 6.85 (d, $J = 8.7$ Hz, 1H), 6.80 (d, $J = 8.7$ Hz, 1H), 4.91 (s, 1H), 3.79 (s, 3H), 3.62 (dd, $J = 10.7$, 3.6 Hz, 1H), 3.43–3.26 (m, 1H), 2.99–2.65 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.8$ (C), 144.0 (C), 138.7 (C), 135.9 (C), 129.4 (2CH), 128.6 (4CH), 128.3 (2CH), 127.4 (CH), 127.2 (2CH), 126.5 (CH), 114.0 (2CH), 63.6 (CH), 63.2 (CH_2), 57.6 (CH), 55.4 (OCH_3), 38.5 (CH_2); HR-MS (ESI): $m/z = 348.1963$ $(M+H)^+$, calculated for $C_{23}H_{26}NO_2$: 348.1964.

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