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Copper-catalyzed asymmetric addition of diethylzinc to Boc-protected imines

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ABSTRACT

A new class of substrates has been tested in the addition of Et_2Zn, catalyzed by copper and phosphoramidite, providing the expected α branched protected amine in quantitative conversion, good yield and excellent enantioselectivity up to 97%.

1. Introduction

Chiral α branched amines are important functionalities in biologically active molecules. As a result, they have become a very important topic in asymmetric catalysis. Due to their poor reactivity, imines have not been studied as much as the carbonyl functions;[1] they have to be protected by an electron-withdrawing group in order to activate the azomethine carbon. In the case of Lewis base activation, Soai was the first to use *N*-diphenylphosphinoyl imines to activate the addition of dialkylzinc, catalyzed by chiral amino alcohols.[2] Recently, Gong reported the in situ formation of the *N*-formyl imine from a stable precursor.[3] In Lewis acid activation, Tomioka was the first to report, in 2000, the Cu-catalyzed addition of diethylzinc to *N*-sulfonyl imines.[4] Many authors followed this up; for example, Wang et al. reported the use of a ferrocene-derived ligand on the same substrate.[5] Charette used his efficient monophosphine oxide ligand, under the same conditions as others, on *N*-diphenylphosphinoyl imines.[6] The in situ formation of *N*-diphenylphosphinoyl imines starting from the amine–sulfinate adduct was introduced.[7] He also designed an innovative way to add dialkylzincs to aryl trifluoromethyl ketimines, generated in situ from a stable hemiaminal-bearing ethoxide as the leaving group, providing the expected compound in excellent enantiomeric excess.[8] Hoveyda and Snapper examined the addition of dialkylzinc reagents to orthomethoxyphenyl-protected imines, catalyzed by a Zr–dipeptide complex.[9] Other nucleophiles such as Grignard reagent or lithium derivatives have been investigated by Toru et al.[10] Tomioka[11] and Alexakis[12] on *N*-(pyridylsulfonyl) imines or paramethoxyphenylimines.

All of these approaches rely on different protecting groups on the imines, but in most cases the protected amines obtained seem to be difficult to cleave. Facing this difficulty, we decided to introduce a different protecting group, for imines, such as *tert*-butoxycarbonyl. At the beginning of our study, there was no literature report on the use of copper and phophoramidite ligands on such additions. However, a recent article, by Feringa et al., disclosing a similar approach onto formylimines, prompted us to report our own results.[13] Herein, we report the use of other phosphoramidite ligands, and a wider scope of electron-donating and -withdrawing substituent on the starting material.

2. Results and discussion

All substrates were easily prepared according to a described procedure.[14] Aromatic aldehydes have been mixed with benzenesulfinic acid sodium salt or *p*-toluenesulfinic acid sodium salt in the presence of *tert*-butyl carbamate under acidic conditions at room temperature to yield the amine–sulfinate adduct, which was converted to the Boc-protected imine under basic conditions in refluxing THF (Scheme 1).

The simplest starting material (Ar = phenyl) was then used in the addition of diethylzinc in toluene at 0 °C with the simplest biphenol-based phosphoramidite ligand **8** and the most used copper salt, $Cu(OTf)_2$. This first experiment allowed us to obtain the expected compound in complete conversion after 15 min and with 75% enantiomeric excess. After a quick screening of the temperature, we observed that in all cases the conversion was complete, and that −40 °C appeared to be the optimal one (Table 1).

We then turned our attention to the ligand. A large number have been tried under the same conditions as described above. Some of the most interesting results are presented in Scheme 2.

With these results we can understand that the amine part of the ligand should not be too hindered (**8** vs **9**), in contrast to the biphenyl part, where the tetramethyl-substituted phosphoramidite ligand induces more selectivity (**8** vs **10**). The binaphthyl ligand **11** was also been tested, but it induced lower enantioselectivity than **10**. Its diastereoisomer was also tested, but with less selectivity. We also wanted to see the activity of one of the new Simplephos ligands, recently described in our laboratories,[15] but unfortunately with less success than its phosphoramidite analogues (**10** vs **13**).

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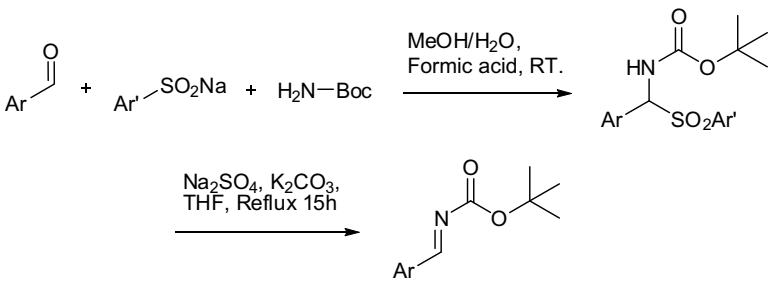


Scheme 1.

Carbene **12**, ferrocene **14** and phosphite **15** ligands were also tested, but without any noteworthy results.

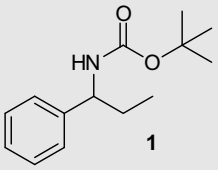
We then tested the influence of the solvent, and dichloromethane appeared to be the best in terms of conversion and selectivity. We finally performed a screening of the copper salt in this solvent (Table 2).

First, we observed that the copper salt did not have a great influence on the selectivity; therefore we decided to work with CuBr. We also studied the ratio of the ligand versus copper salt, and a 1/1 ratio appeared to be the best one in terms of conversion and enantiomeric excess (Table 3).

With these condition in hand, we applied our methodology to different substrates. The results are summarized in Table 4 (Scheme 3).

We observed that the conversion and the selectivity were in the same range as the test substrate and were not dependent on the electronicity of the substituent on the aromatic part of the substrate (entry 4 vs entry 5). It seems that the selectivity was slightly dependent on the hindrance of the aromatic part, if we compare product **6**, entry 7, versus product **7,** entry 8. We were also interested in the amount of the catalyst, and under the same conditions

Table 1
Study of the temperature

Entry	Product	*T* (°C)	ee (%)
1		0	75
2		−20	83
3		−40	86
4		−60	86

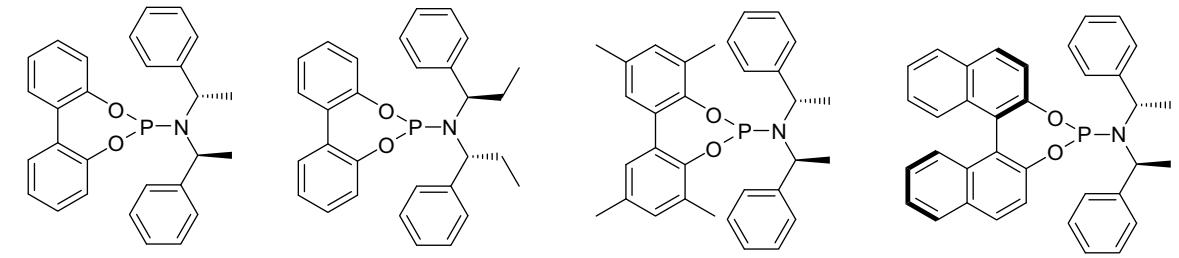
1

Three equivalents of Et_2Zn, 3.6 mol % of **8**, 3 mol % of $Cu(OTf)_2$, in toluene.

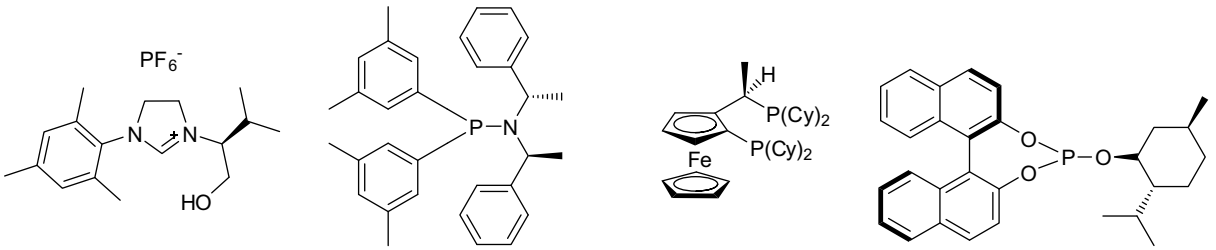
Table 2
Study of copper salts

Entry	CuX	ee (%)
1	$Cu(OTf)_2$	90
2	$Cu[OTf]_2$·benzene	91
3	CuBr	93
4	CuCl	93
5	CuI	91
6	CuTC	91.5
7	CuBr·Me_2S	93
8	$Cu(OAc)_2·H_2O$	92.5
9	$Cu(OAc)_2$	91

Three equivalents of Et_2Zn, 3.6 mol % of **10**, 3 mol % of CuX, in DCM at −40 °C.



8 ee= 86% **9** ee= 78% **10** ee= 89% **11** ee= 82%



12 ee= 23% **13** ee= 66% **14** ee= 51% **15** ee= 7%

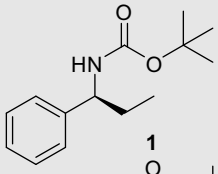
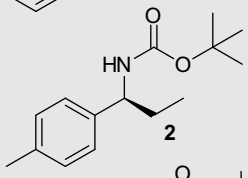
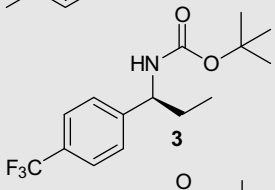
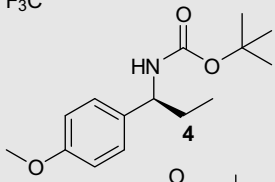
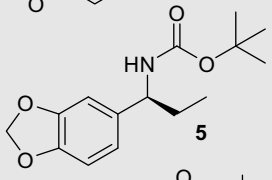
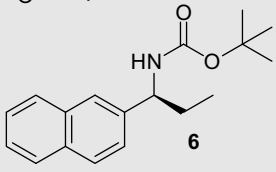
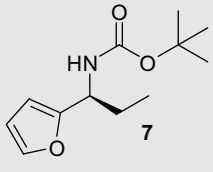
Scheme 2.

Table 3
Study of the ratio between **10** and CuBr

Entry	**10** (mol %)	CuBr (mol %)	Conv (%)	ee (%)
1	5	2.5	87	92
2	6	5	92	93
3	7.5	5	91	93

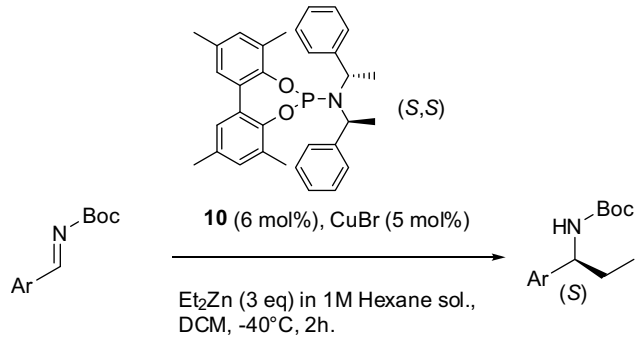
Three equivalents of Et_2Zn, *x* mol % of **10**, *y* mol % of CuBr, in DCM at −40 °C.

Table 4
Study of the scope of the reaction

Entry	Product	Conv. (%)	Yld (%)	ee (%)[b]
1	 **1**	92	88	93 (−)
2[a]		81	—	51 (−)
3	 **2**	94	83	94 (−)
4	 **3**	99	90	96 (−)
5	 **4**	100	85	93 (−)
6	 **5**	100	85	94 (−)
7	 **6**	100	83	90 (−)
8	 **7**	100	87	97 (−)

[a] Reaction performed at −30 °C with 1.5 equiv of Et_3Al, 1 equiv of Et_3N, 10 mol % of ligand **10** and 5 mol % of CuBr in ether for 1 h.
[b] The absolute configuration of **1** has been determined thanks to the specific rotation sign of its corresponding unprotected product (*S*)-(−)-1-phenylpropan-1-amine. The absolute configuration of compounds **2**–**7** was determined by analogy to **1**.

with only 1% of ligand **10** and CuBr, we obtained in quantitative conversion to product **1** in 90% enantiomeric excess. Also, 1.5 equiv of Et_2Zn has been tested without eroding the conversion or selectivity.



Scheme 3.

The use of Et_3Al has also been approached. Here, we present our best results, entry 2. As a Lewis base, triethylamine was added to reduce the nucleophilicity of the Et_3Al by coordination to the empty orbital of the aluminium atom. If the reaction was performed without it, no selectivity was observed. Me_3Al has also been tried, but only addition to the carbonyl functionality of the Boc group without Et_3N and recovery of the starting material with Et_3N have been observed.

3. Conclusion

Herein we have reported a new approach to obtain α chiral branched Boc-protected amine. Excellent conversion, isolated yield and enantioselectivity have been observed.

4. Experimental

4.1. General procedure

To a clean and dry Schlenk tube were added CuBr (0.02 mmol), ligand (0.024 mmol) and substrate (0.4 mmol), then dry dichloromethane (5 ml) was added and the whole mixture was cooled to −40 °C. Then Et_2Zn (1.2 mmol, 1 M solution in hexane) was added dropwise to the mixture. After 2 h, drops of methanol were added, and the whole mixture was warmed to room temperature. Then 3 ml of 1 M HCl solution was added and the product was extracted with 3 ml of DCM three times. Organics were dried over sodium sulfate and concentrated under rotary evaporation. The crude product was purified by column chromatography on silica gel eluted with a mixture of pentane/ether, 20:1.

4.2. *tert*-Butyl 1-phenylpropylcarbamate 1

Purification by column chromatography on silica gel eluted with a mixture of pentane/ether, 20:1, to yield 88% of the expected compound as a white solid. mp = 46 °C, $[\alpha]_D^{20} = -53.5$ (*c* 1.025, $CHCl_3$); ^1H NMR ($CDCl_3$, δ = ppm, *J* = Hz): δ 0.9 (t, 3H, *J* = 7.3), 1.4 (s, 9H), 1.75 (m, 2H), 4.55 (br s, 1H), 4.85 (br s, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$, δ = ppm, *J* = Hz): δ 10.7, 28.4, 29.7, 56.3, 79.3, 126.4, 127, 128.5, 142.8, 155.3; IR (neat): 3385, 2971, 2922, 2873, 1682, 1515, 1495, 1455, 1363, 1264, 1258, 1029, 798, 701, 581; MS (*m*/*z*) 236 (M+1) 223, 201, 180, 155; HRMS calcd for $C_{14}H_{21}NO_2Na$ 258.1464, found 258.1470.

4.3. *tert*-Butyl 1-*p*-tolylpropylcarbamate 2

Purification by column chromatography on silica gel eluted with a mixture of pentane/ether, 20:1, to yield 83% of the expected compound as a white solid. mp = 58 °C, $[\alpha]_D^{20} = -60.7$ (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$, δ = ppm, *J* = Hz): δ 0.9 (t, 3H, *J* = 7.4), 1.4

(s, 9H), 1.75 (m, 2H), 2.45 (s, 3H), 4.5 (br s, 1H), 4.8 (br s, 1H), 7.15 (m, 4H); ^{13}C NMR ($CDCl_3$, δ = ppm, J = Hz): δ 10.7, 21, 28.4, 29.7, 56, 79.2, 125.8, 129.2, 136.6, 139.8, 155.3; IR (neat): 3387, 2977, 2929, 2873, 1682, 1513, 1167, 816; MS (m/z) 249 (M+1) 235, 220, 194, 164; HRMS calcd for $C_{15}H_{23}NO_2Na$ 272.1621, found 272.1617.

4.4. *tert*-Butyl 1-(4-(trifluoromethyl)phenyl)propylcarbamate 3

Purification by column chromatography on silica gel eluted with a mixture of pentane/ether, 20:1, to yield 90% of the expected compound as a white solid. mp = 78 °C, $[\alpha]_D^{20} = -41.5$ (c 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$, δ = ppm, J = Hz): δ 0.9 (t, 3H, J = 7.3), 1.4 (s, 9H), 1.75 (m, 2H), 4.6 (br s, 1H), 4.8 (br s, 1H), 7.4 (d, 2H, J = 8), 7.6 (d, 2H, J = 8); ^{13}C NMR ($CDCl_3$, δ = ppm, J = Hz): δ 10.8, 28.6, 30, 56.3, 79.9, 123, 125.7, 126.9, 129 (q, J = 319), 147.4, 155.5; IR (neat): 3373.3, 2979, 2935, 1683.2, 1522.3, 1331, 1159.4, 1118.1, 613; MS (m/z) 304 (M+1) 289, 280, 248, 200, 187, 167, 159; HRMS calcd for $C_{15}H_{20}F_3NO_2Na$ 326.1338, found 326.1339.

4.5. *tert*-Butyl 1-(4-methoxyphenyl)propylcarbamate 4

Purification by column chromatography on silica gel eluted with a mixture of pentane/ether, 20:1, to yield 85% of the expected compound as a white solid. mp = 73 °C, $[\alpha]_D^{20} = -70.7$ (c 0.995, $CHCl_3$); ^{1}H NMR ($CDCl_3$, δ = ppm, J = Hz): δ 0.9 (t, 3H, J = 7.2), 1.4 (s, 9H), 1.75 (m, 2H), 3.8 (s, 3H), 4.5 (br s, 1H), 4.8 (br s, 1H), 6.9 (d, 2H, J = 8.6), 7.2 (d, 2H, J = 8.6); ^{13}C NMR ($CDCl_3$, δ = ppm, J = Hz): δ 10.7, 28.4, 29.8, 55.2, 55.8, 79.2, 113.8, 127.5, 135, 155.3, 158.6; IR (neat): 3371.9, 2968, 2935, 1683, 1526, 1512, 1240, 1168, 1033, 826; MS (m/z) 266 (M+1) 266, 251, 236, 210, 194, 180; HRMS calcd for $C_{15}H_{23}NO_3Na$ 288.1570, found 288.1567.

4.6. *tert*-Butyl 1-(benzo[*d*][1,3]dioxol-5-yl)propylcarbamate 5

Purification by column chromatography on silica gel eluted with a mixture of pentane/ether, 20:1, to yield 85% of the expected compound as a white solid. mp = 52 °C, $[\alpha]_D^{20} = -63.1$ (c 0.995, $CHCl_3$); ^{1}H NMR ($CDCl_3$, δ = ppm, J = Hz): δ 0.9 (t, 3H, J = 7.3), 1.4 (s, 9H), 1.75 (m, 2H), 4.4 (br s, 1H), 4.8 (br s, 1H), 5.9 (s, 2H), 6.7 (m, 3H); ^{13}C NMR ($CDCl_3$, δ = ppm, J = Hz): δ 10.9, 28.6, 30.1, 56.4, 79.6, 101.2, 107, 108.4, 119.9, 137.2, 146.7, 148, 155.5; IR (neat): 3372, 2974, 2930, 1679, 1520, 1487, 1441, 1241, 1167, 1039, 611; MS (m/z) 280 (M+1) 265, 250, 224, 194, 163; HRMS calcd for $C_{15}H_{22}NO_4$ 280.1543, found 280.1555.

4.7. *tert*-Butyl 1-(naphthalen-2-yl)propylcarbamate 6

Purification by column chromatography on silica gel eluted with a mixture of pentane/ether, 20:1, to yield 83% of the expected compound as a white solid. mp = 73 °C, $[\alpha]_D^{20} = -58.1$ (c 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, δ = ppm, J = Hz): δ 0.9 (t, 3H, J = 7.3), 1.45 (s, 9H), 1.85 (m, 2H), 4.65 (br s, 1H), 4.9 (br s, 1H), 7.35–7.5 (m, 3H), 7.7 (s, 1H), 7.8 (m, 3H); ^{13}C NMR ($CDCl_3$, δ = ppm, J = Hz): δ 11, 28.6, 30, 56.7, 79.6, 124.9, 125.4, 125.9, 126.3, 127.9, 128.1, 128.6, 133, 133.6, 140.4, 155.6; IR (neat): 3381, 2966, 2931, 2872, 1689, 1520, 1505, 1241, 1165, 1074, 1030, 822, 741, 612; MS (m/z) 286 (M+1) 271, 230, 200, 169; HRMS calcd for $C_{18}H_{24}NO_2$ 286.1801, found 286.1810.

4.8. *tert*-Butyl 1-(furan-2-yl)propylcarbamate 7

Purification by column chromatography on silica gel eluted with a mixture of pentane/ether, 20:1, to yield 87% of the expected compound as a colorless oil. $[\alpha]_D^{20} = -99.8$ (c 0.995, $CHCl_3$); ^{1}H NMR ($CDCl_3$, δ = ppm, J = Hz): δ 0.9 (t, 3H, J = 7.2), 1.45 (s, 9H), 1.85 (m, 2H), 4.65 (br s, 1H), 4.85 (br s, 1H), 6.15 (s, 1H), 6.3 (s, 1H), 7.35 (s, 1H); ^{13}C NMR ($CDCl_3$, δ = ppm, J = Hz): δ 10.5, 27.7, 28.6, 50.3, 79.7, 106.1, 110.3, 141.9, 155.2, 155.5; IR (neat): 3337, 2971, 234, 2878, 1694, 1501, 1366, 1164, 1008, 731; MS (m/z) 226 (M+1) 211, 196, 192, 170; HRMS calcd for $C_{12}H_{20}NO_3$ 226.1437, found 226.1442.

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