Iridium-Catalyzed Reductive Coupling of Grignard Reagents and Tertiary Amides

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Procedure (Note 1)

*N,N-Dimethyl-1-phenylpropan-1-ammonium hydrochloride salt (1).* To a flame-dried 1 L three-necked round-bottomed flask equipped with a 3.5 cm Teflon-coated magnetic oval stir bar, a 125 mL addition funnel with pressure-equalization arm topped by a rubber septum, a thermocouple to measure internal temperature, and a rubber septum, is charged dimethylbenzamide (14.9 g, 100 mmol, 1.0 equiv) (Note 2) and carbonylchlorobis(triphenylphosphine)iridium(I) (39.0 mg, 0.05 mmol, 0.05 mol %) under a nitrogen atmosphere (Note 3). Methylene chloride (500 mL) (Note 4) is then added via cannula (Figure 1) before 1,1,3,3-tetramethyldisiloxane (35.3 mL, 200 mmol, 2.0 equiv) (Note 5) is added to the stirring (300 rpm) mixture via syringe over 3 min (Note 6).

The reaction is monitored by silica gel TLC using 50% EtOAc-pentane as the eluent (Figure 2) (Note 7). After 45 min (Note 8) the reaction is complete, and the flask is immersed in a −78 °C dry ice/acetone cooling bath. While the solution is cooling, ethylmagnesium bromide (3.0 M in Et2O, 36.7 mL, 110 mmol, 1.1 equiv) (Note 9) is transferred via cannula to the addition funnel.

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Figure 1. Reaction set-up, (A) before the addition of TMDS (left) and (B) 40 min after the addition of TMDS (right). (Photo provided by checkers)

Figure 2. TLC after 40 min demonstrating absence of starting material (Photo provided by checkers)
(Figure 3). The Grignard reagent is then added dropwise over 8 min to the reaction mixture (Note 10). Subsequently, the cooling bath is removed and stirring (600 rpm) is maintained for an additional 4 h, over which time the reaction temperature reaches 23 °C (Note 11).

![Figure 3. Reaction mixture just before addition of the Grignard reagent (Photo provided by checkers)](image)

The reaction vessel is then placed in an ice bath, and while the temperature is decreasing, 125 mL of saturated aqueous NH₄Cl is added to the addition funnel. Once the internal temperature reaches 5 °C, the aqueous NH₄Cl
solution is slowly added to the stirred reaction mixture. An additional
125 mL of saturated aqueous NH₄Cl is slowly added via the addition funnel
to the stirred reaction mixture (Figure 4) (Note 12). The mixture is transferred
to a 1 L separatory funnel, water (200 mL) and CH₂Cl₂ (100 mL) are used to
wash the flask, and the layers are partitioned. The aqueous layer is extracted.
once with CH₂Cl₂ (200 mL). The combined organic layers are dried over anhydrous Na₂SO₄ (100 g) and vacuum-filtered through a glass funnel stopped with cotton, while applying house vacuum (150 mmHg) (Figure 5). The filtrate is concentrated on a rotary evaporator under reduced pressure (40 °C, 375 mmHg, then 30 mmHg) to afford a colorless oil (approximately 35 g). The residue is transferred to a 500 mL round-bottomed flask and dissolved in Et₂O (200 mL) (Note 13), and the flask is cooled in a 0 °C ice bath. Hydrochloric acid in dioxane (4.0 M, 37.5 mL, 150 mmol, 1.5 equiv) (Note 14) is added continuously over 1 min to the vigorously stirring (1100 rpm) ethereal solution (Figure 6) (Note 15).

![Figure 6. (A) Addition of the HCl in dioxane solution, leading to the (B) precipitation of the HCl salt (Photo provided by submitters)](image)

The resulting biphasic solution is concentrated on a rotary evaporator under reduced pressure (40 °C, 450 mmHg, then 35 mmHg). To the resulting mixture (solid in an oil) is then added EtOAc (200 mL) (Note 16), and the
suspension is stirred in an oil bath set to 70 °C. Methanol (8.0 mL) (Note 17) is added dropwise until all solids dissolve (Figure 7). Additional methanol (2.0 mL) (Note 18) is then added, the stir bar is removed, and the resulting hot solution is then placed in a refrigerator at –22 °C and left to crystallize for 16 h (Note 19). The crystals obtained are then filtered in a 150 mL sintered glass funnel (porosity 2) under house vacuum (150 mmHg) and transferred to a 250 mL round-bottomed flask. The crystals are further dried under high vacuum (0.15 mmHg) for 20 h to afford the desired product 1 (12.1 g, 61%) as white crystals (Figure 8) (Notes 20, 21, 22, and 23).

Figure 7. (A) Resuspension in hot EtOAc, followed by (B) dissolution in EtOAc/MeOH (Photo provided by submitters)
Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of “Prudent Practices in the Laboratory” (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also “Identifying and Evaluating Hazards in Research Laboratories” (American Chemical Society, 2015) which is available via the associated website “Hazard Assessment in Research Laboratories” at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with N,N-dimethylbenzamide, carbonylchlorobis(triphenylphosphine)iridium (I), dichloromethane, 1,1,3,3-tetramethyldisiloxane, ethylmagnesium bromide (3.0 M in diethyl ether), diethyl ether, hydrochloric acid in dioxane (4.0 M), ethyl acetate, and methanol. It should be noted that higher catalyst loadings can potentially generate a significant amount of...
flammable hydrogen gas. It is advisable to conduct these experiments in a large flask, adequately vented to a standard inert gas manifold or bubbler into a fume hood.

2. N,N-Dimethylbenzamide (99%) was purchased from Sigma-Aldrich. An insoluble impurity was removed by dissolving the amide in hot EtOAc (400 mL per 25 grams of starting material) and filtering over Celite, then concentrating first on a rotary evaporator (45 °C, 120 mmHg then 35 mmHg), and then on a Schlenk line (23 °C, 0.15 mmHg, stirred at 600 rpm for 15 h).

3. Carbonylchlorobis(triphenylphosphine)iridium (I) (99%) was purchased from Strem Chemicals, Inc. and used as received.

4. Dichloromethane (anhydrous, ≥ 99.8%) was purchased from Sigma-Aldrich, dried over activated 4Å molecular sieves (1g/10 mL of solvent) for at least 24 h, and degassed by sparging with argon for 2 h prior to starting the reaction.

5. 1,1,3,3-Tetramethyldisiloxane (97%) was purchased from Sigma-Aldrich and used as received.

6. Over circa 15 min, the yellow color of the solution was observed to fade and some gas evolution was observed. The temperature of the reaction gradually increased to 27–30 °C.

7. TLC was performed using 50% EtOAc-pentane as the eluent. An aliquot (50 µL) of the reaction mixture was diluted in CH₂Cl₂ (150 µL) before spotting on the TLC plate and elution. The tertiary amide starting material (Rf = 0.26) and the resultant intermediate (Rf = 0.86) could both be visualized under a UV lamp.

8. Complete disappearance of starting material was observed after 40 min.

9. Ethylmagnesium bromide (3.0 M in diethyl ether) was purchased from Sigma-Aldrich and used as received.

10. The addition was started 15 min after the flask was immersed into the –78 °C bath. The internal reaction temperature was kept below –50 °C at all times during the addition, ranging from –70 °C to –59 °C.

11. The temperature reached 20 °C after 3 h. The reaction mixture remained colorless.

12. The addition was started 10 min after the flask was immersed into the 0°C bath. The internal reaction temperature was kept below 10 °C at all times during the addition. The first drops were carefully added, and overall the addition lasted between 15–25 min. A significant amount of gas evolved at this stage, including ammonia. The reaction mixture should be kept in a fume hood at all times.
13. Diethyl ether (anhydrous, ≥99.7%) was purchased from Sigma-Aldrich and used as received.
14. Hydrochloric acid in dioxane (4.0 M) was purchased from Oakwood Chemical and used as received. Submitters purchased hydrochloric acid in dioxane (4.0 M) from Fluorochem Ltd. and used the solution as received.
15. Immediate formation of a white solid was observed. Vigorous stirring was necessary to maintain homogeneity during precipitation. A suspension was not obtained, but rather a biphasic mixture.
16. Ethyl acetate (anhydrous, 99.8%) was purchased from Sigma-Aldrich and used as received.
17. Methanol (≥99.9%) was purchased from Sigma-Aldrich and used as received.
18. The crystallization was not seeded or initiated.
19. Failure to add additional methanol after the solids dissolve results in a higher yield of product (70-75%) but purity below 97.0%.
20. A second reaction on the same scale provided 12.0 g (60%) of the product.
21. mp : 159–160 °C; run 2 mp : 163–165 °C (lit2 167–169 °C; submitters : 160–162 °C). 1H NMR (400 MHz, CDCl3) δ: 0.73 (t, J = 7.4 Hz, 3H), 2.11–2.23 (m, 1H), 2.42 (dq, J = 13.0, 7.4, 3.8 Hz, 1H), 2.52 (d, J = 5.3 Hz, 3H), 2.67 (d, J = 4.9 Hz, 3H), 3.57 (dt, J = 11.7, 4.5 Hz, 1H), 7.36–7.45 (m, 5H), 12.46 (br s, 1H). 13C NMR (101 MHz, CDCl3) δ: 10.7, 23.8, 38.6, 42.6, 72.6, 129.5, 129.7, 130.3, 131.0. IR (film): 3493, 2938, 2353, 1637, 1466, 1154, 1073, 1006, 922, cm⁻¹. HRMS: (ESI) m/z calcd. for C11H18N [M+H]+ 164.1434, found 164.1439.
22. The purity of the first run was found to be 97.2% with quantitative NMR using 1,3,5-trimethoxybenzene (≥99%, purchased from Sigma-Aldrich and used as received) as internal standard. The purity of the second run (Note 20) was found to be 98.8%.
23. Additional crops of crystals can be obtained as follows: The mother liquor is concentrated on a rotary evaporator under reduced pressure (40 °C, 375 mmHg, then 33 mmHg), and crystallization from hot EtOAc (200 mL)/MeOH (4.0mL), as described previously, gives a second crop of crystals. Finally, the mother liquor is once more concentrated on a rotary evaporator under reduced pressure (40 °C, 375 mmHg, then 40 mmHg), and diethyl ether (200 mL) is added to produce a suspension. This suspension is sonicated for 1 min, then placed at −15 °C for 16 h. Final filtration as previously described yields a third crop of crystals. In the hands of the checkers, the second and third crops of crystals gave
material that was less pure (85–91%) than the first crop, so they were not included in the final yield. The submitters did use material obtained from subsequent recrystallization crops, and their total yields were 75% and 78% for the two runs, respectively.

Working with Hazardous Chemicals

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Discussion

Amines are ubiquitous in the field of organic chemistry, due to their extraordinary Lewis and Brønsted basicity. Secondary amines can be used in organocatalysis applications, providing a chiral template for asymmetric transformations such as α-functionalization of ketones or enantioselective reductive processes, whereas tertiary amines are widely encountered as ligands for transition metal catalysts. As bases, they can sequester acids or buffer the pH of a reaction, while the ammonium salts themselves can be utilized as chiral counterions or as phase-transfer catalysts. Tertiary amines are also found in a wide variety of natural products and drug compounds.

The disconnection of a C–N bond has been a method of choice and allows construction of tertiary amines through reductive amination, amine alkylation, or Buchwald-Hartwig type N-arylation. These methods tend to introduce the amine at a late stage in the synthesis due to the reactive nature of the functional group, or require the use of a protecting group. A reductive approach from an amide offers the possibility to carry the nitrogen-containing moiety through multiple steps as a stable functional group, while enjoying the ease of formation of one of the most - if not the most - established bond-formation methodologies. Reductive activation of the amide carbonyl has been achieved, but often requires stoichiometric use of reactive reagents such as PCl₃ or Tf₂O, or prior functional group manipulation.

Our group and others have reported the reductive activation of amides and lactams, allowing for a mild catalytic system (Ir(CO)Cl(PPh₃)₂ alongside 1,1,3,3-tetramethyldisiloxane) to access synthetically useful hemiaminals, which readily undergo carbon-carbon bond formation with Grignard reagents in a convenient one-pot procedure.
Scheme 1. Grignard addition to amides via reductive activation

Although the catalyst is iridium-based, the cost and scarcity of the metal is balanced by the high turnover number (shown to be at least 2000 on decagram scale), allowing for the use of low (down to 0.05 mol%) catalyst loading.\textsuperscript{13} TMDS is also a very cost-efficient source of hydride,\textsuperscript{14} and together they form a mild yet highly chemoselective catalytic system, allowing great functional group tolerance on the amide moiety. A wide range of Grignard reagents can be coupled, containing various functional groups or handles for further downstream functionalization. sp\textsuperscript{3}, sp\textsuperscript{2} and sp\textsuperscript{hybridized organomagnesium reagents were all linked to the α-position in good to excellent yield. Finally, late-stage functionalization of drugs or natural products was also demonstrated.

In summary, the mild, yet highly active and chemoselective catalytic system formed from Vaska’s complex and 1,1,3,3-tetramethyldisiloxane...
allows reductive coupling of Grignard reagents to amides in an efficient fashion. Given the ubiquitous presence of amides and the widespread availability of Grignard reagents, this reaction offers a new strategy for the efficient and scalable synthesis of tertiary α-branched amines including application in late-stage functionalization.

References

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**Appendix**

**Chemical Abstracts Nomenclature (Registry Number)**

- Dimethylbenzamide: Benzamide, N,N-dimethyl-; (611-74-5)
- Carbonylchlorobis(triphenylphosphine)iridium(I): Iridium, carbonylchlorobis(triphenylphosphine)-; (14871-41-1)
- 1,1,3,3-Tetramethyldisiloxane: Disiloxane, 1,1,3,3-tetramethyl-; (3277-26-7)
- Ethylmagnesium bromide solution: Magnesium, Bromoethyl-; (925-90-6)
- N,N-Dimethyl-1-phenylpropan-1-ammonium hydrochloride salt: N,N-Dimethyl-1-phenyl-1-propylamin-Hydrochlorid; (24301-87-9)
- HCl in dioxane (4.0 M): Hydrochloric acid; (7647-01-0)
Pablo Gabriel completed his Master’s degree at the Graduate School of Montpellier in France. During his studies, he had the opportunity to perform internships with Professor Steve Davies in Oxford in 2014 on asymmetric synthesis of azetidinium ions, and in 2015 at Mane, a fragrance company in southern France. He then came back to Oxford, where he is currently a D. Phil student in the Synthesis for Biology and Medicine CDT program, investigating iridium-catalyzed functionalization of amides under the supervision of Professor Darren J. Dixon.

Lan-Gui Xie received his Ph.D. degree from the University of Science and Technology of China (USTC) in 2012. After that he joined the group of Professor Nuno Maulide at Max-Planck Institut für Kohlenforschung, Germany, for postdoctoral research training and transitioned with the group to the University of Vienna, Austria in 2013. In 2016, Dr Xie was awarded a Marie Curie Individual Fellowship to investigate iridium-catalyzed reductive functionalization of amides under the supervision of Professor Darren J. Dixon at the University of Oxford, UK, and in September 2018 moved to a professorship position at Nanjing Normal University, China.

Darren J. Dixon obtained his MA and D. Phil from the University of Oxford under the supervision of Professor Stephen Davies. After postdoctoral work with Professor Steve Ley FRS he was appointed to the Staff of the Department of Chemistry, University of Cambridge in 2000. In 2004 he took a Senior Lectureship at The University of Manchester and was promoted to Reader in 2007. In 2008, he moved to his current position of Professor of Chemistry, University of Oxford. He directs the EPSRC CDT in Synthesis for Biology and Medicine and his honors include an EPSRC Leadership Fellowship, the RSC Catalysis in Organic Chemistry Award, the AstraZeneca Research Award and Novartis Lectureship.
Karli R. Holman received her B.S. degree from Westmont College, where she worked with Dr. Amanda Silberstein on the development of Ni-catalyzed borylation methodology. She performed internships at UCLA with Dr. Neil Garg and at Apeel Sciences, an agrochemical company in Santa Barbara, CA. Karli is now a Ph.D. candidate at the California Institute of Technology, where she is investigating palladium-catalyzed cyclization reactions toward the total synthesis of natural products under the supervision of Dr. Sarah Reisman.
$^1$H NMR (400 MHz, CDCl$_3$) δ 12.46 (s, 1H), 7.45 – 7.36 (m, 5H), 3.87 (dt, $J = 11.7$, 4.2 Hz, 1H), 2.67 (d, $J = 4.9$ Hz, 3H), 2.52 (d, $J = 5.1$ Hz, 3H), 2.42 (ddq, $J = 13.0$, 7.4, 3.8 Hz, 1H), 2.25 – 2.09 (m, 1H), 0.73 (t, $J = 7.3$ Hz, 3H).
$^{13}$C NMR (101 MHz, CDCl$_3$) δ 131.01, 130.27, 129.73, 129.51, 72.58, 42.64, 38.64, 23.75, 10.73.
Batch 2, run 1:

Molar ratio = (99.6/3)/(100/3) = 0.996
Wt % = (14.1*200*0.996*1)/(17.1*168) = 97.8%
Batch 2, run 2:

Molar ratio = (92.6/3)/(100/3) = 0.926
Wt % = (25.5*200*0.926*1)/(28.9*168) = 97.3%
Batch 2, run 3:

Molar ratio = \frac{110}{100} = 1.10

Wt % = \frac{18.1 \times 200 \times 1.10 \times 1}{24.6 \times 168} = 96.4\%

Average purity over 3 runs for batch 2 = 97.2\%