ORGANOMETALLICS

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Preparation of Substituted Tetrahydroisoquinolines by Pd(II)-Catalyzed NH_2-Directed Insertion of Michael Acceptors into C−H Bonds Followed by NH_2-Conjugated Addition

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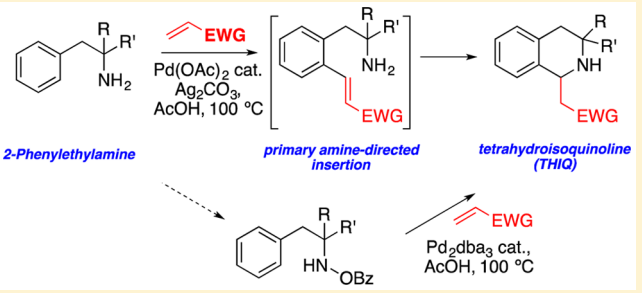
Supporting Information

ABSTRACT: 3,3-Disubstituted tetrahydroisoquinolines are prepared in one step from Michael acceptors and 2-phenylethylamines under Pd catalysis and Ag_2CO_3 as an oxidant. Presumably, activation of an *ortho* C−H bond of the aromatic ring with Pd(II) is directed by the primary amine to form a palladacycle. Insertion of the olefin, subsequent conjugated addition of the amine, and reductive elimination of Pd(0) affords the expected products. Silver carbonate is not necessary when 2-phenylethylamines are converted previously to *N*-benzoyloxy-2-phenylethylamines.



INTRODUCTION

The development of selective methods for the direct conversion of carbon−hydrogen bonds into carbon-heteroatom and carbon−carbon bonds remains a critical challenge in organic chemistry. An interesting approach to address this issue involves the use of substrates that contain coordinating atoms (or directing groups) that bind to the metal center in a first step, and a further rearrangement allows the C−H bond activation. A variety of palladium, rhodium, ruthenium, iridium, rhenium, and copper and to a lesser extent manganese, nickel, iron, and cobalt metal derivatives have been shown to be effective in this process.[1]

Palladium complexes are particularly attractive catalysts for such transformations because ligand-directed C−H functionalization at Pd(II) centers can be used to obtain different types of C−Y bonds (Y being carbon, oxygen, nitrogen, sulfur, or halogen). Furthermore, Pd(II) can activate C−H bonds, both at sp^2 and sp^3 sites, and a wide range of catalytic processes has been described with different nitrogen-based directing groups. These include amides, pyridines, triazoles, pyrroles, imines, oximes, azobenzenes, amines, carboxylic acids, ketones, aldehydes, esters, and hydroxyl derivatives.[2]

In contrast, few examples of the use of primary amines as directing groups have been described in spite of the fact that this functional group is ubiquitous in organic molecules, probably because the NH_2 group is too reactive toward different organic functions and also can easily coordinate too tightly to transition-metal centers. Some examples have been reported of catalytic processes using primary amines as directing groups with palladium,[3] ruthenium,[4] iridium,[5] and rhodium catalysts.[6] It should be noted that in some of these processes, the NH_2 fragment participates in a second subsequent reaction to afford the final organic molecule. Alternatively, Dong et al. have recently described the use of a transient imines generated *in situ* for the palladium-catalyzed arylation of aliphatic C−H bonds of primary amines.[7]

It has been recently reported that the ruthenium- and rhodium-catalyzed *ortho*-alkenylation of benzylamines affords the corresponding isoindolines as a consequence of the reactivity of the five-membered metallacycle formed in the catalytic process.[4b] We have also reported that the NH_2-directed Pd(II)-catalytic carbonylation of quaternary aromatic α-amino esters to yield benzolactams shows a strong bias to six-membered lactams over the five-membered analogues, which can be explained by the easy mode in which the six-membered palladacycle is formed and by its greater reactivity in the catalytic cycle.[3a,8] Taking into account this background and considering also that Vicente et al. have described the synthesis of eight-membered palladacycles derived from the insertion of alkenes into the palladium−carbon bond of six-membered cyclopalladated primary arylamines,[9] we studied the palladium-catalyzed insertion of olefins into the carbon−hydrogen bond of some primary amines, selected to obtain six-membered

Received: December 19, 2016

ACS Publications © XXXX American Chemical Society

DOI: 10.1021/acs.organomet.6b00944
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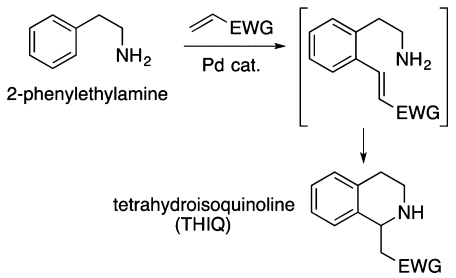
metallacycles, and the possible subsequent intramolecular Michael addition to afford tetrahydroisoquinolines (THIQs), a common and privileged scaffold present in many biologically active compounds (Scheme 1).[10,11]

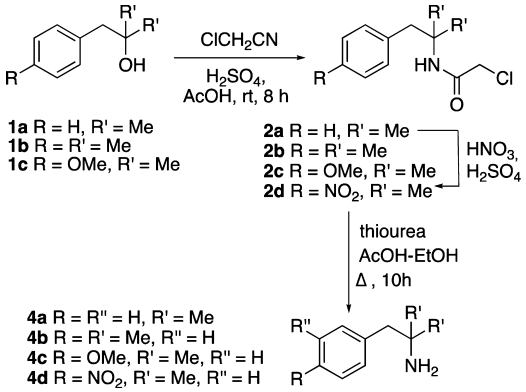
Scheme 1. Synthesis of THIQs from 2-Phenylethylamines



RESULTS AND DISCUSSION

Synthesis of 2-Phenylethylamines. On the basis of our experience with NH_2-directed carbonylations[3a,8] and insertion of allenes,[3b] we initially attempted the cyclization of α,α-disubstituted primary phenylethylamines. Primary amines **4a–c** were obtained by Ritter–Jirgensons reaction[12] from alcohols **1a–c** in a two-step process. 2-Chloroacetonitrile in acetic acid using concentrated H_2SO_4 as catalyst afforded 2-chloroacetamides **2a–c** that reacted with thiourea to produce amines **4a–c**. Nitration of amide **2a** afforded amide **2d** that was converted into amine **4d** by reaction with thiourea (Scheme 2).

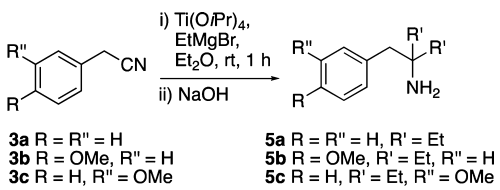
Scheme 2. Synthesis of Primary Amines 4a–d



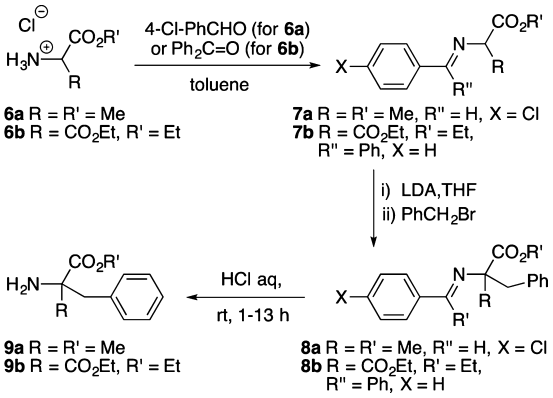
Primary amines **5a–c** were obtained from 2-phenylacetonitriles **3a–c** by reaction with $Ti(OiPr)_4$/EtMgBr in Et_2O (Scheme 3).[13]

Amino esters **9a–b** were obtained by formation of Schiff bases **7a–b** followed by alkylation with benzyl bromide and subsequent acid hydrolysis of the benzylated imines **8a–b** formed (Scheme 4).

Scheme 3. Synthesis of Primary Amines 5a–c



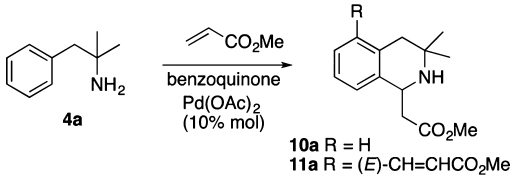
Scheme 4. Synthesis of Amino Esters 9a–b



Reactivity of 2-Phenylethylamines. The preliminary catalytic studies were focused on the reaction of the primary amine **4a** with methyl acrylate using commercially available palladium(II) acetate as catalyst and benzoquinone as the oxidant, in acetic acid at 100 °C. These conditions have shown to be the best for the carbonylation of primary amines catalyzed by palladium, and in this case, the choice of benzoquinone as the oxidant was a key factor for the success of the catalytic process.[3a,8] Furthermore, the use of acetic acid as a solvent facilitates the cyclopalladation reaction and also the partial protonation of the amino group slows down the direct conjugate addition of the amine to methyl acrylate.

Some experiments were performed modifying the benzoquinone/amine ratio, the methyl acrylate/amine ratio, and the reaction time (see Table 1). We found that the insertion of

Table 1. Reaction of Amine 4a with Methyl Acrylate



entry	t (h)	benzoquinone (% mol)	methyl acrylate (% mol)	yield (%)	ratio **10a:11a**
1	3	200	200	41	83:17
2	3	120	120	63	86:14
3	3	120	100	32	91:9
4	6	120	120	35	80:20

methyl acrylate and also the subsequent Michael addition took place to obtain the expected tetrahydroisoquinoline **10a** regioselectively. Unfortunately, the yields of the processes were moderate (32–63%) and compound **11a**, coming from the double insertion process, was also obtained in all cases.

Because Ag_2CO_3 has been shown to be a good oxidant for the palladium-catalyzed alkenylation of oxalyl-amide-protected phenylpropylamine derivatives,[14] we performed some experiments with this silver(I) oxidant (see Table 2). Good results were obtained using 10% molar $Pd(OAc)_2$, 1.1 equiv of silver carbonate and a methyl acrylate/primary amine molar ratio of 2:1, in acetic acid at 100 °C. Under these conditions, the yield of the process was 95%, and the **10a:11a** ratio was 95:5 (Table 2, entry 1).

The reaction between the primary amine **4a** and methyl acrylate was also performed in the same reaction conditions,

DOI: 10.1021/acs.organomet.6b00944
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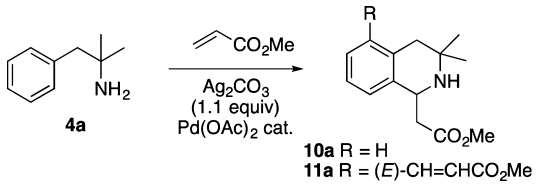
Table 2. Reaction of Amine 4a with Methyl Acrylate and Ag_2CO_3 as Oxidant



entry	t (h)	$Pd(OAc)_2$ (% mol)	methyl acrylate (% mol)	yield (%)	ratio **10a:11a**
1	3	10	200	95	95:5
2	3	10	110	37	92:8
3	1	10	200	28	89:11
4	3	2	200	46	97:3
5	3	4	200	65	97:3
6	3	5	200	45	98:2
7	6	5	200	56	95:5
8[a]	3	10	200	81	95:5

[a]2 equiv of silver acetate as the oxidant.

changing the silver carbonate by the corresponding acetate and hexafluoroantimonate silver salts, in order to evaluate the role of the silver salt in the process. The results obtained when silver acetate was used as the oxidant were of the same order compared to the results obtained with silver carbonate: 81% yield and a **10a:11a** ratio of 95:5 (Table 2, entry 8). In contrast, the catalytic process did not work when $Ag[SbF_6]$ was used as the oxidant. These results can be explained by a M06 density functional theory study on the roles of noninnocent additives in palladium catalyzed C−H bond activation reactions.[15] This work showed that a heterobimetallic Pd(II)-μ-X-Ag(I) species is the most likely catalyst in a palladium acetate amination reaction. There is a short contact between silver(I) and palladium(II) in the transition state, which facilitates the redox process. Besides this, these authors showed that the proton abstraction is performed by the anion bonded to the silver atom. Our findings showing that silver acetate or carbonate salts should be used instead of the hexafluoroantimonate salt agree with this proposal because both acetate and carbonate anions can act as a Brønsted bases as well as bidentate ligands.

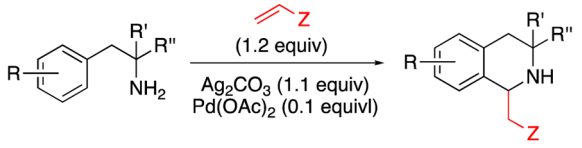
When the reaction was performed with the same primary amine **4a** and *n*-butyl acrylate, in the optimized conditions, the yield of the process was 93%, and the tetrahydroisoquinoline **10b** and double addition product **11b** ratio was 98:2. In this case, the less volatile *n*-butyl acrylate allowed us to reduce the amount of acrylate to 1.2 equiv without a decrease in yield (90%) of **10b**. Therefore, we used these conditions as our standard for a variety of amines and Michael acceptors (Scheme 5).

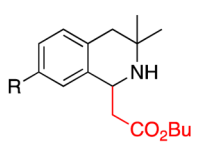
The reaction between *para*-substituted phenylethylamines **4b−d** and *n*-butyl acrylate afforded the expected tetrahydroisoquinolines **10c−e** in 65−85% yield. The reaction works with either electron-deficient or electron-rich groups attached to the phenyl group. The more hindered amines **5a−c** were still reactive, and tetrahydroisoquinolines **12a−c** were formed.

We next explored the reactivity of different activated monosubstituted olefins such as 3-buten-2-one, acrylonitrile, or *N*-acryloylmorpholine with amines **4a** and **5a**. Some of these olefins are volatile and/or are not as good Michael acceptors as *n*-butyl acrylate, and as expected, tetrahydroisoquinolines **13a−b** and **14a−c** were obtained in lower yields. Amino ester **9a** was also reactive with some of these Michael acceptors, and tetrahydroisoquinolines **15a−c** were obtained as a 1:1 mixture of diastereoisomers. No double insertion product was detected in any case, but in the case of *N*-acryloylmorfoline, the formation of a 20% of the product of addition of AcOH to *N*-acryloylmorpholine was observed.

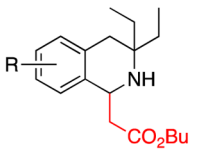
Although the reaction was not diastereoselective, **15a** diastereoisomers could be separated by a flash column chromatography, using a mixture of ethyl acetate/hexane (50/50) as the eluent. A NOESY experiment showed that the hydrogen atom adjacent to the NH fragment presented a NOE interaction with the protons of the methyl group bonded

Scheme 5. Reaction of Primary Amines 4a−d, 5a−c, and 9a−b with Michael Acceptors

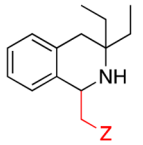




10b 90% (R = H)
10c 85% (R = Me)
10d 70% (R = OMe)
10e 65% (R = NO_2)

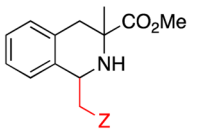


12a 62% (R = H)
12b 54% (R = *p*-OMe)
12c 52% (R = *m*-OMe)

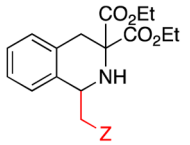


13a 57% (Z = CO_2Me)
13b 42% (Z = CN)

14a 51% (Z = $COCH_3$)
14b 42% (Z = CN)
14c 42% (Z = CON O)



15a 78% (Z = CO_2Bu)
15b 58% (Z = CN)
15c 55% (Z = CON O)



16a 73% (Z = CO_2Bu)
16b 80% (Z = CN)

DOI: 10.1021/acs.organomet.6b00944
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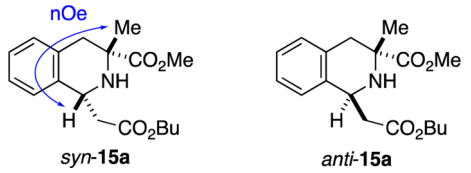
to the chiral carbon atom only in the second eluted diastereomer, showing that these atoms are in *syn* disposition in this diastereoisomer (Chart 1).

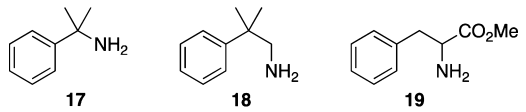
Chart 1. *Syn*-15a and *anti*-15a Diastereomers



Amino ester **9b** reacted with *n*-butyl acrylate and acrylonitrile to afford tetrahydroquinolines **16a–b** in 73% and 80% yield, respectively.

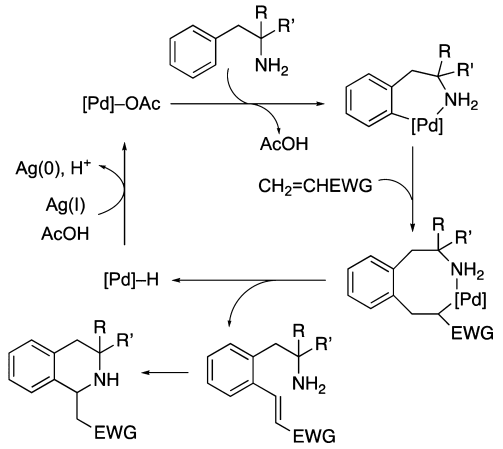
It should be noted that the process does not work with neither the primary amines **17–18** nor with the amino ester **19** (see Chart 2), showing that the formation of a six-membered palladacycle and the presence of a quaternary carbon atom in α position to the amine are key factors for the catalytic process.

Chart 2. Primary Amines 17–19



A plausible mechanism for the alkenylation of primary amines is shown in Scheme 6. The first step is the

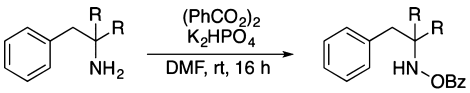
Scheme 6. Plausible Pathway for the *ortho*-Alkenylation



cyclometalation of the amine. A computational study has proposed that this reaction occurs by a highly concerted process in which the palladium(II) center provides electrophilic activation of a C–H bond, and an acetato ligand acts as an intramolecular base for the C–H bond deprotonation.[16] In a second step, the coordination of alkene and subsequent insertion of this molecule affords the corresponding eight-membered metallacycles, closely related to those reported in a stoichiometric reaction by Vicente et al.[9] Then β-elimination and subsequent oxidation of the palladium-hydrido species formed by silver(I) compounds affords the expected *ortho*-alkenylated amines and regenerates the active Pd(II)-acetato species.

Comparison of the results using benzoquinone or silver salts suggested that the oxidant had a key role in this catalytic reaction. Therefore, we explored the use of an internal oxidant. For this purpose, *N*-benzoyloxy-2-phenylethyl-amines **20a–b** were easily prepared from the corresponding amines **1a** and **5a** (Scheme 7).

Scheme 7. Synthesis of *N*-Benzoyloxy-2-phenylethyl-amines 20a–b



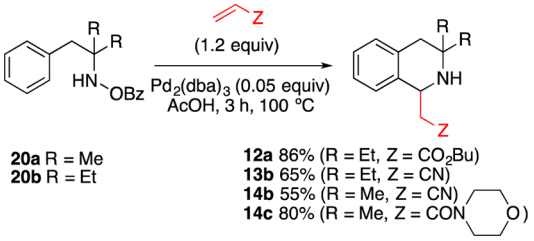
1a R = Me
5a R = Et

20a R = Me, 90%
20b R = Et, 75%

We replaced a NH bond of the primary amine with an N-OR_1 bond, OR_1 being an oxygen-containing fragment (OBz), which can act as an internal oxidant. We performed some experiments of the reaction between *n*-butyl acrylate and the *O*-benzoyl hydroxylamine **20a**. We found that effectively the catalytic process can take place without the addition of any extraneous oxidant to obtain the same compound of the corresponding primary amine (**10b**) under the same conditions used before: $Pd(OAc)_2$ as a catalyst, acetic acid as a solvent, at 100 °C for 3 h. We also found that the yield of the process and the ratio between tetrahydroisoquinoline/double addition product ratio were similar to those obtained in the presence of Ag_2CO_3. Slightly better yields were obtained were obtained when $Pd_2(dba)_3$ was used as a catalyst.

Fortunately, the tetrahydroisoquinolines that were obtained in lower yields with silver cabonate as an oxidant (i.e., **12a**, **13b**, and **14b–c** in Scheme 5) gave higher yields when the corresponding *O*-benzoylhydroxylamines **20a–b** were used under the new conditions (Scheme 8).

Scheme 8. Reaction of *O*-Benzoylhydroxylamines 20a,b with Michael Acceptors



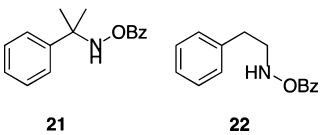
20a R = Me
20b R = Et

12a 86% (R = Et, Z = CO_2Bu)
13b 65% (R = Et, Z = CN)
14b 55% (R = Me, Z = CN)
14c 80% (R = Me, Z = CON O)

The formation of a six-membered palladacycle and the presence of a quaternary carbon atom in α position were also key factors for the catalytic process, because when the reaction was performed with compounds **21** and **22** (see Chart 3), no tetrahydroquinolines were obtained.

The high reactivity of the six-membered metallacycles can explain why this factor plays a key role in the catalytic process.

Chart 3. *O*-Benzoylhydroxylamines 21 and 22



DOI: 10.1021/acs.organomet.6b00944
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In a previous work, we have shown that the palladium-catalyzed carbonylation of amino esters and primary amines shows a strong bias to the six-membered lactams over five-membered analogues.[8] The fact that full substitution of the carbon in the α-position of the coordinating atom facilitates the cyclopalladation reaction and this can be explained by a decrease in $\Delta S^{\ddagger}$ requirements.[17] This specificity can also be related with the well-known Thorpe−Ingold effect in organic cyclization reactions.[18]

CONCLUSIONS

3,3-Disubstituted tetrahydroisoquinolines can be obtained in one step from Michael acceptors and 1,1-disubstituted-2-phenylethylamines with catalytic $Pd(OAc)_2$ and Ag_2CO_3 as an oxidant. A key point is the use of acetic acid as solvent since this, presumably, accelerates C−H activation and inhibits intermolecular conjugate addition of the amine to the Michael acceptor. The type of silver salt is also important, and bidentate anions such as carbonate or acetate seem to be necessary. When 2-phenylethylamines are oxidized previously with benzoyl peroxide to *N*-benzoyloxy-2-phenylethylamines, the same reaction can be achieved without using stoichiometric silver salts. Furthermore, better yields are obtained with Pd(0) for the less electrophilic Michael acceptors than with Ag_2CO_3 and amines. The scope of the reaction is limited to the use of 1,1-disubstituted-2-phenylethylamines.

EXPERIMENTAL SECTION

General Considerations. Amino esters **6a−b**, 2-phenylacetonitriles **3a−c**, the amine **17**, and the alcohol **1a** were obtained from commercial sources and used as received. The alcohols **1b−c** were prepared by addition of methyl magnesium bromide to the commercially available ethyl 2-tolylacetate and (4-methoxyphenyl)-propan-2-one, respectively. Amine **19** was obtained from its commercially available hydrochloric salt, while *O*-benzoylhydroxylamines **21** and **22** were prepared respectively from commercial cumyl amine and phenethylamine following the general procedure for the oxidation of the amines that is reported in this section. Imines **7a** and **8a** were prepared according to our previous work.[8] Imines **7b** and **8b** were obtained by a known procedure.[19] Amine **18** was prepared from 2-phenylacetonitrile **3a** following a described procedure.[20] Benzoyl peroxide was used as Luperox A75. Solvents were distilled and dried before use.[21] ^{1}H (400 MHz) and ^{13}C (101 MHz) nuclear magnetic resonance (NMR) spectra were registered using a Varian Mercury 400 MHz NMR spectrometer. $CDCl_3$ (99.9%) was used as solvent while $SiMe_4$ (TMS) was used as reference. The coupling constants (J) are expressed in Hz, and the chemical shifts are represented in part per million (ppm). The signals multiplicities are reported with the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). More complicated signals are described as combination of the indicated abbreviations: e.g dd (double of doublets), dt (double of triplets), etc. Two-dimensional experiments (NOESY, HSQC) were performed to confirm the signal assignments. Mass spectra (HRMS) were recorded in an Agilent LC/MSD-TOF by CCiTUB at University of Barcelona.

Synthesis of Primary Amines 4a−c from Alcohols. The corresponding tertiary alcohol (5.61 mmol) was dissolved in 2-chloroacetonitrile (2.0 mL, 34 mmol) and acetic acid (2.7 mL). The solution was cooled to 0 °C, and concentrated sulfuric acid (2.7 mL, 50 mmol) was added dropwise. After the addition, the mixture was stirred for 5 h at rt, and then ice was added carefully. The mixture was extracted three times with diethyl ether, and the collected organic phases were washed twice with a saturated solution of Na_2CO_3 and brine. Finally, the organic phase was dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The excess of 2-chloroacetonitrile was removed under vacuum to obtain the 2-chloroacetamide as a white solid, which was directly used for the next steps without further purifications. Thiourea (0.510 g, 6.72 mmol) was added to a solution of the crude 2-chloroacetamide (5.60 mmol) in a 1:5 mixture of acetic acid and ethanol (60 mL). The reaction was heated to reflux overnight. Then it was cooled, and the ethanol was evaporated at reduced pressure. A 2 N aqueous solution of HCl was added, and the resulting aqueous suspension was washed two times with CH_2Cl_2. Solid Na_2CO_3 was added to the aqueous solution until pH = 10−11, which was subsequently extracted three times with CH_2Cl_2. The collected basic organic phases were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure to afford the pure amine.

4a. Colorless oil. 0.567 g (3.81 mmol) from 0.750 g (5.00 mmol) of **1a** (76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.18 (m, 5H), 2.67 (s, 2H), 1.22 (br s, 2H), 1.12 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.4, 130.4, 127.9, 126.2, 51.1, 44.5, 30.3. HRMS (ESI): m/z calcd for $[M + H]^+$, 150.1277; found, 150.1280.

4b. Colorless oil. 0.766 g (4.70 mmol) from 0.918 g (5.61 mmol) of **2b** (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 8.1 Hz, 2H), 2.62 (s, 2H), 2.33 (s, 3H), 1.11 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.7, 135.3, 130.3, 128.7, 50.7, 49.9, 30.3, 21.0. HRMS (ESI): m/z calcd for $[M + H]^+$, 164.1434; found, 164.1428.

4c. Colorless oil. 0.170 g (0.950 mmol) from 0.611 g (3.34 mmol) of **2c** (28%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 3.80 (s, 3H), 2.60 (s, 2H), 1.10 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.1, 131.3, 130.4, 113.4, 55.2, 55.2, 50.1 30.1. HRMS (ESI): m/z calcd for $[M + H]^+$, 180.1383; found, 180.1384.

Synthesis of Primary Amine 4d. Compound **1a** (0.5 mL, 3.2 mmol) was dissolved in 2-chloroacetonitrile (1.25 mL, 19.5 mmol) and acetic acid (1.55 mL). The solution was cooled to 0 °C, and concentrated sulfuric acid (1.55 mL, 29.2 mmol) was added dropwise. After the addition, the mixture was stirred for 5 h at rt, and then ice was added carefully. The mixture was extracted three times with diethyl ether, and the collected organic phases were washed with a saturated solution of Na_2CO_3 (twice) and brine. Finally, the organic phase was dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The excess of 2-chloroacetonitrile was removed at vacuum to obtain 2-chloro-*N*-(2-methyl-1-phenylpropan-2-yl)acetamide as a white solid (0.729 g, 3.24 mmol), which was directly used for the next steps without further purifications. An acidic mixture of concentrated H_2SO_4 (5.3 mL, 97 mmol) and concentrated HNO_3 (6.8 mL, 16 mmol) was added to compound **2a** (3.24 mmol) at 0 °C. After the addition, the mixture was stirred for 30 min at room temperature. The solution was diluted with water and extracted three times with CH_2Cl_2. The collected organic phases were washed with a saturated aqueous solution of Na_2CO_3 and brine. Finally, the organic phase was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel (hexane/ethyl acetate) to afford compound **2d** (638 mg, 73%) as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17−8.14 (d, J = 8.7 Hz, 2H), 7.31−7.29 (d, J = 8.7 Hz, 2H), 6.16 (br s, 1H), 3.97 (s, 2H), 3.23 (s, 2H), 1.39 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.6, 146.9, 145.4, 131.1, 123.3, 54.5, 44.1, 42.9, 27.1, 27.0. HRMS (ESI): m/z calcd for $[M + H]^+$, 271.0844; found, 271.0854.

Thiourea (0.213 g, 2.80 mmol) was added to a solution of compound **2d** (0.638 g, 2.36 mmol) in a 1:5 mixture of acetic acid and ethanol (10 mL). The reaction was heated to reflux overnight. Then it was cooled, and the ethanol was evaporated at reduced pressure. A 2 N aqueous solution of HCl was added, and the resulting aqueous mixture was washed three times with CH_2Cl_2. Then solid sodium carbonate was added until reaching pH 10, and the aqueous solution was extracted three times with CH_2Cl_2. The organic phase was dried over anhydrous Na_2SO_4, filtered, and the solvent was evaporated at reduced pressure to afford the pure amine **4d** as an orange oil (0.389 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 8.6 Hz, 2H), 7.37 (d, J = 8.6 Hz, 2H), 2.77 (s, 2H), 1.25 (br s, 2H), 1.14 (s, 6H). ^{13}C NMR

DOI: 10.1021/acs.organomet.6b00944
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(101 MHz, $CDCl_3$): δ 146.3, 131.1, 124.6, 122.6, 49.7, 49.5, 28.2. HRMS (ESI): m/z calcd for $[M + H]^+$, 195.1128; found, 195.1125.

Synthesis of Primary Amines 5a−c from Nitriles. A 3 M solution of ethyl magnesium bromide in diethyl ether (14 mL, 41 mmol) was added dropwise to a suspension of the corresponding 2-arylacetonitrile (10.24 mmol) and titanium(IV) isopropoxide (3.4 mL, 11.3 mmol) in diethyl ether (20 mL) at 0 °C. The reaction was stirred at rt for 1 h. Then it was cooled again to 0 °C, and a 10% aqueous solution of NaOH (10 mL) was added. The heterogeneous solution was stirred at rt for 30 min and filtered through a Celite pad. The biphasic mixture was extracted twice with diethyl ether. The collected organic phases were extracted several times with a 2 N aqueous solution of HCl. The aqueous layer was basified to pH 10−12 with sodium carbonate and extracted several times with dichloromethane. The organic solution was finally dried over anhydrous Na_2SO_4, filtered, and the solvent was eliminated at reduced pressure to afford the pure amine.

5a. Colorless oil. 1.000 g (5.640 mmol) from 1.2 mL (10 mmol) of **3a** (55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.18 (m, 5H), 2.63 (s, 2H), 1.36 (m, 4H), 0.91 (t, J = 7.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.2, 130.6, 127.9, 126.1, 54.1, 45.8, 31.3, 8.1. HRMS (ESI): m/z calcd for $[M + H]^+$, 178.1590; found, 178.1594.

5b. Colorless oil. 0.559 g (2.70 mmol) from 0.61 mL (4.5 mmol) of **3b** (60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 3.79 (s, 3H), 2.58 (s, 2H), 1.43−1.26 (m, 4H), 0.90 (t, J = 7.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.1, 131.4, 130.0, 113.4, 55.2, 54.1, 44.7, 31.1, 8.0. HRMS (ESI): m/z calcd for $[M + H]^+$, 208.1696; found, 208.1695.

5c. Colorless oil. 0.387 g (1.87 mmol) from 0.62 mL (4.50 mmol) of **3c** (42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23−7.17 (m, 1H), 6.80−6.73 (m, 3H), 3.80 (s, 3H), 2.61 (s, 2H), 1.46−1.30 (m, 4H), 0.91 (t, J = 7.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.3, 128.9, 123.1, 116.5, 111.3, 55.1, 45.6, 31.1, 8.04. HRMS (ESI): m/z calcd for $[M + H]^+$, 208.1696; found, 208.1695.

Synthesis of Primary Amines 9a−b from Imines 8a−b. *Amine **9a***. A suspension formed by the imine **8a**[8] (7.90 g, 24.3 mmol), and a 1 M aqueous solution of HCl (150 mL) was stirred at rt for 1 h, followed by addition of Et_2O. The phases were separated, and the aqueous layer was washed two times with Et_2O. The aqueous phase was basified to pH 10−11 with Na_2CO_3 and extracted three times with Et_2O. The ethereal phase was washed with water and brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated at reduced pressure to give the pure amine **9a** (3.500 g, 74%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.13 (m, 5H), 3.71 (s, 3H), 3.13 (d, J = 13.1 Hz, 1H), 2.81 (d, J = 13.3 Hz, 1H), 1.64 (br s, 2H), 1.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.4, 136.5, 129.9, 128.3, 126.9, 58.8, 52.0, 46.9, 26.6. HRMS (ESI): m/z calcd for $[M + H]^+$, 194.1176; found, 194.1178.

*Amine **9b***. Imine **8b**[19] (1.14 g, 2.70 mmol) was added to a mixture of a 2 N aqueous solution of HCl (10 mL) and Et_2O (50 mL), and the suspension was stirred overnight at rt. The phases were separated, and the organic layer was extracted twice with a 2 N aqueous solution of HCl. The collected aqueous phases were basified to pH 10−11 with Na_2CO_3 and extracted several times with CH_2Cl_2. The collected basic organic phases were washed with brine, dried on anhydrous $MgSO_4$, filtered, and the solvent was evaporated to give the pure amine **9b** (0.510 g, 70%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.24 (m, 3H), 7.20−7.16 (m, 2H), 4.24 (q, J = 7.1 Hz, 4H, 3.32 (s, 2H), 1.84 (br s, 2H), 1.28 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.1, 135.1, 130.2, 128.6, 127.4, 66.4, 62.1, 41.8, 14.2. HRMS (ESI): m/z calcd for $[M + H]^+$, 266.1387; found, 266.1393.

General Method for the Reaction of Amines with Michael Acceptors. The Michael acceptor (0.65 mmol) was added to a suspension of amine (0.54 mmol), $Pd(OAc)_2$ (12 mg, 0.054 mmol), and Ag_2CO_3 (164 mg, 0.595 mmol) in acetic acid (3 mL). The mixture was stirred at 100 °C for 3 h in a sealed vial. Toluene was added, and the solution was filtered through a pad of Celite. The solvents were removed under vacuum. The crude mixture was dissolved in CH_2Cl_2, and a saturated aqueous solution of Na_2CO_3 was added. The aqueous phase was extracted three times with CH_2Cl_2, the collected organic phases were dried over $MgSO_4$, filtered, and the solvent was removed under vacuum. The crude yellow oil was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH or hexane/AcOEt) to give the corresponding tetrahydroisoquinoline.

10a. Yellow oil. 0.111 g (0.475 mmol) from 0.074 g (0.50 mmol) of compound **4a** (95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17−7.03 (m, 4H), 4.46 (dd, J = 8.9, 3.2 Hz, 1H), 3.67 (s, 3H) 3.02 (dd, J = 16.4, 3.2 Hz, 1H), 2.78 (d, J = 15.9 Hz, 1H), 2.71 (dd, J = 16.4, 8.9 Hz, 1H) 2.51 (d, J = 16.0 Hz, 1H), 1.24 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.9, 135.9, 135.1, 129.6, 126.4, 125.9, 124.8, 51.6, 49.7, 49.1, 42.3, 41.1, 31.5, 24.4. HRMS (ESI): m/z calcd for $[M + H]^+$, 234.1449; found, 234.1483.

11a. Yellow oil. 8 mg (0.03 mmol) from 0.074 g (0.50 mmol) of compound **4a** (5%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 15.9 Hz, 1H), 7.43 (dd, J = 6.7, 2.1 Hz, 1H), 7.17−7.03 (m, 2H), 6.32 (d, J = 15.9 Hz, 1H), 4.48 (dd, J = 8.8, 3.3 Hz, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 2.97 (dd, J = 16.4, 3.3 Hz, 1H), 2.78 (d, J = 15.9 Hz, 1H), 2.66 (dd, J = 16.4, 8.8 Hz, 1H), 2.51 (d, J = 16.0 Hz, 1H), 1.29 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.7, 167.4, 142.2, 137.0, 134.7, 133.9, 129.6, 126.4, 124.8, 119.6, 51.6, 49.7, 48.8, 41.9, 39.3, 31.8, 24.5. HRMS ESI: m/z calcd for $[M + H]^+$, 318.1700; found, 318.1702.

10b. Yellow oil. 0.124 g (0.450 mmol) from 0.074 g (0.50 mmol) of compound **4a** (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15−6.98 (m, 4H), 4.41 (dd, J = 8.8, 3.2 Hz, 1H), 4.04 (m, 2H), 2.97 (dd, J = 16.2, 3.3 Hz, 1H), 2.71 (d, J = 15.8 Hz, 1H), 2.65 (dd, J = 16.2, 8.8 Hz, 1H), 2.48 (d, J = 15.8 Hz, 1H), 1.89 (br s, 1H), 1.56−1.48 (m, 2H), 1.34−1.25 (m, 2H), 1.20 (s, 3H), 1.05 (s, 3H), 0.87 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.6, 136.3, 135.5, 129.6, 126.3, 125.8, 124.8, 64.4, 49.8, 48.9, 42.4, 41.5, 31.7, 30.6, 24.5, 19.1, 13.7. HRMS (ESI): m/z calcd for $[M + H]^+$, 276.1958; found, 276.1954.

10c. Yellow oil. 0.123 g (0.425 mmol) from 0.082 g (0.50 mmol) of compound **4b** (85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95−6.90 (m, 3H), 4.41 (dd, J = 8.9, 3.2 Hz, 1H), 4.11−4.06 (m, 2H), 2.99 (dd, J = 16.2, 3.2 Hz, 1H), 2.73 (d, J = 15.7 Hz, 1H), 2.70 (dd, J = 16.2, 8.9 Hz, 1H), 2.48 (d, J = 15.7 Hz, 1H), 2.30 (s, 3H), 1.63−1.54 (m, 2H), 1.40−1.30 (m, 2H), 1.24 (s, 3H), 1.08 (s, 3H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.6, 135.9, 135.2, 132.2, 129.5, 127.2, 125.4, 64.3, 49.7, 48.9, 42.0, 41.5, 31.6, 30.6, 24.4, 21.2, 19.1, 13.7. HRMS (ESI): m/z calcd for $[M + H]^+$, 290.2115; found, 290.2118.

10d. Yellow oil. 0.107 g (0.350 mmol) from 0.090 g (0.50 mmol) of compound **4c** (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (d, J = 8.3 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 6.67 (s, 1H), 4.41 (dd, J = 8.8, 3.3 Hz, 1H), 4.10−4.07 (m, 2H), 3.77 (s, 3H) 2.99 (dd, J = 16.2, 3.3 Hz, 1H), 2.73 (dd, J = 16.2, 8.8 Hz, 1H), 2.67 (d, J = 15.5 Hz, 1H), 2.47 (d, J = 15.5 Hz, 1H), 1.61−1.53 (m, 2H), 1.37−1.30 (m, 2H), 1.25 (s, 3H), 1.08 (s, 3H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.5, 157.7, 137.2, 130.4, 127.4, 112.1, 110.3, 64.4, 55.2, 49.0, 49.0, 41.6, 41.4, 31.6, 30.6, 24.3, 19.1, 13.6. HRMS (ESI): m/z calcd for $[M + H]^+$, 306.2064; found, 306.2068.

10e. Yellow oil. 0.119 g (0.372 mmol) from 0.110 g (0.566 mmol) of compound **4d** (65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.22 (d, J = 8.3 Hz, 1H), 4.49 (dd, J = 8.4, 3.3 Hz, 1H), 4.11−4.08 (m, 2H), 3.06 (dd, J = 16.3, 3.3 Hz, 1H), 2.84 (d, J = 16.6 Hz, 1H), 2.80 (dd, J = 16.3, 8.4 Hz, 1H), 2.65 (d, J = 16.6 Hz, 1H), 1.60−1.56 (m, 2H), 1.37−1.32 (m, 2H), 1.28 (s, 3H), 1.09 (s, 3H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7, 143.5, 138.0, 137.5, 130.6, 121.3, 120.2, 64.7, 49.7, 48.9, 42.6, 40.9, 31.4, 30.6, 24.4, 19.1, 13.6. HRMS (ESI): m/z calcd for $[M + H]^+$, 321.1809; found, 321.1820.

12a. Yellow oil. 0.094 g (0.310 mmol) from 0.088 g (0.50 mmol) of compound **5a** (62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15−7.06 (m, 4H), 4.35 (dd, J = 9.5, 3.1, 1H), 4.12 (q, J = 7.5 Hz, 2H) 3.05 (dd, J = 16.2, 3.1 Hz, 1H), 2.74 (d, J = 15.8 Hz, 1H), 2.65 (dd, J = 16.2, 9.5 Hz, 1H) 2.54 (d, J = 15.8 Hz, 1H), 1.64−1.27 (m, 8H), 0.93 (t, J = 7.4 Hz, 3H), 0.92 (t, J = 7.5 Hz, 3H), 0.85 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.7, 136.9, 135.1, 129.8, 126.2, 125.6, 124.6, 64.4,

DOI: 10.1021/acs.organomet.6b00944
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53.3, 48.8, 41.6, 39.2, 32.0, 30.6, 24.5, 19.1, 13.7, 7.5, 7.3. HRMS (ESI): m/z calcd for $[M + H]^+$, 304.2271; found, 304.2272.

12b. Yellow oil. 0.090 g (0.270 mmol) from 0.104 g (0.502 mmol) of compound **5b** (54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (d, J = 8.3 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 6.63 (s, 1H), 4.29 (dd, J = 9.4, 3.1 Hz, 1H), 4.12−4.08 (m, 2H), 3.76 (s, 3H) 3.00 (dd, J = 16.2, 3.1 Hz, 1H), 2.73 (dd, J = 16.2, 9.4 Hz, 1H), 2.73 (d, J = 15.5 Hz, 1H), 2.46 (d, J = 15.5 Hz, 1H), 1.64−1.23 (m, 8H), 0.91 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H), 0.82 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.6, 157.6, 137.9, 130.6, 127.2, 112.1, 110.2, 64.4, 55.2, 53.4, 49.0, 41.5, 38.4, 31.9, 30.6, 24.3, 19.1, 13.7, 7.5, 7.3. HRMS (ESI): m/z calcd for $[M + H]^+$, 334.2377; found, 334.2383.

12c. Yellow oil. 0.172 g (0.516 mmol) from 0.207 g (1.00 mmol) of compound **5c** (52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, J = 8.5 Hz, 1H), 6.70 (dd, J = 8.5, 2.7 Hz, 1H), 6.60 (d, J = 2.7 Hz, 1H), 4.29 (dd, J = 9.4, 3.1 Hz, 1H), 4.12−4.08 (m, 2H), 3.76 (s, 3H), 3.00 (dd, J = 16.2, 3.1 Hz, 1H), 2.70 (d, J = 15.8 Hz, 1H), 2.60 (dd, J = 16.2, 9.4 Hz, 1H), 2.49 (d, J = 15.8 Hz, 1H), 1.64−1.25 (m, 8H), 0.92 (t, J = 7.5 Hz, 3H), 0.80 (t, J = 7.5 Hz, 3H), 0.83 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.7, 157.9, 136.5, 129.0, 125.7, 114.3, 111.8, 64.4, 55.1, 53.3, 48.3, 41.6, 39.6, 31.9, 30.6, 24.4, 19.1, 13.6, 7.5, 7.3. HRMS (ESI): m/z calcd for $[M + H]^+$, 334.2377; found, 334.2371.

13a. Yellow oil. 0.073 g (0.28 mmol) from 0.089 g (0.50 mmol) of compound **5a** (56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15−7.07 (m, 4H), 4.37 (dd, J = 9.5, 3.1 Hz, 1H), 3.71 (s, 3H), 3.06 (dd, J = 16.4, 3.1 Hz, 1H), 2.74 (d, J = 15.9 Hz, 1H), 2.65 (dd, J = 16.4, 9.5 Hz, 1H), 2.53 (d, J = 15.9 Hz, 1H), 2.21 (br s, 1H), 1.54−1.30 (m, 4H), 0.91 (t, J = 7.6 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.1, 136.8, 135.1, 129.8, 126.3, 125.7, 124.6, 53.4, 51.6, 48.8, 41.3, 39.2, 31.9, 24.5, 7.6, 7.3. HRMS (ESI): m/z calcd for $[M + H]^+$, 262.1801; found, 262.1802.

13b. Yellow oil. 0.083 g (0.36 mmol) from 0.150 g (0.847 mmol) of compound **5a** (43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21−7.09 (m, 4H), 4.32 (dd, J = 7.7, 3.9 Hz, 1H), 2.92 (dd, J = 16.5, 3.9 Hz, 1H), 2.79 (d, J = 15.8 Hz, 1H), 2.70 (dd, J = 16.5, 7.7 Hz, 1H), 2.55 (d, J = 15.8 Hz, 1H), 1.66 (br s, 1H), 1.57−1.44 (m, 2H), 1.44−1.30 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H), 0.82 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.2, 134.8, 130.0, 127.1, 126.0, 124.7, 118.3, 53.8, 49.3, 38.8, 31.8, 26.6, 25.1, 7.5, 7.5. HRMS (ESI): m/z calcd for $[M + H]^+$, 229.1697; found, 229.1699.

14a. Yellow oil. 0.055 g (0.26 mmol) from 0.074 g (0.50 mmol) of compound **4a** (51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17−7.04 (m, 4H), 4.52 (dd, J = 9.0, 3.1 Hz, 1H), 3.12 (dd, J = 17.7, 3.1 Hz, 1H), 2.88 (dd, J = 17.6, 9.0 Hz, 1H), 2.80 (d, J = 15.8 Hz, 1H), 2.51 (d, J = 15.8 Hz, 1H), 2.19 (s, 3H), 2.00 (br s, 1H), 1.24 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 208.6, 136.3, 135.1, 129.7, 126.3, 125.8, 124.6, 50.7, 49.0, 48.9, 42.3, 31.4, 40.7, 24.3. HRMS (ESI): m/z calcd for $[M + H]^+$, 218.1539; found, 218.1533.

14b. Yellow oil. 0.083 g (0.42 mmol) from 0.149 g (1.00 mmol) of compound **4a** (42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23−7.05 (m, 4H), 4.40 (dd, J = 7.5, 3.8 Hz, 1H), 2.92 (dd, J = 16.5, 3.8 Hz, 1H), 2.82 (d, J = 15.7 Hz, 1H), 2.72 (dd, J = 16.5, 7.5 Hz, 1H) 2.53 (d, J = 15.8 Hz, 1H), 1.53 (br s, 1H), 1.28 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.3, 134.2, 129.9, 127.2, 126.2, 124.8, 118.2, 49.9, 49.4, 42.2, 31.4, 26.5, 24.8. HRMS (ESI): m/z calcd for $[M + H]^+$, 201.1386; found, 201.1387.

14c. Yellow oil. 0.060 g (0.21 mmol) from 0.075 g (0.50 mmol) of compound **4a** (42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14−7.02 (m, 4H), 4.56 (dd, J = 9.2, 2.7 Hz, 1H), 3.68−3.39 (m, 8H), 2.93 (dd, J = 16.3, 2.7 Hz, 1H), 2.82 (d, J = 15.8 Hz, 1H), 2.67 (dd, J = 16.2, 9.2 Hz, 1H), 2.47 (d, J = 15.7 Hz, 1H), 2.90 (s, 3H), 2.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.1, 136.3, 135.2, 129.7, 126.2, 125.7, 124.8, 66.8, 66.4, 49.6, 48.9, 45.7, 42.4, 41.8, 40.5, 31.5, 24.2. HRMS (ESI): m/z calcd for $[M + H]^+$, 289.1911; found, 289.1915.

15a. Yellow oil. 0.124 g (0.388 mmol) from 0.097 g (0.50 mmol) of compound **9a** (78%). *Anti*-**15a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15−7.04 (m, 4H), 4.59 (dd, J = 9.8, 3.0 Hz, 1H), 4.14 (m, 2H), 3.59 (s, 3H), 3.23 (d, J = 15.5 Hz, 1H), 2.96 (dd, J = 16.4, 3.0 Hz, 1H), 2.81 (d, J = 15.6 Hz, 1H), 2.60 (dd, J = 16.4, 9.8 Hz, 1H), 1.66−1.59 (m, 2H), 1.44 (s, 3H), 1.42−1.36 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.3, 172.4, 135.6, 133.9, 128.9, 126.4, 126.2, 125.4, 64.5, 58.4, 52.0, 50.6, 43.1, 38.6, 30.6, 27.7, 19.1, 13.7. HRMS (ESI): m/z calcd for $[M + H]^+$: 320.1856, found: 320.1858. *Syn*-**15a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18−7.09 (m, 4H), 4.51 (dd, J = 9.3, 3.3 Hz, 1H), 4.12 (m, 2H), 3.74 (s, 3H), 3.20 (d, J = 15.7 Hz, 1H), 2.99 (dd, J = 16.5, 3.4 Hz, 1H), 2.80 (d, J = 15.7 Hz, 1H), 2.70 (dd, J = 16.5, 9.2, Hz, 1H), 2.03 (s, 3H), 1.63−1.54 (m, 2H), 1.42−1.36 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.2, 172.3, 135.8, 133.4, 129.6, 126.6, 126.3, 124.9, 64.5, 57.0, 52.3, 49.4, 41.3, 37.8, 30.6, 22.5, 19.1, 13.7. HRMS (ESI): m/z calcd for $[M + H]^+$, 320.1856; found, 320.1858.

15b. Yellow oil. 0.071 g (0.29 mmol) from 0.097 g (0.50 mmol) of compound **9a** (58%). *Anti*-**15b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20−7.04 (m, 4H), 4.62 (dd, J = 7.0, 4.0 Hz, 1H), 3.55 (s, 3H), 3.22 (d, J = 15.5 Hz, 1H), 2.89 (d, J = 15.5 Hz, 1H), 2.80 (dd, J = 16.4, 4.0 Hz, 1H), 2.65 (dd, J = 16.4, 7.0 Hz, 1H), 1.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.4, 133.9, 133.6, 129.0, 127.2, 126.7, 125.7, 118.1, 58.7, 52.2, 51.0, 38.5, 28.4, 27.5. HRMS (ESI): m/z calcd for $[M + H]^+$: 245.1285, found: 245.1283. *Syn*-**15b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25−7.13 (m, 4H), 4.48 (dd, J = 7.6, 4.3 Hz, 1H), 3.79 (s, 3H), 3.25 (d, J = 15.8 Hz, 1H), 2.90 (dd, J = 16.6, 4.4 Hz, 1H) 2.84 (d, J = 15.8 Hz, 1H), 2.76 (dd, J = 16.6, 7.5 Hz, 1H), 1.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.8, 133.8, 133.4, 129.9, 127.6, 126.7, 125.0, 117.9, 57.0, 52.5, 49.9, 37.6, 26.4, 23.0. HRMS (ESI): m/z calcd for $[M + H]^+$, 245.1285; found, 245.1283.

15c. Yellow oil. 0.091 g (0.28 mmol) from 0.097 g (0.50 mmol) of compound **9a** (55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19−7.05 (m, 8H), 4.68 (m, 2H), 3.75 (s, 3H), 3.67−3.58 (m, 12H), 3.60 (s, 3H), 3.47−3.35 (m, 4H), 3.23 (m, 2H), 2.91 (m, 2H), 2.79 (m, 2H), 2.69 (dd, J = 16.1, 9.6 Hz, 1H), 2.60 (dd, J = 16.2, 10.1 Hz, 1H), 1.40 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.3, 176.2, 170.1, 169.9, 136.0, 134.2, 133.5, 129.9, 129.0, 126.5, 126.3, 126.1, 126.0, 125.5, 125.0, 66.9, 66.8, 66.5, 66.4, 58.2, 56.8, 52.3, 52.0, 50.8, 49.4, 45.7, 42.5, 41.8, 40.9, 38.8, 37.9, 27.7, 22.4. HRMS (ESI): m/z calcd for $[M + H]^+$, 333.1809; found, 333.1810.

16a. Yellow oil. 0.103 g (0.263 mmol) from 0.095 g (0.36 mmol) of compound **9b** (73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20−7.05 (m, 4H), 4.62 (dd, J = 9.6, 3.1 Hz, 1H), 4.30−4.10 (m, 4H), 3.42 (d, J = 15.7 Hz, 1H), 3.22 (d, J = 15.7 Hz, 1H), 2.94 (dd, J = 16.5, 3.4 Hz, 1H), 2.66 (dd, J = 16.5, 9.6, Hz, 1H), 1.68−1.58 (m, 2H), 1.44−1.34 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.9, 170.2, 169.6, 135.8, 132.3, 128.8, 126.6, 126.5, 125.0, 65.9, 64.5, 62.0, 61.6, 50.5, 42.7, 34.2, 30.6, 19.1, 13.9, 13.6. HRMS (ESI): m/z calcd for $[M + H]^+$, 392.2068; found, 392.2073.

16b. Yellow oil. 0.160 g (0.506 mmol) from 0.167 g (0.63 mmol) of compound **9b** (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26−7.08 (m, 4H), 4.69 (m, 1H), 4.30−4.23 (m, 2H), 4.06 (q, J = 7.1 Hz, 2H), 3.43 (d, J = 15.7 Hz, 1H), 3.31 (d, J = 15.7 Hz, 1H), 2.79 (dd, J = 16.5, 4.6 Hz, 1H), 2.69 (dd, J = 16.5, 6.8 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.07 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4, 168.9, 133.9, 132.3, 129.2, 127.5, 127.1. 125.5, 117.8, 66.1, 62.3, 61.9, 51.2, 34.2, 28.1, 13.9, 13.9. HRMS (ESI): m/z calcd for $[M + H]^+$, 317.1496; found, 317.1491.

Synthesis of Hydroxylamines. A solution of amine (19.4 mmol) in DMF (15 mL) was added to a suspension of benzoyl peroxide (3.68 g, 11.4 mmol) and K_2HPO_4 (2.98 g, 17.1 mmol) in DMF (60 mL), and the mixture was stirred overnight at rt. Water was added, and the contents were stirred for several minutes until all solids dissolved. The mixture was extracted with AcOEt and the organic phase was washed twice with a saturated aqueous solution of $NaHCO_3$. The combined aqueous fractions were extracted three times with AcOEt. The combined organic phases were washed with brine. The organic solution was dried over Na_2SO_4, filtered, and the solvent was evaporated to give the crude hydroxylamine that was purified by flash silica gel chromatography (hexane/ethyl acetate) to obtain the desired product as a colorless oil.

20a. Colorless oil. 2.79 g (10.3 mmol) from 3.68 g (11.4 mmol) of benzoyl peroxide (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 7.7 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.35−

DOI: 10.1021/acs.organomet.6b00944
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7.20 (m, 5H), 2.88 (s, 2H), 1.99 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1, 137.5, 133.3, 130.6, 129.4, 128.6, 128.3, 126.7, 58.7, 45.2, 24.6. HRMS (ESI): m/z calcd for $[M + H]^+$, 270.1489; found, 270.1493.

20b. Colorless oil. 1.21 g (4.07 mmol) from 1.74 g (5.38 mmol) of benzoyl peroxide (76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 7.7 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.50−7.44 (m, 2H), 7.31−7.21 (m, 5H), 2.87 (s, 2H), 1.60−1.40 (m, 4H), 0.98 (t, J = 7.5, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.8, 136.9, 133.1, 130.4, 129.2, 128.5, 128.2, 126.4, 63.1, 40.3, 25.6, 7.6. HRMS (ESI): m/z calcd for $[M + H]^+$, 298.1802; found, 298.1806.

General Method for the Reaction of Hydroxylamines with Michael Acceptors. Butyl acrylate (93 μL, 0.65 mmol) was added to a suspension of the *O*-benzoylhydroxylamine (0.54 mmol) and $Pd_2(dba)_3$ (25 mg, 0.027 mmol) in acetic acid (3 mL). The mixture was stirred at 100 °C for 3 h. Toluene was added, and the solution was filtered through a pad of Celite. The solvents were removed under vacuum, the crude mixture was dissolved in CH_2Cl_2, and a saturated aqueous solution of Na_2CO_3 was added. The aqueous phase was extracted three times with CH_2Cl_2, the collected organic phases were dried over $MgSO_4$, filtered, and the solvent was removed under vacuum.

The crude yellow oil was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH or hexane/AcOEt) to give the corresponding tetrahydroisoquinoline.

12a. 0.140 g (0.460 mmol) from 0.160 g (0.540 mmol) of compound **20b** (86%).

13b. 0.080 g (0.35 mmol) from 0.160 g (0.540 mmol) of compound **20b** (65%).

14b. 0.067 g (0.34 mmol) from 0.165 g (0.610 mmol) of compound **20a** (55%).

14c. 0.129 g (0.448 mmol) from 0.150 g (0.560 mmol) of compound **20a** (80%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.6b00944.

^{1}H and ^{13}C NMR spectra of compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Generalitat de Catalunya (2009SGR1037 and 2014SGR107) and the Spanish Ministerio de Economia y Competitividad (CTQ2009-09692, CTQ2015-65040-P, SAF2014-52223-C2-1-R, and fellowship to A.M.).

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