ACS Catalysis

Research Article

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Synthesis of the *ortho*/*meta*/*para* Isomers of Relevant Pharmaceutical Compounds by Coupling a Sonogashira Reaction with a Regioselective Hydration

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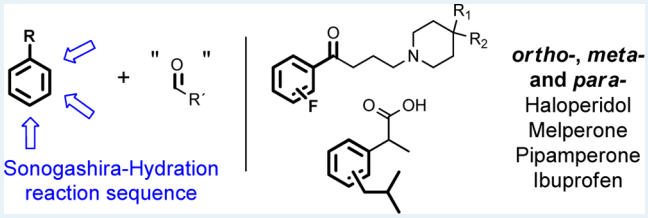
Supporting Information

ABSTRACT: Aryl ketones substituted in *ortho*, *meta*, and *para* position are prepared by a palladium-catalyzed Sonogashira reaction followed by a regioselective hydration of the so-formed alkyne with triflimidic acid or a gold catalyst, under catalytic conditions. This methodology opens a way to obtain substituted aryl alkyl ketones from readily available starting materials, haloarenes, and terminal alkynes. The syntheses of the different regioisomers of haloperidol, melperone, pipamperone, and ibuprofen are presented. Structure−activity relationships for these compounds are studied with dopaminergic and cyclooxigenase binding assays.



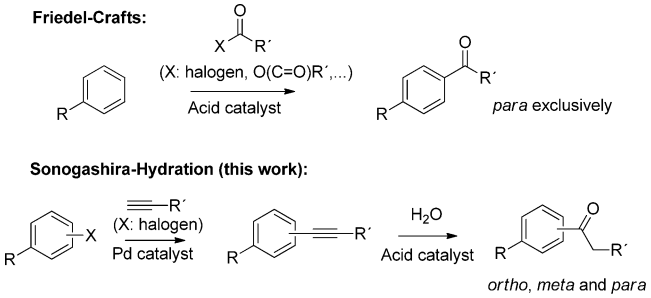
KEYWORDS: *butyrophenones, antipsychotics, NSAIDs, Sonogashira reaction, regioselective hydration*

INTRODUCTION

The acid-catalyzed Friedel−Crafts acylation of aromatic rings is a fundamental process in the fine chemical industry and has allowed the synthesis of acyl arenes during the last century.[1] Many pharmaceuticals, flavors, fragrances, dyes, agrochemicals, and natural products, some of them manufactured in multikilogram quantities, are obtained through Friedel−Crafts intermediates. These intermediates are generally *para*-substituted due to the electronics of the Friedel−Crafts reaction, and this regioselectivity ultimately dictates the biological and chemical properties of the final compound. This inherent limitation of the Friedel−Crafts reaction has not been significantly alleviated by any synthetic method to date,[2] and the corresponding *ortho*- and *meta*-substituted isomers must be prepared by alternative methods, which hinders their widespread exploration. Therefore, synthetic methodologies to prepare *ortho*- and *meta*-substituted aryl ketones are of interest.[3,4]

Scheme 1 shows the synthetic procedure used here to prepare *ortho*-, *meta*-, and *para*-substituted aryl alkyl ketones consisting of a palladium-catalyzed Sonogashira reaction followed by a Brønsted (triflimidic acid) or Lewis (gold) acid-catalyzed Markovnikov hydration of the alkyne product. It is widely reported that the Sonogashira reaction allows the easy formation of new carbon−carbon bonds on substituted aromatic rings[5,6] and that the regioselective hydration of alkynes proceeds with different acid catalysts at the gram scale.[7−9] Both reactions have separately been implemented in industrial processes and multigram synthetic programs.

Scheme 1. Friedel-Crafts Acylation and the Methodology Presented Here



Previous works have shown the possibility of engaging the Sonogashira coupling and the hydration of the so-formed alkyne to form aryl ketones.[10] The regioselectivity of hydration across the triple bond is due to electronic reasons, and in the case of arylalkynes containing electron withdrawing groups, the regioselectivity can be poor. Neighboring groups can speed up the process or invert the inherent regioselectivitiy expected for aryl alkynes,[10e,f] whereas the methodology here presented with triflimidic acid does not require of any anchimeric assistance (see Table S1 in Supporting Information for a complete set of data comparing the different methods). Overall, we will show

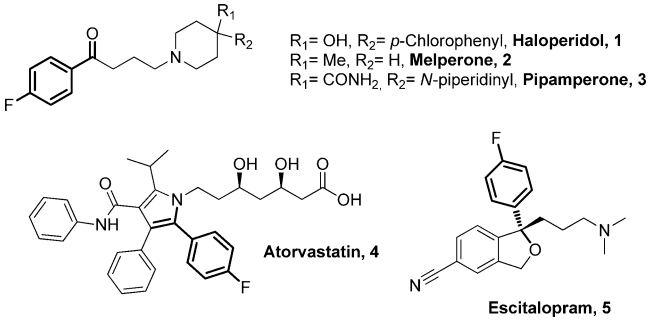
Received: August 23, 2013
Revised: January 10, 2014
Published: January 17, 2014

here that the two-step Sonogashira-hydration procedure with triflimidic acid is regioselective, starts from widely available materials, is fully catalyzed and group-tolerant, operates under mild conditions, and provides an eco-friendly system for the synthesis of aryl alkyl ketones.

RESULTS AND DISCUSSION

The synthesis of some *para*-substituted aryl ketones used as antipsychotics, haloperidol **1**, melperone **2**, and pipamperone **3**, together with the corresponding *ortho/meta* regioisomers and other halogenated derivatives, was attempted using the proposed methodology. The structures of these drugs are shown in Scheme 2. The *para*-substituted fluorobutyrophenones are prepared by Friedel–Crafts acylation of fluorobenzene, and the corresponding *ortho-*, *meta-*, and polysubstituted fluoro derivatives have not been prepared to date.[11] Haloperidol **1** is a "core" medicine in the World Health Organization (WHO) List of Essential Medicines, and in general, *para*-fluorinated compounds are very common in Pharma. For instance, the current first top-selling drug atorvastatin **4** and others such as escitalopram **5** contain this moiety (see also Scheme 2).

Scheme 2. Representative Examples of Widely Used Drugs Containing Aromatic Rings with *para*-Fluoro Ketone Derivatives



The results in Figure 1 show that *para*-fluorinated drugs **1**–**3** and an array of analogues **1a**–**d**, **2a**–**c**, and **3a**–**c** can be prepared in three steps from readily available polihalobenzenes[12,13] in reasonable yields, following the Sonogashira-hydration reaction sequence.

The results show that the Sonogashira coupling is fast and gives good yields of isolated alkynes **6a**–**d**. The coupling must be stopped at 30 min reaction time, because otherwise, the excess of Et_3N removes the terminal chloride and forms the quaternary ammonium salt, which then undergoes Hoffmann elimination. Lesser amounts of Et_3N or other alternative amines do not solve this problem and tend to hamper the final yield of the coupling. The hydration also proceeds well, with moderate to good isolated yields of ketones **7a**–**d**, and the combined isolated yields for the two reactions are >50%. Notice that there are very few reported examples of application in drugs or natural products of the Markovnikov hydration of asymmetric internal alkynes without anchimeric assistance.[14]

The final iodide-catalyzed nucleophilic substitution with the amine is somewhat less effective and gives variable yields depending on the substitution pattern and the amine employed. For instance, the nucleophilic aromatic substitution of the fluoride atom competes with the desired substitution at the terminal position in the *ortho*-fluoro derivatives, and the

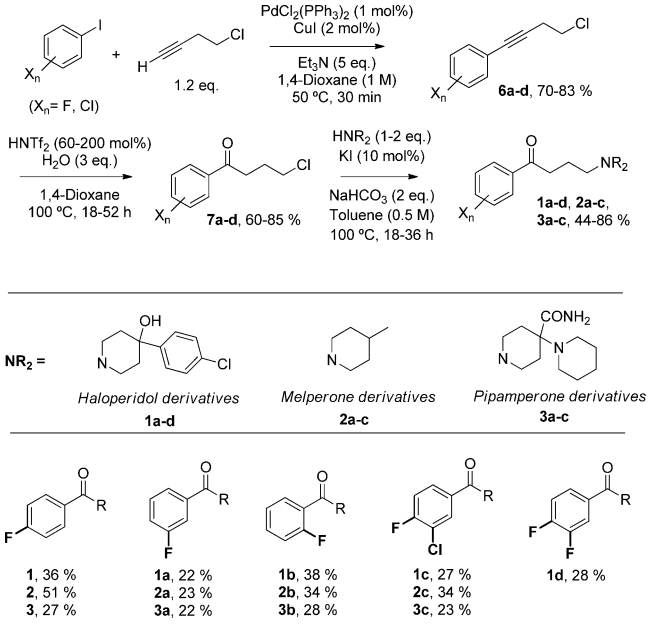


Figure 1. Halo-aromatic butyrophenones obtained by a Sonogashira-hydration–nucleophilic substitution reaction sequence. Combined isolated yields after three steps.

hindered amine for pipamperone derivatives reacts slowly. Nominal water from the reactants can also compete as nucleophile under these basic conditions. In any case, the isolated yields of poly-halo-substituted butyrophenones **1a**–**d**, **2a**–**c**, and **3a**–**c** after three synthetic steps range within the accepted values for other antipsychotic drugs such as olanzapine (48%)[15] and clozapine (50%)[16,17] and also for other drugs and natural products such as praziquantel (45%, drug to treat schistosomiasis and also on the WHO List of Essential Medicines),[18] verapamil (57%, clinical use for hypertension),[19] arundic acid (61%, phase II trials for acute ischemic stroke and clinical development for treatment of Parkinson's and Alzheimer's disease),[20] or trimethylresveratrol (54%, higher activity against several human cancer cell lines than resveratrol itself),[21] all of them prepared in three synthetic steps.

We have evaluated here the binding affinity toward D_1 and D_2 dopaminergic receptors of some of the compounds prepared in the form of hydrochloride salt,[22] and the results are shown in Table 1.

The results in Table 1 show that the selectivity for D_2 receptors (D_1/D_2 value) increases significantly for *ortho-* and *meta*-halobutyrophenones. Notice that the extrapyramidal effects observed for these drugs are associated with the low selectivity for D_2 sites, and any increment in the selectivity for these centers may be reflected in a reduction of the undesired secondary symptoms associated with these drugs. For instance, the *ortho* derivative **1b** increases the selectivity 5 times compared to haloperidol **1**[27] while maintaining an acceptable activity, <100 nM (entry 3). The introduction of a chloro atom in *meta* position, compound **1c**, also improves the selectivity, and this is consistent for the three drugs (compounds **1c**–**3c**, see entries 4, 8, and 11). In particular, **3c** increases 1 order of magnitude the selectivity of D_1/D_2 compared to pipamperone **3** and maintains a comparable activity (entries 9 and 11), as also shown in Figure 2 (for additional binding assays, see Supporting Information).

dx.doi.org/10.1021/cs401075z | ACS Catal. 2014, 4, 722–731

Table 1. Affinity Values (K_i, μM) and Selectivity (Ratio of K_i D_1/K_i D_2) for Dopaminergic Receptors, in Mice, of Fluoro-Substituted Butyrophenones

entry	compd	D_1, K_i (μM)	D_2, K_i (μM)	D_1/D_2
1	**1**	0.025 ± 0.007[b]	0.005 ± 0.0002[b]	5.0[b]
2	**1a**	2.192 ± 0.104	0.554 ± 0.100	3.9
3	**1b**	2.726 ± 0.333	0.099 ± 0.049	27.5
4	**1c**	3.186 ± 0.567	0.254 ± 0.067	12.5
5	**1d**	1.288 ± 0.242	0.541 ± 0.127	2.4
6	**2**	0.148[c]	0.190[c]	0.8[c]
7	**2a**	32.731 ± 4.597	3.023 ± 0.797	10.8
8	**2c**	18.751 ± 0.082	0.971 ± 0.494	19.3
9	**3**	1.249 ± 0.134	0.351 ± 0.107	3.5
10	**3a**	54.921 ± 6.211	1.848 ± 0.412	29.7
11	**3c**	22.361 ± 3.012	0.774 ± 0.033	28.9

[a]Specific D_1 ligand [^{3}H] SCH 23390, Specific D_2 ligand [^{3}H] raclopride. Results expressed as mean ± SEM from three experiments. [b]From refs 23, 24. [c]From refs 25, 26.

These results show structure−activity relationships (SARs),[28] which clearly suggest that the *para*-fluoro substitution in these antipsychotic drugs is, in principle, not a requisite for biological activity and that the move of the fluorine atom or the introduction of new halogen atoms across the ring improve the selectivity of the drug for the D_2 receptor. These are, to our knowledge, the first SAR studies on fluoro-butyrophenones varying the aromatic side, thus complementing those already performed varying the amine[24] or the ketone,[29,30] and expanding the possibilities for incorporating new fluorine atoms on these drugs. The use of fluorine in medicinal chemistry is well-recognized.[31−33] Besides, this study adds understanding to the biochemistry of the dopaminegic receptors D_1 and D_2, which have not been isolated yet.[34,35]

To expand the synthetic results, we tested the Sonogashira-hydration methodology for the preparation of regioisomers of the well-known non-steroideal anti-inflammatory drug (NSAID) ibuprofen **8**, another core medicine in the WHO Essential Medicines List, which is prepared by Friedel−Crafts acylation of isobutylbenzene in industry. Figure 3 shows the synthesis of *meta*-ibuprofen **8a** and *ortho*-ibuprofen **8b** from the corresponding bromoarenes[36] in four steps.[37]

The results in Figure 3 show that *meta*- and *ortho*-ibuprofen **8a,b** can be prepared by a palladium-catalyzed Sonogashira reaction followed by TMS-deprotection and Markovnikov hydration of the terminal alkyne at room temperature under gold-catalyzed conditions.[8,38−40] Notice that the regioselectivity of hydration of terminal alkynes with gold catalysts is

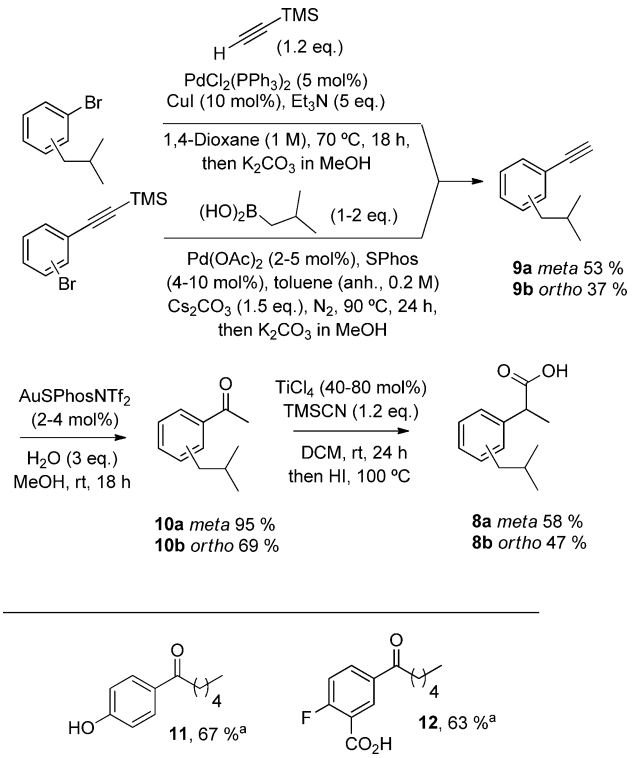


Figure 3. Synthesis of *meta*-ibuprofen **8a** and *ortho*-ibuprofen **8b** (top), isolated yields. Synthesis of alkyl aryl ketones obtained by the Sonogashira-hydration reaction sequence (bottom), combined GC yields after two steps.

completely Markovnikov, thus the use of triflimidic acid can be avoided. Comparative studies about the hydration of aryl alkynes with different metal and Brønsted catalysts can be found elsewhere.[14] The isobutyl chain is installed by palladium-catalyzed Suzuki reaction, before or after the Sonogashira coupling (see Supporting Information for details). Yields are moderate to good for the *meta* isomer and lower for the *ortho* isomer, probably due to the steric hindrance imparted by the bulky alkyl substituent. In any case, the corresponding ketones **10a,b** could be converted to *meta*- and *ortho*-ibuprofen **8a,b** after hydrocyanation followed by a one-pot hydrolysis−dehydration process under reported conditions.[37] With these compounds in hand, the two regioisomers were submitted to biological screening for cyclooxygenase activity (COX-1 and COX-2). The results in Figure 4 show that the COX-1 inhibition observed for the two acids is very similar, which is explained by the increasing steric hindrance around the acid

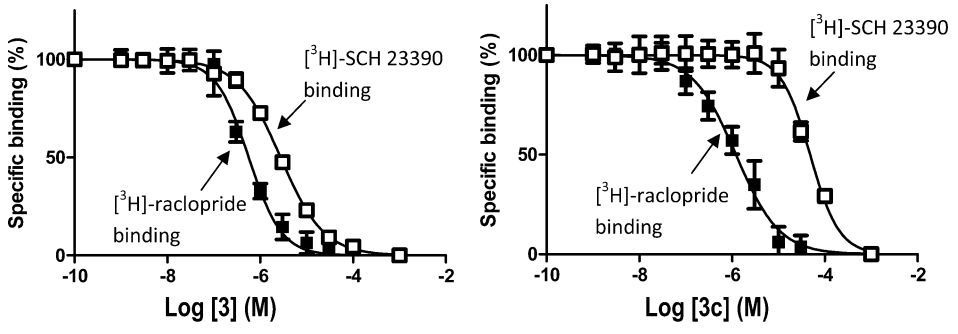


Figure 2. Plot of binding−concentration for pipamperone **3** and the *meta*-chloro-substituted derivative **3c**. The selectivity to D_2 receptors increases significantly for **3c** while maintaining a similar activity to **3**.

dx.doi.org/10.1021/cs401075z | ACS Catal. 2014, 4, 722−731

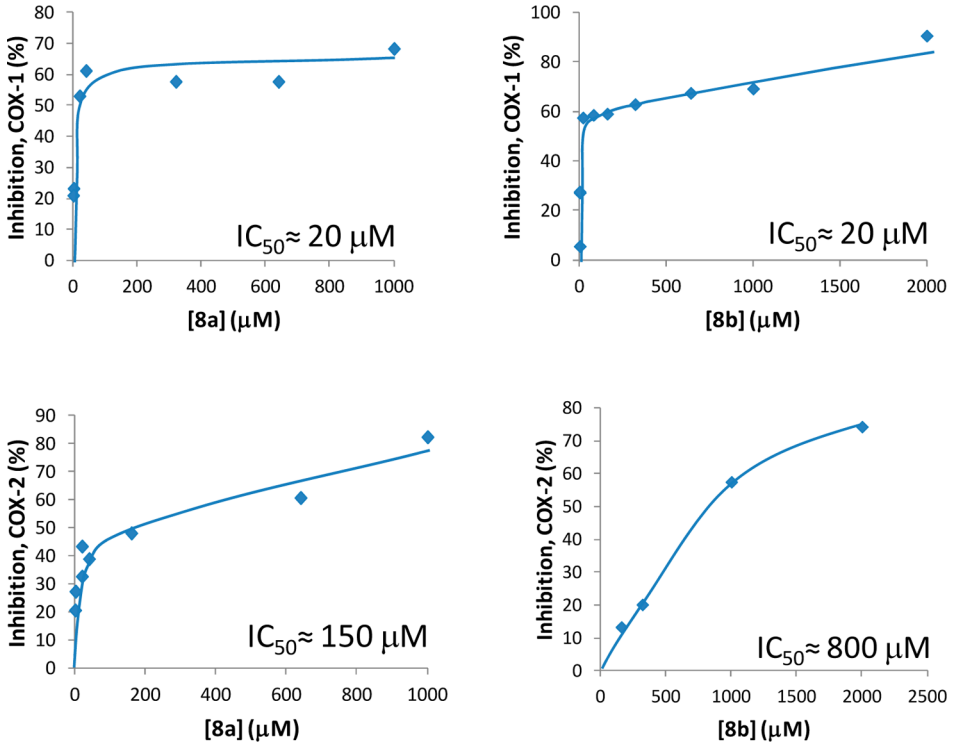


Figure 4. Percent inhibition of COX-1 and COX-2 with the concentration of ibuprofen derivative.

function when compared to the *para*-substituted, as also evidenced by the ^{1}H NMR signals of compound **8b**. This result is consistent with the proposed mechanism of action of ibuprofen **8** that consists in the interaction of the carboxylic acid group with the COX-1 receptor within a narrow cone-like cavity that has no room for bulky groups nearby and only allows the entrance of linear *para*-substituted rings or, in general, flat molecules.[41] The COX-2 receptor has a cavity 17% bigger than COX-1 and does not discriminate so strongly depending on the steric hindrance that surrounds the carboxylic group.[42] Therefore, it could very well occur that the bioactivity of the two isomers *meta* **8a** and *ortho* **8b** differs in the case of COX-2. The results show that **8a** inhibits the COX-2 receptor 5 times more efficiently than **8b**. Although the overall activity of the regioisomers **8a**,**b** is lower than ibuprofen **8**, the results presented here show a possible way to enhance the selectivity for COX-2 receptors, which is in turn one of the main current challenges in medicinal chemistry.[42]

Finally, we used the Sonogashira-hydration synthetic route to prepare other butyrophenones having functional groups incompatible with the Friedel–Crafts reaction. Figure 3 shows that the acyl group can be readily furnished on phenols and benzoic acids under these reaction conditions, to give ketones **11** and **12** in good yields. These results confirm that the methodology presented here opens a way to prepare acylated substrates that can not be prepared by direct Friedel–Crafts acylation.

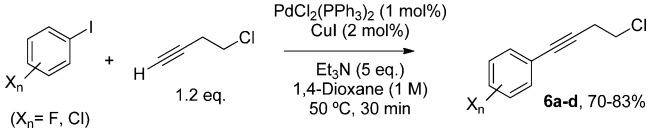
CONCLUSIONS

A Sonogashira coupling followed by hydration with triflimidic acid gives susbtituted alkyl aryl ketones in good yields and selectivity, giving access to bioactive compounds. The presence of neighboring functional groups for anchimeric assistance in the hydration step is not required and the applicability of the method has been demonstrated by the synthesis of previously unreported *ortho*-, *meta*-, and *para*-substituted analogues of the widely used drugs melperone, haloperidol, pipamperone, and ibuprofen. The catalytic sequence presented here opens a new way to obtain substituted aryl alkyl ketones and to design new retro-synthetic routes.

EXPERIMENTAL SECTION

Synthesis of 4-Chloro-1-butyne. 3-Butynol (3.02 mL, 40 mmol) and pyridine (256 μL, 4 mmol) were placed in a 10 mL round-bottomed flask, and the mixture was cooled in an ice bath. Then, thionyl chloride (2.91 mL, 40 mmol) was added dropwise for 10 min. The flask was shaken occasionally during the addition, and after the thionyl chloride was added, the mixture was heated under reflux for 30 min. Fractional distillation of the products gave 4-chloro-1-butyne as a yellow liquid (3.34 mL). Isolated yield: 95%. IR (ν, cm-1): 3335 (i, Csp^3-H), 3324 (i), 3005 (l, C–H), 2967 (l, C–H), 2924 (l, C–H), 2358 (l), 2339 (m), 1275 (i), 1260 (i), 764 (vi), 751 (vi), 645 (vi). GC-MS (m/z, $M^{+\bullet}$ 88), major peaks found: 88 (50%), 73 (1%), 62 (2%), 53 (100%), 39 (6%). ^{1}H NMR (δ, ppm; J, Hz): 3.60 (CH_2, t, J = 7.2), 2.66 (CH_2, td, J = 7.2, 2.6), 2.08 (CH, t, J = 2.6). ^{13}C NMR (δ, ppm): 80.2 (C), 70.4 (CH), 41.9 (CH_2–Cl), 22.8 (CH_2).

Synthesis of Fluorinated Aminobutyrophenones from Aromatic Halides, Alkynes, and Amines (Figure 1). *Sonogashira*



Coupling. $PdCl_2(PPh_3)_2$ (88 mg, 1 mol %) and copper iodide (40 mg, 2 mol %) were placed in a 50 mL round-bottomed flask equipped with a magnetic bar and then nondried 1,4-dioxane (10 mL), the corresponding iodide (10 mmol), 4-chloro-1-butyne (1 mL, ~12 mmol, 1.2 equiv), and triethylamine (345 μL, 2.5 mmol, 5 equiv) were added. The flask was capped with a rubber septum, and the resulting mixture was placed in a preheated oil bath at 50 °C and magnetically stirred for 30 min. One aliquot was taken for GC analysis, and the rest

dx.doi.org/10.1021/cs401075z | ACS Catal. 2014, 4, 722–731

was diluted in diethyl ether (100 mL) after cooling (the ammonium salt can be observed as crystals in some cases), removing the solids by filtration. The resulting solution was purified by column chromatography (*n*-hexane) to yield the corresponding alkyne product (see below for details).

Alkyne ***6***. The reaction crude was purified by column chromatography using *n*-hexane as an eluent. Isolated yield: 1.27 g (70%). R_f (*n*-hexane): 0.50. IR (ν, cm^{-1}): 2959 (l, C−H), 2920 (l, C−H), 2000−1600 (l, overtones), 1508 (vi, arC−C), 1232 (i, arC−F), 1157 (l), 834 (i), 533 (m). GC-MS (*m*/*z*, $M^{+\bullet}$ 182), major peaks found: 182 (50%), 146 (25%), 133 (100%), 120 (12%), 107 (10%). ^{1}H NMR (δ, ppm; *J*, Hz): 7.42−7.35 (2C−H arom, mult), 7.03−6.94 (2C−H arom, mult), 3.67 (CH_2, t, *J* = 7.2), 2.86 (CH_2, t, *J* = 7.2). ^{13}C NMR (δ, ppm; *J*, Hz): 162.3 (C, d, J^1_{C-F} = 248.6), 133.5 (2CH, d, J^3_{C-F} = 8.2), 118.2 (C, d, J^4_{C-F} = 3.8), 115.5 (2CH, d, J^2_{C-F} = 22.2), 85.3 (C), 81.4 (C), 42.1 (CH_2), 27.3 (CH_2).

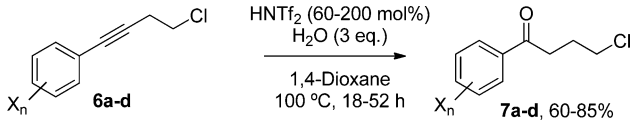
Alkyne ***6a***. The reaction crude was purified by column chromatography using *n*-hexane as an eluent. Isolated yield: 1.51 g (83%). R_f (*n*-hexane): 0.66. IR (ν, cm^{-1}): 2965 (l, C−H), 1599 (m), 1515 (i, arC−C), 1419 (m, $-CH_2$), 1302 (l), 1216 (m), 820 (m), 773 (m, alC-Cl). GC-MS (*m*/*z*, $M^{+\bullet}$ 182), major peaks found: 182 (100%), 147 (80%), 133 (100%), 120 (26%), 107 (27%), 75 (27%), 49 (27%). ^{1}H NMR (δ, ppm; *J*, Hz): 7.17−7.06 (2C−H arom, mult), 7.04−6.97 (C−H arom, mult), 6.92−6.86 (C−H arom, mult), 3.55 (CH_2, t, *J* = 7.2), 2.75 (CH_2, t, *J* = 7.2). ^{13}C NMR (δ, ppm; *J*, Hz): 162.2 (C, d, J^1_{C-F} = 245.9), 129.7 (CH, d, J^3_{C-F} = 8.8), 127.5 (CH, d, J^4_{C-F} = 3.3), 124.9 (C, d, J^3_{C-F} = 9.9), 118.4 (CH, d, J^2_{C-F} = 22.5), 115.3 (CH, d, J^2_{C-F} = 20.8), 86.8 (C_{alkyne}), 81.2 (C_{alkyne}, d, J^4_{C-F} = 3.3), 41.9 (CH_2), 23.6 (CH_2). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{10}H_8ClF$, 182.0299; found, 182.0269.

Alkyne ***6b***. The reaction crude was purified by column chromatography using *n*-hexane as an eluent. Isolated yield: 1.36 g (75%). R_f (*n*-hexane): 0.31. IR (ν, cm^{-1}): 2964 (l, C−H), 2918 (l, C−H), 2000−1600 (l, overtones), 1493 (vi, arC−C), 1448 (m), 1257 (i, arC−F), 1217 (m), 1105 (m), 757 (vi, alC−Cl). GC-MS (*m*/*z*, $M^{+\bullet}$ 182), major peaks found: 182 (40%), 146 (21%), 133 (100%), 120 (3%), 107 (2%). ^{1}H NMR (δ, ppm; *J*, Hz): 7.36−7.30 (C−H arom, mult), 7.23−7.15 (C−H arom, mult), 7.02−6.98 (C−H arom, mult), 6.97−6.92 (C−H arom, mult), 3.61 (CH_2, t, *J* = 7.3), 2.84 (CH_2, t, *J* = 7.3). ^{13}C NMR (δ, ppm; *J*, Hz): 162.8 (C, d, J^1_{C-F} = 250.8), 133.6 (CH, d, J^4_{C-F} = 1.1), 129.8 (CH, d, J^3_{C-F} = 8.3), 123.9 (CH, d, J^4_{C-F} = 3.8), 115.4 (CH, d, J^2_{C-F} = 20.9), 111.6 (C, d, J^2_{C-F} = 15.4), 91.0 (C_{alkyne}, d, J^3_{C-F} = 3.3), 75.8 (C_{alkyne}), 41.9 (CH_2), 23.9 (CH_2). ^{19}F NMR (δ, ppm; *J*, Hz): −110.60 (mult). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{10}H_8ClF$, 182.0299; found, 182.0271.

Alkyne ***6c***. The reaction crude was purified by column chromatography using *n*-hexane as an eluent. Isolated yield: 1.58 g (73%). R_f (*n*-hexane): 0.35. IR (ν, cm^{-1}): 2964 (l, C−H), 2918 (l, C−H), 2000−1600 (l, overtones), 1497 (vi, arC−C), 1265 (m, arC−F), 1062 (m, arC−Cl), 822 (m). GC-MS (*m*/*z*, $M^{+\bullet}$ 217), major peaks found: 216 (36%), 180 (7%), 167 (100%), 146 (36%), 132 (10%). ^{1}H NMR (δ, ppm; *J*, Hz): 7.37 (C−H arom, dd, *J* = 7.2, 2.0), 7.18 (C−H arom, ddd, *J* = 8.7, 4.5, 2.0), 6.97 (C−*H* arom, t, *J* = 8.7), 3.58 (CH_2, t, *J* = 7.1), 2.78 (CH_2, t, *J* = 7.1). ^{13}C NMR (δ, ppm; *J*, Hz): 157.8 (C, d, J^1_{C-F} = 251.4), 133.7 (CH), 131.5 (CH, d, J^3_{C-F} = 7.7), 116.5 (CH, d, J^2_{C-F} = 21.4), 86.6 (C_{alkyne}), 80.2 (C_{alkyne}), 41.9 (CH_2), 23.6 (CH_2). ^{19}F NMR (δ, ppm; *J*, Hz): −114.00 (mult.). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{10}H_7Cl_2F$, 215.9909; found, 215.9893.

Alkyne ***6d***. The reaction crude was purified by column chromatography using *n*-hexane as an eluent. Isolated yield: 1.6 g (80%). R_f (*n*-hexane): 0.25. IR (ν, cm^{-1}): 2965 (l, C−H), 1599 (m), 1515 (vi, arC−C), 1419 (m, $-CH_2$), 1302 (m), 1216 (m, arC−F), 820 (m), 773 (m, alC−Cl). GC-MS (*m*/*z*, $M^{+\bullet}$ 200), major peaks found: 200 (45%), 165 (17%), 151 (100%), 125 (5%), 101 (4%). ^{1}H NMR (δ, ppm; *J*, Hz): 7.24−7.17 (C−H arom, mult), 7.16−7.10 (C−H arom, mult), 7.09−7.02 (C−H arom, mult), 3.66 (CH_2, t, *J* = 7.1), 2.86 (CH_2, t, *J* = 7.1). ^{13}C NMR (δ, ppm; *J*, Hz): 150.4 (C, dd, J^1_{C-F} = 250.8, J^2_{C-F} = 12.1), 149.8 (C, dd, J^1_{C-F} = 248.0, J^2_{C-F} = 12.6), 128.2 (CH, dd, J^3_{C-F} = 6.6, J^4_{C-F} = 3.8), 120.6 (CH, d, J^2_{C-F} = 19.2), 119.9 (C, dd, J^3_{C-F} = 7.7, J^4_{C-F} = 4.4), 117.3 (CH, dd, J^2_{C-F} = 18.1, J^3_{C-F} = 1.1), 86.3 (C_{alkyne}, d, J^5_{C-F} = 1.7), 80.4 (C_{alkyne}, dd, J^4_{C-F} = 2.7, J^5_{C-F} = 1.7), 41.9 (CH_2), 23.6 (CH_2). ^{19}F NMR (δ, ppm; *J*, Hz): −136.30 (mult), −137.34 (mult). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{10}H_7ClF_2$, 200.0204; found, 200.0216.

Markovnikov Hydration. The purified alkyne (5 mmol) was treated with a solution of $HNTf_2$ (60−200 mol %) in 1,4-dioxane in a



preheated oil bath at 100 °C, under magnetic stirring, for 18−52 h, and the corresponding ketone was purified by column chromatography after cooling.

Ketone ***7***. The reaction crude was purified by column chromatography using 20% AcOEt in *n*-hexane as an eluent. Isolated yield: 850 mg (85%). R_f (20% AcOEt in *n*-hexane): 0.66. GC-MS (*m*/*z*, $M^{+\bullet}$ 200), major peaks found: 200 (1%), 164 (1%), 138 (43%), 123 (100%), 107 (10%). ^{1}H NMR (δ, ppm; *J*, Hz): 8.03−7.97 (2C−H arom, mult), 7.17−7.09 (2C−H arom, mult), 3.68 (CH_2, t, *J* = 6.2), 3.15 (CH_2, t, *J* = 7.0), 2.22 (CH_2, tt, *J* = 7.0, 6.2). ^{13}C NMR (δ, ppm; *J*, Hz): 197.3 (C═O), 166.1 (C, d, J^1_{C-F} = 254.7), 133.2 (C, d, J^4_{C-F} = 4.3), 130.6 (2CH, d, J^3_{C-F} = 9.3), 115.9 (2CH, d, J^2_{C-F} = 22.2), 44.6 (CH_2), 35.2 (CH_2), 26.7 (CH_2).

Ketone ***7a***. The reaction crude was purified by precipitation of the catalyst and polimerization products with *n*-hexane. Isolated yield: 600 mg (60%). GC-MS (*m*/*z*, $M^{+\bullet}$ 200), major peaks found: 200 (5%), 164 (4%), 138 (40%), 123 (100%), 107 (15%). ^{1}H NMR (δ, ppm; *J*, Hz): 7.76 (C−H arom, dt, *J* = 7.7, 1.1), 7.68−7.62 (C−H arom, mult), 7.45 (C−H arom, td, *J* = 8.1, 5.6), 7.27 (C−H arom, tdd, *J* = 8.1, 2.6, 1.1), 3.67 (CH_2, t, *J* = 6.2), 3.17 (CH_2, t, *J* = 7.0), 2.23 (CH_2, tt, *J* = 7.0, 6.2). ^{13}C NMR (δ, ppm; *J*, Hz): 197.8 (C═O, d, J^4_{C-F} = 1.7), 162.9 (C, d, J^1_{C-F} = 248.1), 138.7 (C, d, J^3_{C-F} = 6.1), 130.3 (CH, d, J^3_{C-F} = 7.1), 123.8 (CH, d, J^4_{C-F} = 3.3), 120.2 (CH, d, J^2_{C-F} = 21.4), 114.8 (CH, d, J^2_{C-F} = 22.5), 44.5 (CH_2), 35.4 (CH_2), 26.6 (CH_2). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{10}H_{10}ClFO$, 200.0404; found, 200.0400.

Ketone ***7b***. The reaction crude was purified by column chromatography using *n*-hexane as an eluent. Isolated yield: 630 mg (63%). R_f (*n*-hexane): 0.38. IR (ν, cm^{-1}): 2963 (l, C−H), 2925 (l, C−H), 1686 (vi, C═O), 1609 (i), 1480 (m, arC−C), 1453 (vi), 1272 (m, arC−F), 1213 (m), 763 (vi, alC−Cl). GC-MS (*m*/*z*, $M^{+\bullet}$ 200), major peaks found: 200 (1%), 138 (39%), 123 (100%), 95 (3%), 75 (8%). ^{1}H NMR (δ, ppm; *J*, Hz): 7.87 (C−H arom, td, *J* = 7.4, 1.9), 7.56−7.48 (C−H arom, mult), 7.23 (C−H arom, ddd, *J* = 7.9, 6.8, 1.1), 7.14 (C−H arom, ddd, *J* = 11.4, 8.3, 1.1), 3.66 (CH_2, t, *J* = 6.3), 3.18 (CH_2, td, *J* = 7.0, 3.0), 2.22 (CH_2, t, *J* = 6.3). ^{13}C NMR (δ, ppm; *J*, Hz): 197.2 (C═O, d, J^3_{C-F} = 3.8), 162.0 (C, d, J^1_{C-F} = 254.7), 134.6 (CH, d, J^3_{C-F} = 9.3), 130.5 (CH, d, J^4_{C-F} = 2.7), 125.3 (CH), 124.4 (CH, d, J^3_{C-F} = 3.3), 116.7 (CH, d, J^2_{C-F} = 23.6), 44.4 (CH_2), 40.3 (CH_2, d, J^4_{C-F} = 7.7), 26.6 (CH_2, d, J^5_{C-F} = 1.6). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{10}H_{10}ClFO$, 200.0404; found, 200.0417.

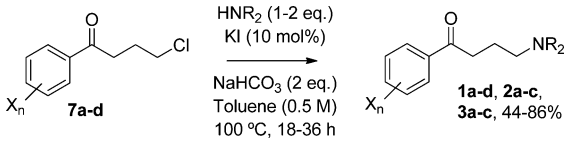
Ketone ***7c***. The reaction crude was purified by column chromatography using 10% AcOEt in *n*-hexane as an eluent. Isolated yield: 725 mg (62%). R_f (10% AcOEt in *n*-hexane): 0.44. IR (ν, cm^{-1}): 2964 (l, C−H), 2927 (l, C−H), 1689 (vi, C═O), 1592 (i), 1496 (l, arC−C), 1402 (m, $-CH_2$), 1249 (vi, arC−F), 1059 (m, arC−Cl), 698 (m, alC−Cl). GC-MS (*m*/*z*, $M^{+\bullet}$ 235), major peaks found: 234 (1%), 172 (41%), 157 (100%), 129 (29%), 109 (7%), 94 (6%). ^{1}H NMR (δ, ppm; *J*, Hz): 8.04 (C−H arom, dd, *J* = 7.2, 2.2), 7.88 (C−H arom, ddd, *J* = 8.7, 4.5, 2.2), 7.23 (C−H arom, t, *J* = 8.7), 3.67 (CH_2, t, *J* = 6.2), 3.14 (CH_2, t, *J* = 7.0), 2.22 (CH_2, tt, *J* = 7.0, 6.2). ^{13}C NMR (δ, ppm; *J*, Hz): 196.3 (C═O), 161.1 (C, d, J^1_{C-F} = 257.4), 133.9 (C, d, J^4_{C-F} = 3.8), 131.0 (CH), 128.4 (CH, d, J^3_{C-F} = 8.8), 121.9 (C, d, J^2_{C-F} = 22.2), 116.8 (CH, d, J^2_{C-F} = 21.4), 44.4 (CH_2), 35.2 (CH_2), 26.5 (CH_2). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{10}H_9Cl_2FO$, 234.0014; found, 234.0002.

Ketone ***7d***. The reaction crude was purified by column chromatography using 10% AcOEt in *n*-hexane as an eluent. Isolated

dx.doi.org/10.1021/cs401075z | ACS Catal. 2014, 4, 722−731

yield: 710 mg (65%). R_f (10% AcOEt in *n*-hexane): 0.48. IR (ν, cm^{-1}): 2924 (l, C−H), 2000−1700 (l, overtones), 1685 (vi, C═O), 1276 (m), 1261 (m), 764 (vi, alC−Cl), 750 (vi). GC-MS (*m*/*z*, $M^{+\bullet}$ 218), major peaks found: 218 (1%), 182 (<1%), 156 (44%), 141 (100%), 113 (34%), 63 (7%). ^{1}H NMR (δ, ppm; *J*, Hz): 7.83−7.73 (2C−H arom, mult), 7.29−7.19 (C−H arom, mult), 3.67 (CH_2, t, *J* = 6.1), 3.13 (CH_2, t, *J* = 7.0), 2.21 (CH_2, quint, *J* = 6.5). ^{13}C NMR (δ, ppm; *J*, Hz): 196.3 (C═O, d, J^4_{C-F} = 1.6), 153.7 (C, dd, J^1_{C-F} = 247.5, J^2_{C-F} = 13.2), 150.3 (C, dd, J^1_{C-F} = 241.5, J^2_{C-F} = 12.6), 133.8 (C, d, J^3_{C-F} = 4.4), 125.0 (CH, d, J^2_{C-F} = 7.1), 124.9 (CH, d, J^2_{C-F} = 7.7), 117.2 (CH, dd, J^2_{C-F} = 18.1, J^3_{C-F} = 1.6), 44.4 (CH_2), 35.2 (CH_2), 26.5 (CH_2). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{10}H_9ClF_2O$, 218.0310; found, 218.0330.

Amine Nucleophilic Substitution. The purified ketone (0.5 mmol) was placed in a vial equipped with a magnetic bar and potassium



iodide (1−10 mol %), sodium bicarbonate (2 equiv), anhydrous toluene (0.5 M), and the corresponding amine (1−2 equiv). The vial was closed and heated in a preheated oil bath at 100 °C for 18−36 h under magnetic stirring. The resulting mixture was purified by column chromatography or preparative TLC on silica to obtain the final aminobutyrophenones.

Haloperidol ***1***. The reaction crude was purified by column chromatography using AcOEt/MeOH/NH_4OH (95:5:1) as an eluent. Isolated yield: 112 mg (60%). R_f (AcOEt/MeOH/NH_4OH 95:5:1): 0.60. GC-MS (*m*/*z*, $M^{+\bullet}$ 375), major peaks found: 375 (1%), 237 (98%), 224 (100%), 206 (26%), 165 (8%), 123 (16%), 95 (7%). ^{1}H NMR (δ, ppm; *J*, Hz): 8.03−7.95 (2C−H arom, mult), 7.41−7.35 (2C−H arom, mult), 7.32−7.26 (2C−H arom, mult), 7.17−7.08 (2C−H arom, mult), 3.53 (O−H, bs), 3.01 (CH_2, t, *J* = 6.8), 2.97−2.88 (CH_2, m), 2.67−2.55 ($2CH_2$, m), 2.20−2.07 (CH_2, m), 2.06−1.98 (CH_2, m), 1.77−1.67 (CH_2, m). ^{13}C NMR (δ, ppm): 198.0 (C═O), 164.0 (C, d, J^1_{C-F} = 254.7), 146.4 (C), 133.4 (C, d, J^4_{C-F} = 2.7), 132.9 (C), 130.7 (2CH, d, J^3_{C-F} = 9.3), 128.4 (2CH), 126.1 (2CH), 115.6 (2CH, d, J^2_{C-F} = 21.9), 70.6 (C−OH), 57.4 (CH_2−N), 49.1 ($2CH_2$−N), 37.6 ($2CH_2$), 36.0 (CH_2), 21.0 (CH_2).

Butyrophenone ***1a***. The reaction crude was purified by column chromatography using *n*-Hex/AcOEt (50:50) then AcOEt/MeOH/NH_4OH (70:30:1) as eluents. Isolated yield: 83.5 mg (44%). R_f (AcOEt/MeOH/NH_4OH 70:30:1): 0.10. ^{1}H NMR (δ, ppm; *J*, Hz): 7.69 (C−H arom, dt, *J* = 7.7, 1.2), 7.60 (C−H arom, ddd, *J* = 9.6, 2.5, 1.7), 7.38 (C−H arom, td, *J* = 8.1, 5.6), 7.32−7.27 (C−H arom, mult), 7.23−7.15 (4C−H arom, mult), 5.64 (O−H, bs), 2.91 (CH_2, t, *J* = 6.9), 2.74−2.65 (CH_2, mult), 2.44−2.28 ($2CH_2$, mult), 1.97−1.82 ($2CH_2$, mult), 1.63−1.53 (CH_2, mult). ^{13}C NMR (δ, ppm): 198.6 (C═O, d, J^4_{C-F} = 2.2), 162.8 (C, d, J^1_{C-F} = 247.5), 147.0 (C), 139.3 (C, d, J^3_{C-F} = 6.1), 132.5 (C), 130.2 (CH, d, J^3_{C-F} = 7.7), 128.2 (2 × CH), 126.1 (2 × CH), 123.8 (CH, d, J^4_{C-F} = 3.3), 119.8 (CH, d, J^2_{C-F} = 21.4), 114.7 (CH, d, J^2_{C-F} = 22.0), 70.9 (C−OH), 57.6 (CH_2−N), 49.2 ($2CH_2$−N), 38.1 (2 × CH_2), 36.3 (CH_2), 21.8 (CH_2). ^{19}F NMR (δ, ppm; *J*, Hz): −111.91 (mult). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{21}H_{23}ClFNO_2$, 376.1474; found, 376.1469.

Butyrophenone ***1b***. The reaction crude was purified by column chromatography using AcOEt/MeOH/NH_4OH (95:5:0.5) as an eluent. Isolated yield: 150 mg (80%). R_f (AcOEt/MeOH/NH_4OH 95:5:0.5): 0.66. IR (ν, cm^{-1}): 3435 (bs, OH), 2947 (l, C−H), 2921 (l, C−H), 2831 (l), 1681 (l, C═O), 1593 (l), 1486 (l, arC−C), 1383 (l, $-CH_2$), 1129 (l, N−alC), 1095 (l, arC−Cl), 912 (vi), 828 (l), 745 (vi). GC-MS (*m*/*z*, $M^{+\bullet}$ 375), major peaks found: 375 (1%), 237 (44%), 224 (100%), 206 (26%), 172 (22%), 139 (27), 123 (30%), 77 (14%), 42 (14). ^{1}H NMR (δ, ppm; *J*, Hz): 7.49−7.36 (4C−H arom, mult), 7.35−7.27 (2C−H arom, td, *J* = 8.7, 1.9), 7.17 (C−H arom, d, *J* = 7.8), 7.06 (C−H arom, td, *J* = 7.4, 1.0), 3.26 (CH_2, td, *J* = 12.0, 2.5), 3.14−3.05 (CH_2, mult), 2.87−2.77 (CH_2, mult), 2.54−2.40 (CH_2, mult), 2.26−2.02 (O−H + CH_2, mult), 1.97−1.80 (CH_2, mult), 1.47−1.63 (CH_2, mult). ^{13}C NMR (δ, ppm): 207.2 (C═O), 162.8 (C, d, J^1_{C-F} = 247.5), 147.0 (C), 139.3 (C, d, J^3_{C-F} = 6.1), 132.5 (C), 130.2 (CH, d, J^3_{C-F} = 7.7), 128.2 (2 × CH), 126.1 (2 × CH), 123.8 (CH, d, J^4_{C-F} = 3.3), 119.8 (CH, d, J^2_{C-F} = 21.4), 114.7 (CH, d, J^2_{C-F} = 22.0), 70.9 (C−OH), 57.6 (CH_2−N), 49.2 ($2CH_2$−N), 38.1 (2 × CH_2), 36.3 (CH_2), 21.8 (CH_2). ^{19}F NMR (δ, ppm; *J*, Hz): −111.91 (mult). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{21}H_{23}ClFNO_2$, 376.1474; found, 376.1472.

Butyrophenone ***1c***. The reaction crude was purified by column chromatography using AcOEt/MeOH/NH_4OH (95:5:0.5) as an eluent. Isolated yield: 122 mg (60%). R_f (AcOEt/MeOH/NH_4OH 95:5:0.5): 0.58. IR (ν, cm^{-1}): 3137 (bs, OH), 2949 (m, C−H), 2938 (m, C−H), 2821 (m), 1685 (vi, C═O), 1594 (m), 1493 (m, arC−C), 1400 (i, $-CH_2$), 1251 (i, arC−F), 1080 (i, arC−Cl), 821 (i), 547 (l). ^{1}H NMR (δ, ppm; *J*, Hz): 8.04 (C−H arom, dd, *J* = 7.0, 2.2), 7.89 (C−H arom, ddd, *J* = 8.5, 4.5, 2.2), 7.31 (2C−H arom, dt, *J* = 8.9, 2.2), 7.29 (2C−H arom, dt, *J* = 8.9, 2.2), 7.22 (C−H arom, t, *J* = 8.5), 2.96 (CH_2, t, *J* = 7.0), 2.81−2.72 (CH_2, mult), 2.49−2.37 ($2CH_2$, mult), 2.04−1.89 ($2CH_2$, mult), 1.86 (O−H, bs), 1.71−1.61 (CH_2, mult). ^{13}C NMR (δ, ppm): 197.2 (C═O), 160.9 (C, d, J^1_{C-F} = 256.9), 146.7 (C), 134.5 (C, d, J^4_{C-F} = 3.8), 132.8 (C), 131.0 (CH, d, J^3_{C-F} = 1.1), 128.3 (CH, d, J^3_{C-F} = 8.2), 128.4 (2CH), 126.0 (2CH), 121.8 (C−Cl, d, J^2_{C-F} = 18.1), 116.7 (CH, d, J^2_{C-F} = 21.4), 71.0 (C−OH), 57.6 (CH_2−N), 49.2 ($2CH_2$−N), 38.1 ($2CH_2$), 36.2 (CH_2), 21.8 (CH_2). HRMS (ESI) *m*/*z*: [$M - H^+$] calcd for $C_{21}H_{21}Cl_2FNO_2$, 408.0933; found, 408.0944.

Butyrophenone ***1d***. The reaction crude was purified by column chromatography using AcOEt/MeOH/NH_4OH (95:5:0.5) as an eluent. Isolated yield: 107 mg (54%). R_f (AcOEt/MeOH/NH_4OH 95:5:0.5): 0.34. IR (ν, cm^{-1}): 3445 (bs, OH), 2948 (m, C−H), 2926 (l, C−H), 2822 (l), 1687 (i, C═O), 1611 (m), 1514 (m, arC−C), 1427 (l, $-CH_2$), 1283 (vi, arC−F), 1125 (l, arC−Cl), 826 (l), 537 (m). ^{1}H NMR (δ, ppm; *J*, Hz): 7.82−7.64 (2C−H arom, mult), 7.31 (2C−H arom, d, *J* = 8.9), 7.26−7.12 (3C−H arom, mult), 2.89 (CH_2, t, *J* = 7.0), 2.76−2.65 (CH_2, mult), 2.45−2.30 ($2CH_2$, mult), 1.99−1.75 (O−H + $2CH_2$, mult), 1.60 (CH_2, d, *J* = 8.9). ^{13}C NMR (δ, ppm): 197.3 (C═O), 161.9 (C), 160.9 (C), 146.8 (C), 132.8 (C), 132.3 (C), 128.4 (2CH), 126.0 (2CH), 124.8 (C−H), 117.4 (CH, d, J^2_{C-F} = 18.0), 71.0 (C−OH), 57.6 (CH_2−N), 49.3 ($2CH_2$−N), 38.3 ($2CH_2$), 36.2 (CH_2), 21.8 (CH_2). ^{19}F NMR (δ, ppm; *J*, Hz): −130.20 (mult), −136.12 (mult). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{21}H_{22}ClF_2NO_2$, 394.1380; found, 394.1371.

Melperone ***2***. The reaction crude was purified by column chromatography using AcOEt/MeOH/NH_4OH (95:5:1) as an eluent. Isolated yield: 113 mg (86%). R_f (AcOEt/MeOH/NH_4OH 95:5:1): 0.50. GC-MS (*m*/*z*, $M^{+\bullet}$ 263), major peaks found: 263 (1%), 165 (4%), 125 (54%), 112 (100%), 95 (9%), 70 (6%). ^{1}H NMR (δ, ppm; *J*, Hz): 8.00−7.94 (2C−H arom, mult), 7.13−7.05 (2C−H arom, mult), 2.99−2.85 ($2CH_2$, mult), 2.42 (CH_2, t, *J* = 7.3), 2.02−1.88 ($2CH_2$, mult), 1.64−1.53 (CH_2, mult), 1.42−1.27 (C−H, m), 1.26−1.13 (CH_2, mult), 0.88 (CH_3, d, *J* = 6.2). ^{13}C NMR (δ, ppm): 198.3 (C═O), 165.5 (C, d, J^1_{C-F} = 254.1), 133.5 (C, d, J^4_{C-F} = 3.3), 130.6 (2CH, d, J^3_{C-F} = 9.3), 115.5 (2CH, d, J^2_{C-F} = 21.9), 57.8 (CH_2−N), 53.6 ($2CH_2$−N), 36.2 (CH_2), 33.8 ($2CH_2$), 30.6 (CH), 21.7 (CH_3), 21.4 (CH_2).

Butyrophenone ***2a***. The reaction crude was purified by column chromatography using AcOEt/MeOH (80:20) as an eluent. Isolated yield: 60.5 mg (46%). R_f (AcOEt/MeOH 80:20): 0.8. ^{1}H NMR (δ, ppm; *J*, Hz): 7.70 (C−H arom, dt, *J* = 7.7, 1.1), 7.55 (C−H arom, ddd, *J* = 9.4, 2.6, 1.6), 7.40 (C−H arom, td, *J* = 8.1, 5.6), 7.21 (C−H arom, tdd, *J* = 8.1, 2.6, 1.1), 3.52−3.40 (CH_2, mult), 3.10−3.04 ($2CH_2$, mult), 2.89−2.77 (CH_2, mult), 2.29−2.20 (CH_2, mult), 1.88−1.78 (C−H, mult), 1.75−1.62 (CH_2, mult), 0.95 (CH_3, d, *J* = 6.0). ^{13}C NMR (δ, ppm): 197.2 (C═O, d, J^4_{C-F} = 2.2), 162.6 (C, d, J^1_{C-F} = 248.1), 138.1 (C, d, J^3_{C-F} = 6.1), 130.3 (CH, d, J^3_{C-F} = 7.1), 123.8 (CH, d, J^4_{C-F} = 3.3), 120.3 (CH, d, J^2_{C-F} = 21.4), 114.5 (CH, d, J^2_{C-F} = 22.5), 56.2 (CH_2−N), 52.6 ($2CH_2$−N), 30.6 (2 × CH_2), 29.1 (CH_2), 28.7 (CH), 20.7 (CH_2), 18.4 (CH_3). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{16}H_{22}FNO$, 264.1758; found, 264.1761.

dx.doi.org/10.1021/cs401075z | *ACS Catal.* 2014, 4, 722−731

Butyrophenone ***2b***. The reaction crude was purified by column chromatography using AcOEt/MeOH (95:5) as an eluent. Isolated yield: 89.5 mg (72%). R_f (AcOEt/MeOH/NH_4OH 95:5:0.5): 0.95. IR (ν, cm^{-1}): 2932 (l, C−H), 2848 (l, C−H), 2811 (l), 1671 (i, C═O), 1611 (m), 1594 (l), 914 (vi, N−alC), 745 (vi). ^1H NMR (δ, ppm; J, Hz): 7.40−7.35 (C−H arom, mult), 7.34−7.29 (C−H arom, mult), 7.09−7.05 (C−H arom, mult), 7.04−6.98 (C−H arom, mult), 3.73−3.66 (CH_2, mult), 3.24−3.12 ($2CH_2$, mult), 2.78−2.66 (CH_2, mult), 1.97−1.87 (CH_2, mult), 1.78−1.67 (CH_2, mult), 1.49−1.23 (C−H + CH_2, mult), 0.98 (CH_3, d, J = 6.3). ^{13}C NMR (δ, ppm): 197.2 (C═O, d, J^4_{C-F} = 2.2), 162.6 (C, d, J^1_{C-F} = 248.1), 138.1 (C, d, J^3_{C-F} = 6.1), 130.3 (CH, d, J^3_{C-F} = 7.1), 123.8 (CH, d, J^4_{C-F} = 3.3), 120.3 (CH, d, J^2_{C-F} = 21.4), 114.5 (CH, d, J^2_{C-F} = 22.5), 56.2 (CH_2−N), 52.6 ($2CH_2$−N), 30.6 (2 × CH_2), 29.1 (CH_2), 28.7 (CH), 20.7 (CH_2), 18.4 (CH_3). HRMS (ESI) m/z: [M − H^+] calcd for $C_{16}H_{21}FNO$, 262.1607; found, 262.1605.

Butyrophenone ***2c***. The reaction crude was purified by column chromatography using AcOEt/MeOH/NH_4OH (95:5:0.5) as an eluent. Isolated yield: 112 mg (75%). R_f (AcOEt/MeOH/NH_4OH 95:5:0.5): 0.55. IR (ν, cm^{-1}): 2949 (i, C−H), 2925 (i, C−H), 2804 (m), 2767 (m), 1688 (vi, C═O), 1592 (i), 1492 (i, arC−C), 1457 (m, $-CH_2$), 1399 (m, $-CH_3$), 1260 (vi), 1247 (vi, arC−F), 1126 (m, N−alC), 1061 (m, arC−Cl), 818 (m). ^1H NMR (δ, ppm; J, Hz): 8.04 (C−H arom, dd, J = 7.2, 2.2), 7.88 (C−H arom, ddd, J = 8.5, 4.5, 2.2), 7.20 (C−H arom, t, J = 8.6), 2.93 (CH_2, t, J = 7.1), 2.88−2.79 (CH_2, mult), 2.37 (CH_2, t, J = 7.1), 1.98−1.85 ($2CH_2$, mult), 1.62−1.52 (CH_2, mult), 1.22−1.06 (CH_2, mult), 1.38−1.25 (C−H, mult), 0.89 (CH_3, d, J = 6.4). ^{13}C NMR (δ, ppm): 197.5 (C═O), 161.1 (C, d, J^1_{C-F} = 257.4), 134.4 (C, d, J^4_{C-F} = 3.8), 131.0 (CH), 128.4 (CH, d, J^3_{C-F} = 8.8), 121.6 (C, d, J^2_{C-F} = 22.2), 116.7 (CH, d, J^2_{C-F} = 21.4), 57.8 (CH_2−N), 53.8 ($2CH_2$−N), 36.3 (CH_2), 34.1 ($2CH_2$), 30.8 (CH), 21.8 (CH_3), 21.7 (CH_2). ^{19}F NMR (δ, ppm; J, Hz): −108.27 (mult). HRMS (ESI) m/z: [M^+] calcd for $C_{16}H_{21}ClFNO$, 298.1368; found, 298.1364.

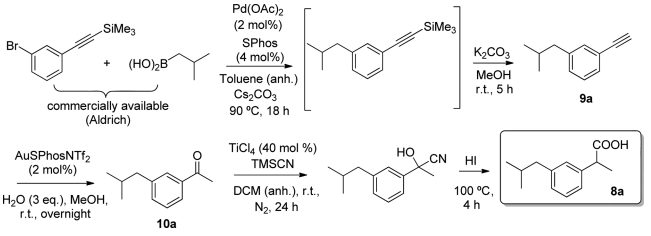
Pipamperone ***3***. The reaction crude was purified by column chromatography using AcOEt/MeOH/NH_4OH (95:5:1) as an eluent. Isolated yield: 85.0 mg (46%). R_f (AcOEt/MeOH/NH_4OH 95:5:1): 0.33. GC-MS (m/z, $M^{+\bullet}$ 375), major peaks found: 375 (1%), 357 (1%), 331 (100%), 292 (20%), 246 (16%), 220 (7%), 208 (7%), 194 (33%), 165 (79%), 138 (64%), 123 (50%), 110 (21%), 95 (9%). ^1H NMR (δ, ppm; J, Hz): 7.95−7.88 (2C−H arom, mult), 7.05 (2C−H arom, d, J = 8.7), 6.58 (N−H, bs), 5.82 (N−H, bs), 2.86 (CH_2, t, J = 7.2), 2.71−2.61 (CH_2, mult), 2.44−2.22 ($4CH_2$, mult), 1.85 (CH_2, quint, J = 7.2), 1.74−1.64 ($2CH_2$, mult), 1.51−1.40 ($2CH_2$, mult), 1.39−1.29 (CH_2, mult). ^{13}C NMR (δ, ppm): 198.3 (C═O), 178.4 (H_2N−C═O), 165.4 (C, d, J^1_{C-F} = 254.1), 133.5 (C, d, J^4_{C-F} = 3.3), 130.5 (2 × CH, d, J^3_{C-F} = 8.8), 115.3 (2 × CH, d, J^2_{C-F} = 22.0), 64.5 (C−N), 57.4 (CH_2−N), 50.3 ($2CH_2$−N), 47.3 ($2CH_2$−N), 36.2 (CH_2), 29.1 (2 × CH_2), 26.9 (2 × CH_2), 24.7 (CH_2), 21.9 (CH_2). ^{19}F NMR (δ, ppm; J, Hz): −105.89 (mult). HRMS (ESI) m/z: [M^+] calcd for $C_{21}H_{30}FN_3O_2$, 375.2395; found, 375.2383.

Butyrophenone ***3a***. The reaction crude was purified by column chromatography using AcOEt/MeOH/NH_4OH (95:5:1) as an eluent. Isolated yield: 84.5 mg (45%). R_f (AcOEt/MeOH/NH_4OH 95:5:1): 0.30. ^1H NMR (δ, ppm; J, Hz): 7.65 (C−H arom, dt, J = 7.9, 1.1), 7.55 (C−H arom, ddd, J = 9.6, 2.6, 1.7), 7.38 (C−H arom, td, J = 7.9, 5.6), 7.16 (C−H arom, tdd, J = 8.3, 2.6, 1.0), 6.60 (N−H, bs), 5.12 (N−H, bs), 2.85 (CH_2, t, J = 7.1), 2.66−2.54 (CH_2, mult), 2.4−2.2 ($4CH_2$, mult), 1.70−1.57 ($2CH_2$, mult), 1.48−1.25 ($4CH_2$, mult). ^{13}C NMR (δ, ppm): 198.7 (C═O), 178.5 (H_2N−C═O), 162.6 (C, d, J^1_{C-F} = 247.5), 139.2 (C, d, J^3_{C-F} = 6.0), 130.0 (CH, d, J^3_{C-F} = 7.7), 123.6 (CH, d, J^4_{C-F} = 3.3), 119.5 (CH, d, J^2_{C-F} = 21.4), 114.5 (CH, d, J^2_{C-F} = 22.5), 64.3 (C−N), 57.2 (CH_2−N), 50.2 ($2CH_2$−N), 47.2 ($2CH_2$−N), 36.3 (CH_2), 29.0 (2 × CH_2), 26.8 (2 × CH_2), 24.7 (CH_2), 21.9 (CH_2). ^{19}F NMR (δ, ppm; J, Hz): −112.12 (mult). HRMS (ESI) m/z: [M^+] calcd for $C_{21}H_{30}FN_3O_2$, 375.2395; found, 375.2401.

Butyrophenone ***3b***. The reaction crude was purified by column chromatography using AcOEt/MeOH/NH_4OH (95:5:1) as an eluent. Isolated yield: 113 mg (60%). R_f (AcOEt/MeOH/NH_4OH 95:5:1): 0.50. GC-MS (m/z, $M^{+\bullet}$ 375), major peaks found: 357 (1%), 331 (100%), 292 (17%), 246 (19%), 220 (12%), 208 (12%), 194 (31%), 165 (76%), 138 (66%), 123 (57%), 110 (24%), 98 (14%). ^1H NMR (δ, ppm; J, Hz): 7.86 (C−H arom, td, J = 7.7, 2.0), 7.54−7.45 (C−H arom, mult), 7.21 (C−H arom, ddd, J = 7.7, 7.0, 1.1), 7.11 (C−H arom, ddd, J = 11.4, 8.3, 1.1), 6.70 (N−H, bs), 5.16 (N−H, bs), 2.98 (CH_2, td, J = 7.0, 2.82), 2.91−2.81 (CH_2, mult), 2.60−2.55 ($4CH_2$, mult), 2.00−1.69 ($3CH_2$, mult), 1.58−1.49 ($2CH_2$, mult), 1.58−1.38 (CH_2, mult). ^{13}C NMR (δ, ppm; J, Hz): 197.9 (C═O), 178.6 (H_2N−C═O), 163.5 (C, d, J^1_{C-F} = 254.7), 134.3 (CH, d, J^3_{C-F} = 9.3), 130.6 (CH, d, J^4_{C-F} = 2.7), 125.8 (C, d, J^2_{C-F} = 20.0), 124.3 (CH, d, J^4_{C-F} = 3.3), 116.6 (CH, d, J^2_{C-F} = 23.6), 64.5 (C−N), 57.3 (CH_2−N), 50.2 ($2CH_2$−N), 47.5 ($2CH_2$−N), 41.1 (CH_2, d, J^4_{C-F} = 7.1), 28.7 (2 × CH_2), 27.0 (2 × CH_2), 24.9 (CH_2), 21.3 (CH_2). ^{19}F NMR (δ, ppm; J, Hz): −108.78 (mult). HRMS (ESI) m/z: [M^+] calcd for $C_{21}H_{30}FN_3O_2$, 376.2395; found, 376.2391.

Butyrophenone ***3c***. The reaction crude was purified by column chromatography using AcOEt/MeOH/NH_4OH (95:5:1) as an eluent. Isolated yield: 102 mg (50%). R_f (AcOEt/MeOH/NH_4OH 95:5:1): 0.35. GC-MS (m/z, $M^{+\bullet}$ 410), major peaks found: 391 (1%), 365 (100%), 326 (17%), 280 (14%), 254 (7%), 242 (10%), 228 (24%), 199 (65%), 157 (46%), 138 (79%), 110 (30%), 98 (14%), 84 (12%). ^1H NMR (δ, ppm; J, Hz): 8.04 (C−H arom, dd, J = 7.2, 2.2), 7.87 (C−H arom, ddd, J = 8.5, 4.6, 2.2), 7.21 (C−H arom, t, J = 8.5), 6.74 (N−H, bs), 5.19 (N−H, bs), 2.94 (CH_2, t, J = 7.0), 2.89−2.80 (CH_2, mult), 2.60−2.40 ($4CH_2$, mult), 2.00−1.95 (CH_2, mult), 1.69−1.89 ($2CH_2$, mult), 1.58−1.49 ($2CH_2$, mult), 1.46−1.38 (CH_2, mult). ^{13}C NMR (δ, ppm): 197.0 (C═O), 178.6 (H_2N−C═O), 161.6 (C−F), 134.4 (C), 131.0 (CH), 128.4 (CH, d, J^3_{C-F} = 8.2), 121.6 (C−Cl), 116.5 (CH, d, J^2_{C-F} = 22.0), 64.5 (C−N), 57.1 (CH_2−N), 50.2 ($2CH_2$−N), 47.5 ($2CH_2$−N), 36.1 (CH_2), 28.6 (2 × CH_2), 27.0 (2 × CH_2), 24.9 (CH_2), 21.5 (CH_2). ^{19}F NMR (δ, ppm; J, Hz): −108.17 (mult). HRMS (ESI) m/z: [M − $3H^+$] calcd for $C_{21}H_{26}ClFN_3O_2$, 406.1698; found, 406.1694.

Synthesis of the Regioisomers of Ibuprofen (Figure 3, Top). *meta-Ibuprofen* ***8a***. *Synthesis of Alkyne* ***9a***. Palladium acetate (40 mg, 2 mol %) and SPhos (187 mg, 4.0 mol %) were placed in a 25 mL round-bottomed flask and anhydrous toluene (10 mL) was added. The mixture was magnetically stirred at room temperature for 10 min. Then, the orange solution was added over a mixture of *meta*-bromophenyltrimethylsilylacetylene (1.9 mL, 8.8 mmol), isobutylboronic acid (1.08 g, 10.6 mmol, 1.2 equiv), and cesium carbonate (4.3 g, 1.5 equiv) in anhydrous toluene (8 mL), previously weighed in a 50 mL round-bottomed flask, and the final mixture was placed in a preheated oil bath at 90 °C and magnetically stirred for 18 h. After cooling, DCM (50 mL) was added, and the mixture was filtered. Volatiles in the filtrates were removed under reduced pressure, the resulting crude was redissolved in MeOH (15 mL), and potassium carbonate was added (7 g, 5 equiv). The mixture was magnetically stirred at room temperature for 5 h. DCM (20 mL) was added and the mixture was filtrated and concentrated under reduced pressure. Purification by column chromatography (hexane) yields the terminal alkyne **9a**. The reaction crude was purified by column chromatography using *n*-hexane as eluent. Isolated yield: 736 mg (53%). R_f (*n*-hexane): 0.45. ^1H NMR (δ, ppm; J, Hz): 7.28 (C−H arom, ddd, J = 3.0, 3.1, 9.0), 7.24 (C−H arom, m), 7.16 (C−H arom, dd, J = 3.0, 6.1), 7.65 (C−H arom, ddd, J = 3.1, 6.1, 6.1), 2.98 (*CH*, s), 2.39 (CH_2, d, J = 9.0), 1.80 (CH, m, J = 7.0), 0.84 (CH_3, d, J = 6.0). ^{13}C NMR (δ, ppm): 142.0 (C), 132.9 (CH), 129.9 (CH), 129.6 (CH), 128.2 (CH), 121.9 (C), 84.1 (C), 76.8 (CH), 45.2 (CH_2), 30.2 (CH), 22.4 (CH_3). HRMS (ESI) m/z: [M^+] calcd for $C_{12}H_{14}$, 158.1096; found, 158.1100.

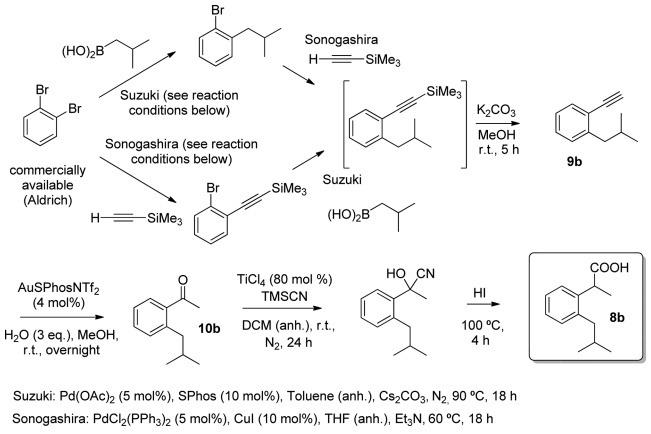


dx.doi.org/10.1021/cs401075z | ACS Catal. 2014, 4, 722−731

Synthesis of Ketone ***10a***. $AuSPhosNTf_2$ (47.6 mg, 2 mol %) was placed in a 25 mL round-bottomed flask and methanol (5 mL) was added. Then, the terminal alkyne **9a** (420 mg, 2.7 mmol) and water (140 μL, 3 equiv) were added and the mixture was magnetically stirred at room temperature overnight. Direct purification by column chromatography (3−5% AcOEt in hexane) yields the corresponding ketone **10a**. The reaction crude was purified by column chromatography using as eluent 3−5% AcOEt in *n*-hexane. Isolated yield: 451 mg (95%). R_f (5% AcOEt in *n*-hexane): 0.38. ^{1}H NMR (δ, ppm; *J*, Hz): 7.87 (C−H arom, m), 7.84 (C−H arom, mult), 7.45 (C−H arom, dd, *J* = 6, 1), 7.43 (C−H arom, m), 2.68 (CH_3, s), 2.625 (CH_2, d, *J* = 3), 1.98 (CH, m, *J* = 6.1), 1.00 (CH_3, 1.00, *J* = 6). ^{13}C NMR (δ, ppm): 198.3 (C═O), 142.2 (C), 137.1 (C), 134.012 (CH), 128.7 (CH), 128.3 (CH), 125.9 (CH), 45.2 (CH_2), 30.2 (CH), 22.3 (CH_3). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{12}H_{16}O$, 176.1201; found, 176.1213.

Synthesis of Carboxylic Acid ***8a***. $TiCl_4$ (439 μL) was dissolved in anhydrous DCM (40 mL). A part of this solution (4.5 mL, 40 mol %) was added over a preformed solution of the ketone **10a** (250 mg, 1.4 mmol) in anhydrous DCM (3 mL) after adding TMSCN (211 μL, 1.2 equiv). The mixture was magnetically stirred at room temperature for 24 h. After the solvent was removed under reduced pressure, the mixture was redissolved in a 1:1 (v/v) solution of HCl (3 M) and acetonitrile (7 mL) and stirred for 1 h. Then, the mixture was concentrated under reduced pressure, diluted with water (15 mL), and extracted with AcOEt (3 × 25 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$, filtrated, and evaporation of the solvent gave an inseparable mixture (same R_f values) of the cyanohydrin product and minor amounts of the starting ketone. ^{1}H NMR (δ, ppm; *J*, Hz): 7.26 (C−H arom, m), 7.06 (C−H arom, dt, *J* = 7.5, 1.4), 3.65 (OH, bs), 2.42 (CH_2, d, *J* = 7.2), 1.78 (CH, m), 1.78 (CH_3, s), 0.81 (CH_3, d, *J* = 6.6). ^{13}C NMR (δ, ppm): 142.7 (C), 140.7 (C), 137.1 (C), 129.9 (CH), 128.7 (CH), 125.2, 121.9 (C), 121.8 (CH), 70.8 (C), 45.4 (CH_2), 30.3 (CH), 22.3 (CH_3), 22.4 (CH_3). Aqueous HI (57 wt %, 400 μL) was added to the mixture (40 mg, 0.2 mmol) in a sealable vial, and the mixture was magnetically stirred in a preheated oil bath at 100 °C for 4 h. Alternatively, potassium iodide (333 mg, 2 mmol) and H_3PO_4 (85 wt % in water, 205 μL, 3 mmol) can be used instead of HI, at 135 °C reaction temperature. After they were cooled, organics were extracted with DCM (5 × 4 mL), and the combined organic phases were washed with $NaHCO_3$ saturated aqueous solution (20 mL), water (20 mL), and brine (20 mL). After the samples were dried over $MgSO_4$, filtrated, and the solvent was evaporated, purification on preparative TLC (20% AcOEt in hexane) gave the *meta*-ibuprofen derivative **8a**. R_f (75% AcOEt in hexane) = 0.75. The reaction crude was purified by column chromatography using 75% AcOEt in *n*-hexane as eluent. Isolated yield over two steps: 24.0 mg (58%). R_f (75% AcOEt in *n*-hexane) = 0.75. ^{1}H NMR (δ, ppm; *J*, Hz): 7.16 (C−H arom, t, *J* = 7.5), 7.06 (C−H arom, dt, *J* = 7.22, *J* = 1.55), 6.99 (C−H arom, m), 3.64 (CH, c, *J* = 7.15), 2.39 (CH_2, d, *J* = 7.14), 1.78 (CH, m), 1.44 (CH_3, d, *J* = 7.17), 0.82 (CH_3, d, *J* = 6.6). ^{13}C NMR (δ, ppm; *J*, Hz): 199.6 (C−OOH), 142.3 (C), 139.7 (C), 128.5 (CH), 128.6 (CH), 128.3 (CH), 124.9 (CH), 45.5 (CH_2), 45.3 (CH), 30.3 (CH), 22.5 (CH_3), 18.3 (CH_3). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{13}H_{18}O_2$, 206.1307; found, 206.1319.

ortho-Ibuprofen 8b. *Synthesis of Alkyne* ***9b***. $PdCl_2(PPh_3)_2$ (745 mg, 5 mol %) and copper iodide (405 mg, 10 mol %) were placed in a 100 mL round-bottomed flask equipped with a magnetic bar and then anhydrous THF (13 mL), the dibromide (2.7 mL, 21.3 mmol), trimethylsilylacetylene (3.24 mL, 21.3 mmol), and triethylamine (13.5 mL) were added. The flask was capped with a rubber septum, and the resulting mixture was placed in a preheated oil bath at 60 °C and magnetically stirred overnight. One aliquot was taken for GC analysis, and the rest was diluted in diethyl ether (100 mL) after cooling. The solids were removed by filtration, and the resulting solution was purified by column chromatography to yield 2.0 g of the alkyne product (37%) with minor amounts of the corresponding bis-alkyne. Then, palladium acetate (66 mg, 5 mol %) and SPhos (246 mg, 10 mol %) were placed in a 25 mL round-bottomed flask and magnetically stirred at room temperature for 10 min after addition of anhydrous



Suzuki: $Pd(OAc)_2$ (5 mol%), SPhos (10 mol%), Toluene (anh.), Cs_2CO_3, N_2, 90 °C, 18 h
Sonogashira: $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), THF (anh.), Et_3N, 60 °C, 18 h

toluene (5 mL). Then, the above alkyne mixture, isobutylboronic acid (1.2 g, 12 mmol), cesium carbonate (3.9 g, 1.5 equiv), and anhydrous toluene (25 mL) were added, and the final mixture was placed in a preheated oil bath at 90 °C and magnetically stirred for 18 h under nitrogen atmosphere. After the sample was cooled, DCM (50 mL) was added, and the mixture was filtered. Volatiles in the filtrates were removed under reduced pressure, the resulting crude was redissolved in MeOH (15 mL), and potassium carbonate was added (7 g). The mixture was magnetically stirred at room temperature for 5 h. DCM (20 mL) was added, and the mixture was filtrated and concentrated under reduced pressure. The reaction crude was purified by column chromatography using as eluent 3−5% *n*-hexane. Isolated yield: 461 mg (37%). R_f (*n*-hexane): 0.26. ^{1}H NMR (δ, ppm; *J*, Hz): 7.58 (C−H arom, dt, *J* = 1.2, 7.4), 7.34 (C−H arom, m), 7.24 (C−H arom, m), 3.31 (C−H, s), 2.79 (CH_2, d, *J* = 7.25), 2.11 (CH, m), 1.04 (CH_3, d, *J* = 6.8). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{12}H_{14}$, 158.1096; found, 158.1088.

Synthesis of Ketone ***10b***. $AuSPhosNTf_2$ (57.1 mg, 4 mol %) was placed in a 25 mL round-bottomed flask, and methanol (5 mL) was added. Then, the terminal alkyne **9b** (288 mg, 1.6 mmol) and water (84 μL, 3 equiv) were added, and the mixture was magnetically stirred at room temperature overnight. The reaction crude was purified by column chromatography using as eluent 3−5% AcOEt in *n*-hexane. Isolated yield: 194 mg (69%). R_f (*n*-hexane): 0.40. GC-MS (*m*/*z*, $M^{+\bullet}$ 176), major peaks found: 176 (100%), 161 (100%), 133 (90%), 119 (32%), 91 (56%), 43 (75%). ^{1}H NMR (δ, ppm; *J*, Hz): 7.58 (C−H arom, dd, *J* = 1.5, 7.7), 7.32 (C−H arom, td, *J* = 1.5, 7.7), 7.32 (C−H arom, dd, *J* = 1.5, 7.7), 2.73 (CH_2, d, *J* = 7.1), 2.52 (CH_3, s), 1.79 (CH_2, m), 0.86 (CH_3, d, *J* = 6.7). ^{13}C NMR (δ, ppm): 202.4 (C═O), 141.46 (C), 138.5 (C), 132.0 (CH), 130.9 (CH), 128.9 (CH), 125.7 (CH), 42.7 (CH_2), 30.3 (CH), 30.1 (CH_3), 22.5 (CH_3). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{12}H_{16}O$, 176.1201; found, 176.1225.

Synthesis of Carboxylic Acid ***8b***. $TiCl_4$ (439 μL) was dissolved in anhydrous DCM (40 mL). A part of this solution (6.4 mL, 80 mol %) was added over a preformed solution of the ketone **10b** (198 mg, 1 mmol) in anhydrous DCM (2 mL) after adding TMSCN (151 μL, 1.2 equiv). The mixture was magnetically stirred at room temperature for 24 h. After the solvent was removed under reduced pressure, the mixture was redissolved in a 1:1 (v/v) solution of HCl (3 M) and acetonitrile (5 mL) and stirred for 1 h. Then, the mixture was concentrated under reduced pressure, diluted with water (10 mL), and extracted with AcOEt (3 × 20 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtrated, and evaporation of the solvent gave an inseparable mixture (same R_f values) of the cyanohydrin product and minor amounts of the starting ketone. ^{1}H NMR (δ, ppm; *J*, Hz): 7.44 (C−H arom, m), 7.28 (C−H arom, m), 7.18 (C−H arom, m), 7.10 (C−H arom, m), 2.88 (CH_2, dd, *J* = 7.4, 8.5), 2.31 (CH_3, s), 2.13 (CH, m), 0.93 (CH_3, dd, *J* = 6.6, 10.9). ^{13}C NMR (δ, ppm): 142.7 (C), 140.7 (C), 137.1 (C), 129.9 (CH), 128.7 (CH), 125.2, 121.9 (C), 121.8 (CH), 70.8 (C), 45.4 (CH_2), 30.3 (CH), 22.3 (CH_3), 22.4 (CH_3). Aqueous HI (57 wt %, 200 μL) was added to the mixture (20 mg, 0.1 mmol) in a sealable vial, and the mixture was magnetically stirred in a preheated oil bath at 100

dx.doi.org/10.1021/cs401075z | ACS Catal. 2014, 4, 722−731

°C for 2−4 h. After the samples were cooled, organics were extracted with DCM (5 × 4 mL), and the combined organic phases were washed with $NaHCO_3$ saturated aqueous solution (10 mL), water (10 mL), and brine (10 mL). Alternatively, solid $NaHCO_3$ (67 mg) can be added before extracting. After the samples were dried over $MgSO_4$, they were filtrated, and the solvent was evaporated. Purification on preparative TLC (20% AcOEt in *n*-hexane) gives a two-step combined yield of 47% (9.7 mg) of the *ortho*-ibuprofen derivative **8b**. R_f (25% AcOEt in *n*-hexane): 0.32. GC-MS (*m*/*z*, $M^{+\bullet}$ 206), major peaks found: 206 (43%), 164 (14%), 133 (28%), 117 (100%), 105 (18%), 91 (31%). ^{1}H NMR (δ, ppm; *J*, Hz): 7.24 (C−H arom, m), 7.11 (C−H arom, dt, *J* = 8.1, 1.2), 7.09 (C−H arom, d, *J* = 14.1), 7.05 (C−H arom, m), 3.94 (CH, d, *J* = 7.1), 2.49 (CH_2, m), 1.79 (CH_2, m), 1.39 (CH_3), 0.86 (CH_3, d, *J* = 6.7). ^{13}C NMR (δ, ppm): 180.3 (COOH), 139.2 (C), 138.4 (C), 133.8 (CH), 126.8 (CH), 126.8 (CH), 126.5 (CH), 42.3 (CH_2), 40.3 (CH), 29.9 (CH), 22.6 (CH_3), 18.6 (CH_3). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{13}H_{18}O_2$, 206.1307; found, 206.1328.

Procedure for the Synthesis of Ketone 12 (Figure 3, Bottom). $PdCl_2(PPh_3)_2$ (4.4 mg, 1 mol %) and copper iodide (2 mg, 1 mol %) were placed in a 1.5 mL vial equipped with a magnetic bar and then nondried 1,4-dioxane (0.5 mL), the corresponding iodide (0.5 mmol) and alkyne (0.6 mmol, 1.2 equiv), and triethylamine (345 μL, 2.5 mmol, 5 equiv) were added. The flask was closed, and the resulting mixture was placed in a preheated oil bath at 70 °C and magnetically stirred for 18 h. One aliquot was taken for GC analysis and the rest was diluted in diethyl ether (1.5 mL) after cooling (the ammonium salt can be observed as crystals in some cases), removing the solids by filtration. The reaction crude was purified by column chromatography using 15% MeOH in AcOEt as an eluent. GC-MS (*m*/*z*, $M^{+\bullet}$ 220), major peaks found: 220 (46%), 205 (100%), 191 (11%), 177 (50%), 161 (26%), 146 (64%), 133 (60%), 115 (27%) 101 (17%), 28 (25%). ^{1}H NMR (δ, ppm, acetone-d_6; *J*, Hz): 7.78 (C−H arom, dd, *J* = 7.4, 2.2), 7.28 (C−H arom, ddd, *J* = 8.5, 4.5, 2.2), 6.89 (C−H arom, dd, *J* = 10.7, 8.5), 4.02 (CO_2H, bs), 2.22 (CH_2, t, *J* = 6.8), 1.43−1.24 (2 CH_2, m), 1.31 (CH_3, t, *J* = 7.2). ^{13}C NMR (δ, ppm, acetone-d_6): 171.9 (CO_2H), 162.6 (C, d, J^1_{C-F} = 256.3), 143.0 (CH), 137.3 (CH, d, J^3_{C-F} = 10.9), 125.4 (C−CO_2H, d, J^2_{C-F} = 10.9), 121.5 (C, d, J^4_{C-F} = 3.8), 118.3 (CH, d, J^2_{C-F} = 24.2), 91.7 (C_{alkyne}), 80.8 (C_{alkyne}), 32.4 (CH_2), 23.5 (CH_2), 20.2 (CH_2), 14.8 (CH_3). ^{19}F NMR (δ, ppm; *J*, Hz): 65.12 (s). This internal alkyne was then submitted to hydration conditions by heating a solution in 1,4-dioxane with $HNTf_2$ in a preheated oil bath at 100 °C, under magnetic stirring for 18−52 h and following the formation of ketone **12** by GC and GC-MS, using dodecane as an external standard. GC-MS (*m*/*z*, $M^{+\bullet}$ 238), major peaks found: 238 (2%), 195 (4%), 182 (89%), 167 (100%), 139 (13%), 83 (13%). ^{1}H NMR (δ, ppm, acetone-d_6; *J*, Hz): 8.48−8.32 (C−H arom, mult), 8.15−8.07 (C−H arom, mult), 7.28−7.17 (C−H arom, mult), 4.74 (CO_2H, bs), 2.92 (CH_2, t, *J* = 7.2), 1.66−1.55 (CH_2, mult), 1.33−1.18 (2 CH_2, mult), 0.83 (CH_3, t, *J* = 7.0). ^{19}F NMR (δ, ppm; *J*, Hz): −82.15 (s). HRMS (ESI) *m*/*z*: [M^+] calcd for $C_{13}H_{15}FO_3$, 238.1005; found, 238.1001.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General and experimental procedures, compound characterization, binding assays, and copies of the NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support by the Severo Ochoa program and Consolider-Ingenio 2010 (proyecto MULTICAT) from MCIINN is acknowledged, and also to the King Saud University. A.L.-P. thanks ITQ for a contract. J.R. C.-A. and P.R.M. thank MCIINN for the concession of a FPU contract.

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