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$TiCl_4$-Catalyzed Indirect Anti-Markovnikov Hydration of Alkynes: Application to the Synthesis of Benzo[*b*]furans

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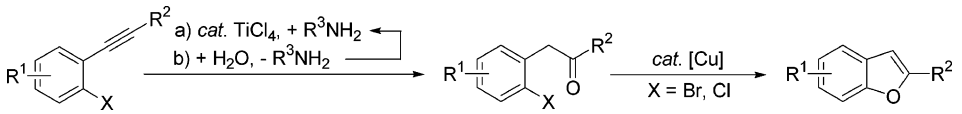

An efficient methodology for the indirect anti-Markovnikov hydration of unsymmetrically substituted terminal and internal alkynes is based on $TiCl_4$-catalyzed hydroamination reactions. Its application to *ortho*-alkynylhaloarenes, followed by a copper-catalyzed O-arylation, provides flexible access to substituted benzo[*b*]furans.

Introduction

The regioselective functionalization of unsymmetrically substituted alkynes is of fundamental importance in synthetic organic chemistry.[1] The hydration of carbon−carbon triple bonds provides direct access to substituted ketones and aldehydes.[2] Traditionally, toxic mercury(II) compounds were employed for the addition of water to alkynes, yielding the corresponding Markovnikov products.[1−3] Similar regioselectivities were accomplished through the use of expensive late transition-metal catalysts.[2,4] Hydration reactions with excellent anti-Markovnikov selectivities were achieved for *terminal* alkynes with ruthenium-based catalysts.[2,5,6] However, a general protocol for highly selective anti-Markovnikov hydration reactions of internal alkynes has proven elusive. An overall, *indirect* hydration[6] of an alkyne is accomplished through a sequence consisting of a regioselective hydroamination and the subsequent hydrolysis of the generated imine.

Pioneering studies on zirconium-[7] and titanium-catalyzed[8] hydroamination reactions of alkynes[9] set the stage for the development of more elaborate titanium-based hydroamination catalysts.[10,11] We on the contrary felt attracted by the possibility of employing inexpensive $TiCl_4$ as precatalyst for preparatively useful intermolecular hydroamination reactions of alkynes.[12]

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(1) (a) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368−3398. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079−3159.

(2) (a) Hintermann, L.; Labonne, A. *Synthesis* **2007**, 1121−1150. (b) Tani, K.; Kataoka, Y. In *Catalytic Heterofunctionalization;* Togni, A., Grützmacher, H., Eds.; Wiley-VCH: Weinheim, 2001; pp 171−216.

(3) For selected recent examples of the use of strong Brønsted acids, see: (a) Le Bras, G.; Provot, O.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron Lett.* **2006**, *47*, 5497−5501. (b) Tsuchimoto, T.; Joya, T.; Shirakawa, E.; Kawakami, Y. *Synthesis* **2000**, 1777−1778 and references therein.

(4) Selected examples: (a) Meier, I. K.; Marsella, J. A. *J. Mol. Catal.* **1993**, *78*, 31−42. [Au]: (b) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4563−4565. (c) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729−3731. [Pt]: (d) Hiscox, W.; Jennings, P. W. *Organometallics* **1990**, *9*, 1997−1999. (e) Hartman, J. W.; Hiscox, W. C.; Jennings, P. W. *J. Org. Chem.* **1993**, *58*, 7613−7614. [Rh]: (f) Blum, J.; Huminer, H.; Alper, H. *J. Mol. Catal.* **1992**, *75*, 153−160. [Ir]: (g) Hirabayashi, T.; Okimoto, Y.; Saito, A.; Morita, M.; Sakaguchi, S.; Ishii, Y. *Tetrahedron* **2006**, *62*, 2231−2234 and references therein.

(5) (a) Tokunaga, M.; Wakatsuki, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 2867−2869. (b) Suzuki, T.; Tokunaga, M.; Wakatsuki, Y. *Org. Lett.* **2001**, *3*, 735−737. (c) Tokunaga, M.; Suzuki, T.; Koga, N.; Fukushima, T.; Horiuchi, A.; Wakatsuki, Y. *J. Am. Chem. Soc.* **2001**, *123*, 11917−11924. (d) Wakatsuki, Y.; Hou, Z.; Tokunaga, M. *Chem. Rec.* **2003**, *3*, 144−157. (e) Grotjahn, D. B.; Incarvito, C. D.; Rheingold, A. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3884−3887. (f) Grotjahn, D. B.; Lev, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 12232−12233. (g) Grotjahn, D. B. *Chem.−Eur. J.* **2005**, *11*, 7146−7153. (h) Alvarez, P.; Bassetti, M.; Gimeno, J.; Mancini, G. *Tetrahedron Lett.* **2001**, *42*, 8467−8470. (i) Chevallier, F.; Breit, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 1599−1602. (j) Labonne, A.; Kribber, T.; Hintermann, L. *Org. Lett.* **2006**, *8*, 5853−5856.

(6) Oestreich, M. *Sci. Synth.* **2007**, *25*, 199−211.

(7) (a) Walsh, P. J.; Hollander, F. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 8729−8731. (b) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708−1719. (c) Duncan, A. P.; Bergman, R. G. *Chem. Rec.* **2002**, *2*, 431−445.

(8) For a first titanium-catalyzed intermolecular hydroamination of an alkyne, see: (a) Hill, J. E.; Profilet, R. D.; Fanwick, P. E.; Rothwell, I. P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 664−665. See also: (b) McGrane, P. L.; Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1992**, *114*, 5459−5460. (c) McGrane, P. L.; Livinghouse, T. *J. Org. Chem.* **1992**, *57*, 1323−1324. (d) Polse, J. L.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 13405−13414.

(9) A review: Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104−114.

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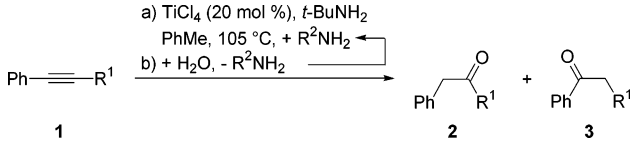
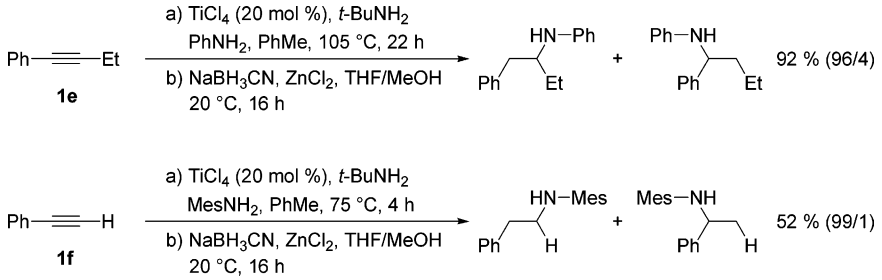
TABLE 1. Indirect $TiCl_4$-Catalyzed Hydration of Alkynes[a]



entry	R^2NH_2	R^1		hydrolysis method	isolated yield (%)	ratio **2**/**3**[b]
1	*t*-$BuNH_2$	Ph	(**1a**)		(8)[c]	
2	$CyNH_2$	Ph	(**1a**)	A	84	
3	$PhMeCHNH_2$	Ph	(**1a**)	B	93	
4	*sec*-$BuNH_2$	Ph	(**1a**)	A	78	
5	*n*-$OctNH_2$	Ph	(**1a**)	A	66[d]	
6	*n*-$BuNH_2$	*n*-Hex	(**1b**)	A	84[d]	55/45
7	*n*-$OctNH_2$	*n*-Hex	(**1b**)	A	80[d]	54/46
8	*sec*-$BuNH_2$	*n*-Hex	(**1b**)	A	86	56/44
9	$PhMeCHNH_2$	*n*-Hex	(**1b**)	B	80	64/36
10	$MesCH_2NH_2$	*n*-Hex	(**1b**)	B	94	86/14
11	$PhNH_2$	*n*-Hex	(**1b**)	A	92	91/9
12	$MesNH_2$	*n*-Hex	(**1b**)	B	82	98/2
13	$PhNH_2$	*i*-Pr	(**1c**)	A	91	82/18
14	$PhNH_2$	*t*-Bu	(**1d**)	A	78[e]	2/98
15	$PhNH_2$	*n*-Hex	(**1b**)		—[f]	

[a] Reaction conditions: (a) **1** (1.0 mmol), R^2NH_2 (1.0 mmol), $TiCl_4$ (20 mol %), *t*-$BuNH_2$ (1.2 mmol), PhMe (2 mL), 22 h, 105 °C. (b) Hydrolysis methods: A: SiO_2, CH_2Cl_2, 20 °C. B: aqueous HCl (2 N), 20 °C. Isolated yields refer to mixtures of regioisomeric products. Mes = 1,3,5-$Me_3C_6H_2$. [b] ^1H NMR analysis. [c] GC conversion. [d] 170 °C. [e] 150 °C. [f] Without *t*-$BuNH_2$.

SCHEME 1. $TiCl_4$-Catalyzed Anti-Markovnikov Hydroamination with Subsequent Reduction



Given the practical importance of efficient and economical ketone synthesis, we wished to make use of our protocol for regioselective indirect hydration reactions of internal alkynes. Herein, we report on the development of an operationally simple and regioselective yet efficient indirect anti-Markovnikov hydration of alkynes and its application to the synthesis of benzo[*b*]-furans.

Results and Discussion

At the outset of our studies, we explored $TiCl_4$-catalyzed hydroamination reactions with alkyl amines, as our previously developed protocol had thus far been only applied to intermolecular hydroaminations with aniline and hydrazine derivatives (Table 1).[12,13] While *t*-$BuNH_2$ gave only a sluggish conversion of an internal alkyne (entry 1), we were pleased to observe that other alkyl amines proved to be viable substrates for $TiCl_4$-catalyzed intermolecular hydroamination reactions (entries 2−4).

Notably, challenging *n*-alkyl-substituted amines[10f] could be converted in high yields as well (entries 5−7). However, more selective anti-Markovnikov hydrations of internal and terminal alkynes were accomplished when using more sterically hindered amines (entries 6−12). Hence, synthetically useful regioselectivities could be obtained with aniline derivatives, giving rise to anti-Markovnikov hydration products (entries 11 and 12) or, after reduction, to the corresponding secondary amines (Scheme 1). Alkynes bearing a primary or secondary alkyl substituent yielded the anti-Markovnikov indirect hydration products with high regioselectivities (entries 11−13). On the contrary, alkyne **1d** with a tertiary alkyl substituent required harsher reaction conditions and gave, likely because of steric interactions, the Markovnikov product predominantly (entry 14). Importantly, no conversion of alkyne **1b** was achieved in the absence of *t*-$BuNH_2$ (entry 15), highlighting its importance as precursor to an amido ligand as well as for the formation of catalytically active titanium imido species.[12a] The amines can be potentially

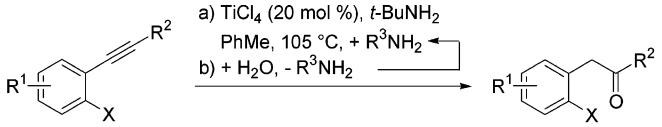
(10) Selected recent examples: (a) Buil, M. L.; Esteruelas, M. A.; Lopez, A. M.; Mateo, A. C.; Onate, E. *Organometallics* **2007**, *26*, 554−565. (b) Swartz, D. L., II; Odom, A. L. *Organometallics* **2006**, *25*, 6125−6133. (c) Smolensky, E.; Kapon, M.; Eisen, M. S. *Organometallics* **2005**, *24*, 5495−5498. (d) Tillack, A.; Khedkar, V.; Jiao, H.; Beller, M. *Eur. J. Org. Chem.* **2005**, 5001−5012. (e) Hoover, J. M.; Petersen, J. R.; Pikul, J. H.; Johnson, A. R. *Organometallics* **2004**, *23*, 4614−4620. (f) Heutling, A.; Pohlki, F.; Doye, S. *Chem.−Eur. J.* **2004**, *10*, 3059−3071. (g) Zhang, Z.; Schafer, L. L. *Org. Lett.* **2003**, *5*, 4733−4736. (h) Lorber, C.; Choukroun, R.; Vendier, L. *Organometallics* **2004**, *23*, 1845−1850. (i) Shi, Y.; Ciszewski, J. T.; Odom, A. L. *Organometallics* **2001**, *20*, 3968−3969. (j) Johnson, J. S.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, *123*, 2923−2924 and references therein.

(11) For review articles, see: (a) Odom, A. L. *Dalton Trans.* **2005**, 225−233. (b) Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2003**, 935−946.

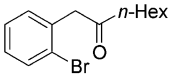
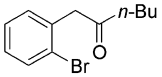
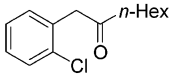
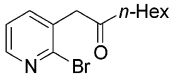
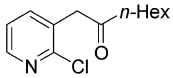
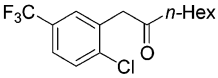
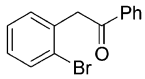
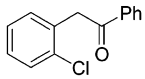
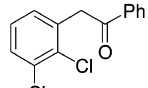
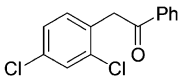
(12) (a) Ackermann, L. *Organometallics* **2003**, *22*, 4367−4368. (b) Ackermann, L.; Born, R. *Tetrahedron Lett.* **2004**, *45*, 9541−9544. (c) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Chem. Commun.* **2004**, 2824−2825.

(13) Abbiati, G.; Casoni, A.; Canevari, V.; Nava, D.; Rossi, E. *Org. Lett.* **2006**, *8*, 4839−4842.

TABLE 2. Indirect Hydration of *ortho*-Alkynylhaloarenes 1[a]



1 **2**

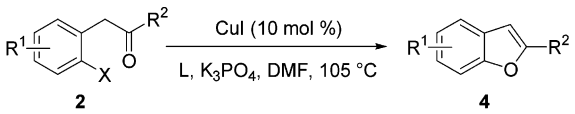
entry	R^3	product	isolated yield	ratio **2**/**3**[b]
1	Oct	 **2a**	65 %[c]	53/47
2	Ph		95 %	96/4
3	Mes		90 %	99/1
4	Ph	 **2b**	92 %	92/8
5	Ph	 **2c**	95 %	92/8
6	*p*-Tol	 **2d**	75 %	99/1
7	*p*-Tol	 **2e**	90 %	99/1
8	Ph	 **2f**	87 %	99/1
9	Ph	 **2g**	77 %	47/53
10	Mes		78 %[d]	80/20
11	Ph	 **2h**	86 %	54/46
12	Mes		79 %[d]	86/14
13	Ph	 **2i**	90 %	67/33
14	Mes		91 %[d]	97/3
15	Ph	 **2j**	88 %	60/40
16	Mes		86 %[d]	97/3

[a] Reaction conditions: (a) **1** (1.0 mmol), R^3NH_2 (1.0−1.3 mmol), $TiCl_4$ (20 mol %), *t*-$BuNH_2$ (1.2 mmol), PhMe (2 mL), 22 h, 105 °C. (b) Hydrolysis: aqueous HCl (2 N), 20 °C. Isolated yields refer to mixtures of regioisomeric products. Mes = 1,3,5-$Me_3C_6H_2$. [b] ^{1}H NMR analysis. [c] 170 °C. [d] (a) **1** (1.0 mmol), R^3NH_2 (1.0 mmol), $TiCl_4$ (20 mol %), *t*-$BuNH_2$ (1.2 mmol), PhMe (2 mL), 22 h, 120 °C. (b) Aqueous HCl (2 N), 100 °C.

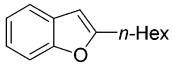
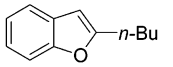
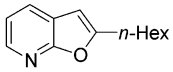
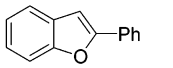
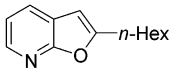
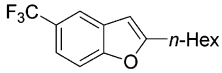
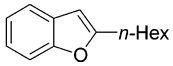
recovered through an acidic workup procedure (entries 3, 9, 10, and 12), rendering the overall approach atom economical.

The benzo[*b*]furan motif is an essential substructure in a large number of natural and unnatural biologically active compounds, and therefore it continues to induce extensive synthetic efforts.[14] Recently, intramolecular copper-catalyzed[15] O-arylations of enolates with aryl iodides and bromides were elegantly used to access the benzo[*b*]furan scaffold.[16]

TABLE 3. Copper-Catalyzed Benzo[*b*]furan Synthesis[a]



2 **4**

entry	**2**	L	X	**4**		isolated yield
1	**2a**	---	Br		**4a**	82 %
2	**2b**	---	Br		**4b**	82 %
3	**2d**	---	Br		**4c**	80 %
4	**2g**	---	Br		**4d**	65 %
5	**2e**	---	Cl		**4c**	56 %
6	**2f**	---	Cl		**4e**	12 %[b]
7	**2f**	L-Proline	Cl		**4e**	45 %
8	**2f**	$MeNH(CH_2)_2NHMe$	Cl		**4e**	67 %
9	**2f**	$Me_2NCH_2CO_2H$	Cl		**4e**	69 %
10	**2c**	$Me_2NCH_2CO_2H$	Cl		**4a**	37 %

[a] Reaction conditions: **2** (0.7 mmol), K_3PO_4 (1.4 mmol), CuI (10 mol %), L (30 mol %), DMF (2 mL), 105 °C, 22 h; yields of isolated products. [b] GC conversion.

Consequently, we applied the $TiCl_4$-catalyzed indirect hydration protocol to *ortho*-alkynylhaloarenes (Table 2). Simple anilines proved valuable for regioselective indirect hydration reactions of alkyl-(hetero)aryl-substituted alkynes (entries 2 and 4−8). To achieve preparatively useful selectivities with diaryl-substituted alkynes, the use of a sterically hindered aniline proved beneficial (entries 9−16).

Finally, we used ketones **2** as starting materials for a copper-catalyzed benzo[*b*]furan synthesis (Table 3). Substrates bearing bromide substituents as leaving groups could be cyclized without stabilizing ligand (entries 1−4). Importantly, the protocol proved not only applicable to aryl bromides, but also to less reactive chlorides. Here, most efficient catalysis was achieved with $Me_2NCH_2CO_2H$[17] as ligand (entries 5−10).

In conclusion, we reported on $TiCl_4$-catalyzed indirect hydration reactions of unsymmetrically substituted internal and terminal alkynes, employing both aryl and alkyl amines. With aryl amines highly selective anti-Markovnikov selectivities were achieved. The power of our protocol was illustrated with its application to an efficient benzo[*b*]furan synthesis.

Experimental Section

Representative Procedure for the $TiCl_4$-Catalyzed Indirect Hydration of Alkynes, 1-Phenyloctan-2-one (Table 1, Entry 12). *t*-$BuNH_2$ (0.130 mL, 1.20 mmol) was added to a solution of $TiCl_4$ (0.022 mL, 0.20 mmol, 20 mol %) in toluene (2 mL) under N_2. Mesitylamine (0.135 g, 1.00 mmol) and **1b** (0.186 g, 1.00 mmol) were added. The solution was stirred at 105 °C for 22 h. At ambient temperature, aqueous HCl (2 N, 10 mL) was added, and the reaction mixture was stirred at 20 °C for 24 h. H_2O (50 mL) was added, and the separated aqueous phase was extracted with Et_2O (3 × 60 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (*n*-pentane/Et_2O, 30/1) to yield 1-phenyloctan-2-one (167 mg, 82%, purity: 98% by ^1H NMR and GC analysis) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.35−7.20 (m, 5H), 3.68 (s, 2H), 2.44 (t, J = 7.4 Hz, 2H), 1.55 (tt, J = 7.1, 7.1 Hz, 2H), 1.31−1.24 (m, 6H), 0.87 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, DEPT, $CDCl_3$) δ = 209.0 (CO), 134.8 (C_q), 129.8 (CH), 129.1 (CH), 127.3 (CH), 50.5 (CH_2), 42.4 (CH_2), 31.9 (CH_2), 29.2 (CH_2), 24.1 (CH_2), 22.9 (CH_2), 14.4 (CH_3). IR (ATR): 2955, 2928, 2858, 1709, 1496, 1454, 698 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 204 (1) [M^+], 113 (100), 91 (44), 85 (37),

(14) For a recent review, see: Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Curr. Org. Chem.* **2006**, *10*, 1423−1455 and references therein.

(15) For related palladium-catalyzed transformations, see: (a) Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2501−2504. (b) Willis, M. C.; Taylor, D.; Gillmore, A. T. *Org. Lett.* **2004**, *6*, 4755−4757. (c) Willis, M. C.; Taylor, D.; Gillmore, A. T. *Tetrahedron* **2006**, *62*, 11513−11520. (d) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694−10695.

(16) (a) Chen, C.-y.; Dormer, P. G. *J. Org. Chem.* **2005**, *70*, 6964−6967. (b) Carril, M.; SanMartin, R.; Tellitu, I.; Dominguez, E. *Org. Lett.* **2006**, *8*, 1467−1470.

(17) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164−5173.

65 (11), 57 (17), 43 (100). HR-MS (EI) *m*/*z* calcd for $C_{14}H_{20}O$ 204.1514, found 204.1528.

Representative Procedure for Cu-Catalyzed Benzo[*b*]furan Synthesis, 2-*n*-Hexylbenzo[*b*]furan (4a) (Table 3, Entry 1). K_3PO_4 (0.293 g, 1.38 mmol) and CuI (0.013 g, 0.07 mmol, 10 mol %) were added to a solution of **2a** (0.195 g, 0.69 mmol) in DMF (2 mL) under N_2. The solution was stirred at 105 °C for 22 h. At ambient temperature, brine (60 mL) and Et_2O (60 mL) were added to the reaction mixture. The separated aqueous phase was extracted with Et_2O (2 × 60 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (*n*-pentane) to yield **4a** (114 mg, 82%) as a colorless liquid. The spectral data are in accordance with those reported in the literature.[18] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.57−7.54 (m, 1H), 7.51−7.47 (m, 1H), 7.31−7.22 (m, 2H), 6.45−6.44 (m, 1H), 2.84 (dt, *J* = 7.5, 0.9 Hz, 2H), 1.82 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.50−1.37 (m, 6H), 1.00−0.95 (m, 3H). ^{13}C NMR (75 MHz, DEPT, $CDCl_3$) δ = 159.8 (C_q), 154.6 (C_q), 129.0 (C_q), 123.0 (CH), 122.3 (CH), 120.1 (CH), 110.7 (CH), 101.7 (CH), 31.6 (CH_2), 28.9 (CH_2), 28.4 (CH_2), 27.7 (CH_2), 22.6 (CH_2), 14.0 (CH_3). IR (ATR): 2954, 2928, 2858, 1602, 1588, 1454, 1253, 1167, 792, 749, 738 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 202 (23) [M^+], 145 (5), 131 (100), 107 (5), 95 (12), 77 (6). HR-MS (EI) *m*/*z* calcd for $C_{14}H_{18}O$ 202.1358, found 202.1335.

(18) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017−8028.

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Supporting Information Available: Additional experimental procedures, characterization data, as well as ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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