Aqueous DMF−Potassium Carbonate as a Substitute for Thallium and Silver Additives in the Palladium-Catalyzed Conversion of Aryl Bromides to Acetyl Arenes

Karl S. A. Vallin, Mats Larhed, and Anders Hallberg*

*Department of Organic Pharmaceutical Chemistry, Uppsala University, BMC,
Box-574, SE− 751 23 Uppsala, Sweden*

Anders.Hallberg@farmkemi.uu.se

Highly selective palladium-catalyzed internal α-arylations of alkyl vinyl ethers with aryl and heteroaryl bromides were conveniently conducted in aqueous DMF with potassium carbonate as base and with DPPP as bidentate ligand. The corresponding acetyl arene products were, after hydrolysis, isolated in good to excellent yields. This Heck reaction procedure does not require toxic thallium or expensive silver salt additives, is promoted by water, and is suggested to proceed via charged organopalladium intermediates. Single-mode microwave irradiation was utilized in one example to shorten the reaction time.

Introduction

Palladium-catalyzed Heck arylation of acyclic electron-deficient monosubstituted olefins leads predominantly to vinylic substitution at the least hindered terminal position.[1−3] Arylation of electron-rich olefins, such as vinyl ethers, can be controlled to deliver vinyl ethers substituted either at the terminal β-position[4] or at the internal α-position.[5] Cabri et al. demonstrated that the employment of bidentate ligands resulted in highly α-selective arylations of alkyl vinyl ethers.[6,7] This reaction, relying on the creation of cationic organopalladium intermediates, constitutes a new, general, and efficient entry to acetylated aromatic products from aryl triflates or aryl halides. The related ligand-controlled highly regioselective palladium-catalyzed α-vinylation of alkyl vinyl ethers efficiently affords 1,3-dienes and acetals with both classic and microwave-mediated heating.[8] With aryl or vinyl triflates, ionization occurs by spontaneous dissociation of the weakly palladium(II)-coordinating triflate counterion. Toxic thallium(I) or costly silver(I) salts were needed as additives in the reactions where aryl bromides were employed.[6,9] This disadvantage limited the utility of this important class of arylating agents in α-arylations, in particular for their use in parallel synthesis and large-scale reactions. Although the role of the thallium or silver additives is not fully elucidated, it is proposed that these additives promote halide abstraction[9,10] and thus forma-

tion of a cationic π-complex, essential for the charged controlled α-selectivity.[6]

An alternative method to support ionization and formation of a cationic π-complex from aryl bromides could be to increase the polarity of the DMF-based reaction mixture. To develop a "green" procedure we decided to probe the potential of water as a cheap and environmentally friendly polar additive to the Heck cocktail.[3,11,12] Very recently, Xiao demonstrated a highly selective internal Heck arylation of butyl vinyl ether with aryl halides in the highly polar ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmin][BF₄]).[13]

We herein report that an efficient conversion of aryl bromides to acetyl arenes can be accomplished also in absence of thallium and silver additives provided that the arylations are conducted in a polar aqueous DMF medium with potassium carbonate as base and 1,3-bis-(diphenylphosphino) propane (DPPP) as ligand (eq 1). In addition, vinyl bromides were converted into the corresponding α,β-unsaturated methyl ketones via the water promoted Heck vinylation reaction.
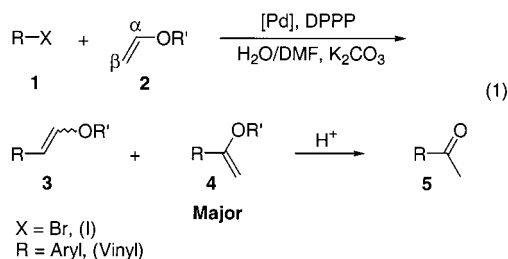
Results

In the initial experiments we reacted 1-bromo naphthalene (**1e**) with butyl vinyl ether (**2a**) in DMF with

(1) Heck, R. F. *Org React.* **1982**, *27*, 345−390.
(2) De Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379−2411.
(3) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.
(4) Larhed, M.; Andersson, C. M.; Hallberg, A. *Acta Chem. Scand.* **1993**, *47*, 212−217.
(5) Hallberg, A.; Westfelt, L.; Holm, B. *J. Org. Chem.* **1981**, *46*, 5414−5415.
(6) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481−1486.
(7) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2−7.
(8) Vallin, K. S. A.; Larhed, M.; Johansson, K.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 4537−4542.
(9) Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, *32*, 687−690.

(10) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896.
(11) Bumagin, N. A.; More, P. G.; Beletskaya, I. P. *J. Organomet. Chem.* **1989**, *371*, 397−401.
(12) Wang, J. X.; Hu, Z.; Wei, B. G.; Bai, L. *J. Chem. Res. S* **2000**, 484−485.
(13) Xu, L. J.; Chen, W. P.; Ross, J.; Xiao, J. L. *Org. Lett.* **2001**, *3*, 295−297.

Table 1. Regioselective Internal Arylation and Vinylation of Vinyl Ethers with Organo Halides[a]

entry	aryl halide or vinyl bromide	olefin	H$_2$O/DMF	time (h)	temp °C[b]	4/3[c]	isolated yield 5 (%)[d]
1	4-MeO-PhBr	**1a**	**2a**	0.0/12.5	16	80	99/1	**5a** 93
2	4-MeO-PhBr	**1a**	**2a**	0.75/12.5	16	80	99/1	**5a** 95
3	4-MeO-PhBr	**1a**	**2a**	1.5/12.5	16	80	99/1	**5a** 92
4	PhBr	**1b**	**2a**	0.0/12.5	86	80	99/1	**5b** 89
5	PhBr	**1b**	**2a**	0.75/12.5	16	80	99/1	**5b** 87
6	PhBr	**1b**	**2a**	1.5/12.5	16	80	99/1	**5b** 82
7	PhBr	**1b**	**2a**	1.5/12.5[e]	48	80	99/1	**5b** 86
8	PhBr	**1b**	**2a**	1.5/12.5[f]	48	80	99/1	**5b** 89
9	PhBr	**1b**	**2b**	1.5/12.5	16	80	99/1	**5b** 85
10	PhBr	**1b**	**2c**	1.5/12.5	16	80	99/1	**5b** 85
11	PhBr	**1b**	**2d**[g]	1.5/12.5	40	80	99/1	**5b** 73
12	4-Me-PhBr	**1c**	**2a**	1.5/12.5	16	80	99/1	**5c** 94
13	2-Me-PhBr	**1d**	**2a**	1.5/12.5	16	80	99/1	**5d** 88
14	1-Br-naphthyl	**1e**	**2a**	1.5/12.5	16	80	98/2	**5e** 96
15	1-Br-naphthyl	**1e**	**2a**[h]	3.0/12.5	16	100	98/2	**5e** 92
16	4-Cl-PhBr	**1f**	**2a**	1.5/12.5	66	80	96/4	**5f** 81
17	4-Cl-PhBr	**1f**	**2a**[h]	3.0/12.5	16	100	99/1	**5f** 71
18	4-F$_3$C-PhBr	**1g**	**2a**	1.5/12.5	240	80	93/7	**5g** 48
19	4-F$_3$C-PhBr	**1g**	**2a**	1.5/12.5	86	100	99/1	**5g** 62
20	4-F$_3$C-PhBr	**1g**	**2a**	3.0/12.5	86	80	99/1	**5g** 54
21	4-F$_3$C-PhBr	**1g**	**2a**[h]	3.0/12.5	16	100	99/1	**5g** 70
22	4-F$_3$C-PhBr	**1g**	**2a**[h]	6.0/12.5	16	100	99/1	**5g** 45
23	4-F$_3$C-PhBr	**1g**	**2a**[h]	3.0[i]/12.5	30	100	99/1	**5g** 61
24	4-NC−PhBr	**1h**	**2a**	1.5/12.5	240	80	99/1	**5h** 66[j]
25	4-NC-PhBr	**1h**	**2a**[h]	3.0/12.5	16	100	99/1	**5h** 86
26	3-Br-pyridyl	**1i**	**2a**[h]	3.0/12.5	16	100	99/1	**5i** 64
27	4-Br-pyridyl[k]	**1j**	**2a**[h]	3.0/12.5	48	100	99/1	**5j** 62
28	3-Br-thienyl	**1k**	**2a**	1.5/12.5	48	100	99/1	**5k** 66
29	1-I-naphthyl	**1l**	**2a**	1.5/12.5	16	80	99/1	**5e** 82
30	α-Br-styrene	**1m**	**2a**	1.5/12.5[m]	168	40	98/2	**5l** 23
31	α-keto-vinyl-Br[l]	**1n**	**2a**	1.5/12.5[m]	40	80	96/4	**5m** 18

[a] The reactions were performed in 5.0 mmol scale under a nitrogen atmosphere in sealed Pyrex tubes with 1.0 equiv of **1**; 2.5 equiv of **2**, 0.030 equiv of Pd(OAc)$_2$, 0.066 equiv of DPPP, 1.2 equiv of K$_2$CO$_3$, 0.0−6.0 mL of water, and 12.5 mL of dry DMF. [b] Oil bath. [c] α/β, Determined by GC/MS and ^{1}H NMR. [d] Purity >95% by GC/MS. [e] 2.5 equiv of LiCl was added. [f] 2.5 equiv of LiBr was added. [g] 0.75 equiv of **2d** was utilized. [h] 5.0 equiv of **2a** was utilized. [i] Water was exchanged with MeOH. [j] Only 88% conversion of **1h**. [k] HCl salt. [l] 2-Bromo-4,4-dimethyl-2-cyclohexen-1-one. [m] Dry DMSO instead of dry DMF, 1.0 mmol scale.

triethylamine as base, but omitted the thallium additive. An α/β (**4/3**) selectivity of 75/25 was encountered, corroborating the low regioselectivity in absence of thallium salts previously reported.[6,14] Addition of water to this reaction medium resulted in a very slow reaction.[15] However, we found that substitution of triethylamine for potassium carbonate as base and use of a 3.0/12.5 water/DMF solvent system produced an high regioselectivity of 98/2. An analogous Heck cocktail with water, potassium carbonate, and triethylamine also delivered a regioselective and smooth reaction (**4/3** = 96/4).[16]

The preparative results from the vinylation reactions with high regioselectivities of a series of aryl, heteroaryl and vinyl halides (**1a−n**) with alkyl vinyl ethers (**2a−d**, Chart 1) in the water/DMF medium are presented in Table 1. The corresponding aryl methyl ketones (**5a−k**) were isolated after acidic treatment in good to excellent yields in all of the investigated reactions (eq 1). To afford smooth and selective transformations, the addition of water was needed with all aryl bromides except for the electron-rich **1a**. Increased water content in the reaction medium enhanced the reaction rates in general. With the electron-poor **1f−j**, a larger amount of water and/or higher reaction temperature was found to be crucial for high α-selectivities (entries 16−22, 24−27). In addition, water could be exchanged by methanol without loss of

Chart 1

2a   **2b**

2c   **2d**
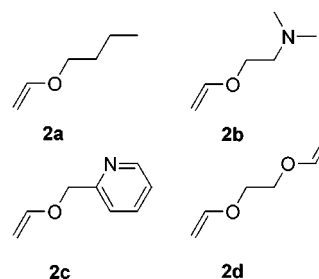
selectivity (entry 23). Five equivalents of olefin **2a** were necessary for complete conversion of the aryl bromides in the reactions with 3.0−6.0 mL of water.

The nitrogen-functionalized vinyl ethers **2b** and **2c** undergoes β-arylation via nitrogen−palladium coordination in the presence of monodentate ligands or under ligand-less conditions.[4] Utilizing the aqueous DMF/potassium carbonate/DPPP system, the phenylations resulted in high selectivity of the α-position of the vinyl ethers (entries 9 and 10). Furthermore, double phenylation of the bis vinyl ether **2d** (only 0.75 equiv of olefin) provided **5b** in good yield (73%, entry 11).

The low isolated yield in entry 22 (45% of **5g**) is a consequence of an accelerated dehalogenation process that was observed at high water content. Contrary to the internal couplings with aryl bromides, the analogous aryl iodides delivered essentially nonselective product mixtures of **3** and **4** under water/DMF/potassium carbonate conditions.[17] The only exception to this lack of selectivity was experienced with naphthyl iodide **1l** which was

(14) Andersson, C.-M.; Hallberg, A.; Daves, G. D. *J. Org. Chem.* **1987**, *52*, 3529−3536.

(15) A noncomplete conversion of **1e** was observed after 4 days at 80 °C (water/DMF = 1.5/12.5). The major product was the corresponding methyl ketone **5e**.

(16) The reaction was performed according to entry 15 in Table 1 but with an extra addition of 1.2 mmol of triethylamine.

vinylated successfully and with high regioselectivity (entry 29). Vinylation of α-bromostyrene (**1m**) gave the expected α,β-unsaturated methyl ketone after hydrolysis but in a low yield (23%) due to homocoupling and formation of 1,3-diphenyl-1-butyn-3-ene.[18,19] Apparently, **1m** eliminates hydrobromic acid to give phenylacetylene which undergoes a subsequent Sonogashira coupling with unreacted **1m**. Rapid dehalogenation of 2-bromo-4,4-dimethyl-2-cyclohexen-1-one (**1n**) explains the low yield of **5m** (entry 31).[8]

Unfortunately, the couplings reported in Table 1 require long reaction times, which is a drawback for rapid combinatorial applications. By exploiting the single-mode microwave heating technique,[20–23] the reaction time for the phenylation of **2a** could be shortened to 1 h at 122 °C in a microwave synthesizer (eq 2). Attempts to truncate the reaction time further, by raising the reaction temperature, did not improve the outcome and led to a substantial loss of regioselectivity.
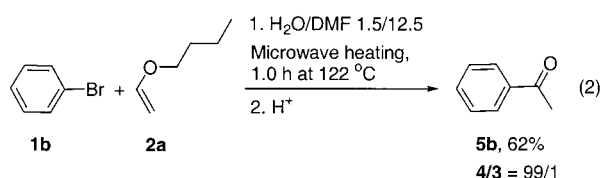
Discussion

We believe that the high α-preference encountered in the internal couplings of aryl bromides in water/DMF with potassium carbonate as base is attributed to the generation of a key cationic aryl palladium π-intermediate (**6**) via displacement of the bromide. We speculate that such ionization could be facilitated in the highly polar reaction system. A likely reaction path for the aqueous Heck procedure is presented in eq 3. The greater
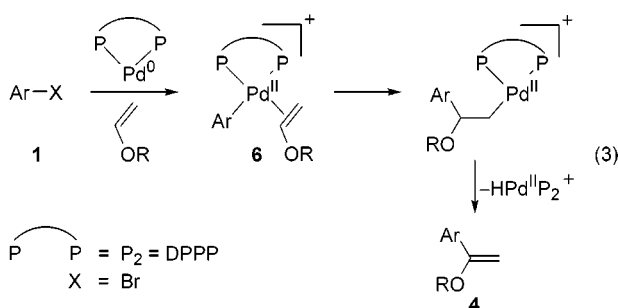
the contribution of a cationic complex **6**, the higher the overall reaction rate and selectivity. We interpret the powerful effect from the non-amine carbonate base as a consequence of an increased ionic strength in the medium. The addition of water to the reaction mixture increases the concentration of dissolved potassium carbonate. Furthermore, electron-poor aryl bromides are not capable of completely converting **1** and **2** into the charged intermediate **6** unless a large portion of water is added

to increase the polarity. In fact, the polarity of the reaction system might be determining whether the reaction will proceed in a neutral or cationic Heck-pathway with aryl bromides (Overman's *hidden gate*).[3,24] The potential importance of an aryl palladium hydroxide species,[3,25,26] that might play a pivotal role for the outcome of the reaction, can at present not be excluded, although the selectivity with electron-rich bromides do not rely on the presence of water (Table 1, entries 1 and 4).

Furthermore in two experiments in Table 1 (entries 7 and 8), the influence of different halide salts on the reaction was investigated. The effect of both the LiCl and LiBr additives was a retained regioselectivity but decreased reaction rate compared to the standard reaction in entry 6.[27] Thus, it is reasonable to assume that the ionic pathway was partly impeded by the formation of a neutral palladium(II) halide intermediate.

The poor regioselectivities encountered with aryl iodides is most likely a consequence of the formation of a neutral oxidative addition complex with a palladium-coordinating iodide.[6] The relatively high trans effect exerted by the iodide[28] can promote a dissociation of one of the phosphorus atoms in the bidentate ligand and induce the subsequent generation of a neutral π-complex. Therefore, after insertion and hydridopalladium halide elimination, a higher extent of linear **3** is formed.

By addition of water as an ionization-accelerating additive, we had initially hoped to increase the scope of this protocol to include also internal α-arylations of noncyclic N-alkylated enamides. The low regioselectivities encountered in aqueous DMF/potassium carbonate/DPPP-mediated reactions of aryl bromides with this class of olefins (typically α/β =70/30) were in sharp contrast to the excellent selectivities reported in the DPPP-controlled enamide/aryl triflate couplings (α/β = 100/0).[7] This unexpected result suggested to us that the olefin itself could lend assistance for the transition between the neutral and cationic mechanism. Thus, it seems that the enamides disfavor the cationic reaction path by being less efficient at trapping the trivalent cationic palladium complex formed in an equilibrium mixture (path A, a dissociative ligand-exchange process, eq 4). Another explanation could be that in an apical attack (path B, an associative ligand-exchange process), the incoming enamide might not exchange the bromide as readily as the more reactive vinyl ethers do.

(17) Low α-selectivities were encounted with the following aryl iodides: 4-methoxyiodobenzene (α/β = 85/15), iodobenzene (α/β = 72/28), 4-bromoiodobenzene (α/β = 79/21), 4-(trifluoromethyl)iodobenzene (α/β = 73/27).

(18) Andersson, C.-M.; Hallberg, A. *J. Org. Chem.* **1989**, *54*, 1502–1505.

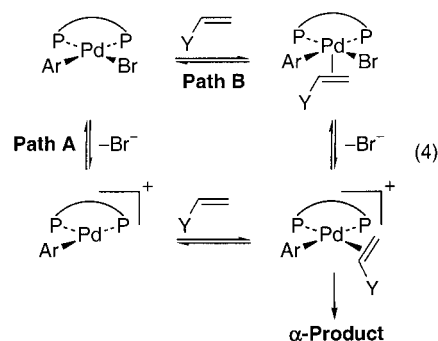(19) Temperatures above 40 °C resulted in reduced regioselectivity.

(20) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665–1692.

(21) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582–9584.

(22) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213–223.

(23) Kaiser, N. F. K.; Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3596–3598.

Conclusion

In summary, we have demonstrated that aryl and heteroaryl bromides are efficiently converted to the corresponding acetyl arenes in high yields and selectivities by conducting the reactions in an aqueous DMF medium with potassium carbonate as base. The developed Heck process merits attention due to the convenient, nonexpensive, and environmentally benign experimental procedure.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded in CDCl$_3$ at 270 and 67.8 MHz. Mass spectra were recorded at an ionizing voltage of 70 eV (EI). The GC/MS was equipped with a HP-1 (25 m × 0.20 mm) capillary column. The regioisomers were assumed to have the same GC/MS response factor. All nonmicrowave reactions were conducted under nitrogen in heavy-walled Pyrex tubes sealed with a screwcap fitted with a Teflon gasket silicon septum. Microwave heating was performed under nitrogen in a (Smith Synthesizer) single-mode microwave cavity, from Personal Chemistry AB, producing continuous irradiation at 2450 MHz. Both conventional and microwave-mediated reactions were performed with magnetic stirring. All reactions were allowed to proceed until complete consumption of the starting aryl or vinyl halide, utilizing an appropriate choice of thermal heating time or microwave irradiation time and temperature. Column chromatography was performed using commercially available silica gel 60 (particle size: 0.040–0.063 mm, Merck). The isolated acetyl arenes (**5a**–**k**) and α,β-unsaturated methyl ketones (**5l**, **5m**) are commercially available or have previously been characterized, and the data obtained corresponded satisfactory with MS and NMR literature data.[6,14,29,30]

Materials. The vinyl ethers **2a** and **2d**, aryl and vinyl halides **1a**–**m**, palladium(II) acetate, 1,3-bis(diphenylphos-phino)propane (DPPP), and potassium carbonate were purchased from commercial suppliers and were used directly as received. The vinyl ethers **2b** and **2c** were prepared as previously described using a mercury(II)-catalyzed transetherification procedure.[4] Bromo-4,4-dimethyl-2-cyclohexen-1-one (**1n**) was prepared by literature procedure.[31] DMF and DMSO was stored over activated 4 Å molecular sieves.

General Procedure for the Thermal α-Arylation of Vinyl Ether 2a–d (Table 1). A mixture of the corresponding aryl halide (5.0 mmol), vinyl ether (3.75–25.0 mmol), Pd(OAc)$_2$ (0.0334 g, 0.150 mmol), DPPP (0.136 g, 0.330 mmol), K$_2$CO$_3$ (0.83 g, 6.0 mmol), 0.400 g naphthalene (internal standard), lithium halide (when present), and 0.0–6.0 mL water (or 3.0 mL methanol) in 12.5 mL of DMF was stirred under N$_2$ in a sealed tube (for reaction time, temperature, and amount of water, see Table 1). Samples were periodically taken and partitioned between diethyl ether and 0.1 M NaOH. The organic layers were dried over K$_2$CO$_3$(s) before analyses by GC/MS. After complete consumption of the starting aryl halide, the reaction was cooled to room temperature and hydrolyzed by adding 20 mL of 5% HCl for 30 min. All reactions were worked up by extraction with CH$_2$Cl$_2$ and 10% K$_2$CO$_3$ (aq). The products **5a**–**k** were purified by column chromatography on silica gel. Eluents: isohexane/ethyl acetate.

Thermal α-Vinylation of 1m and 1n with Vinyl Ether 2a. The vinylation of **2a** was performed as described under General Procedure for the Thermal α-Arylation of Vinyl Ether **2a**–**d** but in a 1.0 mmol scale using vinyl bromides **1m** and **1n** and employing DMSO instead of DMF as organic solvent. The products **5l** and **5m** were purified as described for the acetyl arenes.

Microwave Heated Internal α-Phenylation of 2a with Bromobenzene (eq 2). The microwave-assisted phenylation of **2a** was performed as described under General Procedure for the Thermal α-Arylation of Vinyl Ether 2a–d but in a 1.0 mmol scale in a Smith process vial. The reaction temperature was 122 °C with a microwave irradiation time of 60 min. The product **5b** was purified as described for the conventionally heated products.

(24) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488–6499.

(25) Crisp, G. T.; Gebauer, M. G. *Tetrahedron* **1996**, *52*, 12465–12474.

(26) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168.

(27) In a separate experiment with **1b** and **2a**, LiI (2.5 equiv) was found to decrease the reaction rate more strongly than LiCl and LiBr (73% conversion of **1b** after 3 days, **4/3** = 99/1).

(28) Appelton, T. G.; Clark, H. C.; Manzer, L. E. *Coord. Chem. Rev.* **1973**, *10*, 335–422.

(29) Meyer, W. L.; Brannon, M. J.; Burgos, C.; Goodwin, T. E.; Howard, R. W. *J. Org. Chem.* **1985**, *50*, 438–447.

(30) Najera, C.; Sansano, J. M. *Tetrahedron* **1990**, *46*, 3993–4002.

(31) Bordwell, F. G.; Wellman, K. M. *J. Org. Chem.* **1963**, *28*, 2544–2547.