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Organic Iron for the $PdCl_2/FeCl_3$-Cocatalyzed Coupling Cyclization of 2,3-Allenoates in the Presence of Allylic Bromides

Bo Chen[a] and Shengming Ma*[a, b]

In memory of Professor Xian Huang

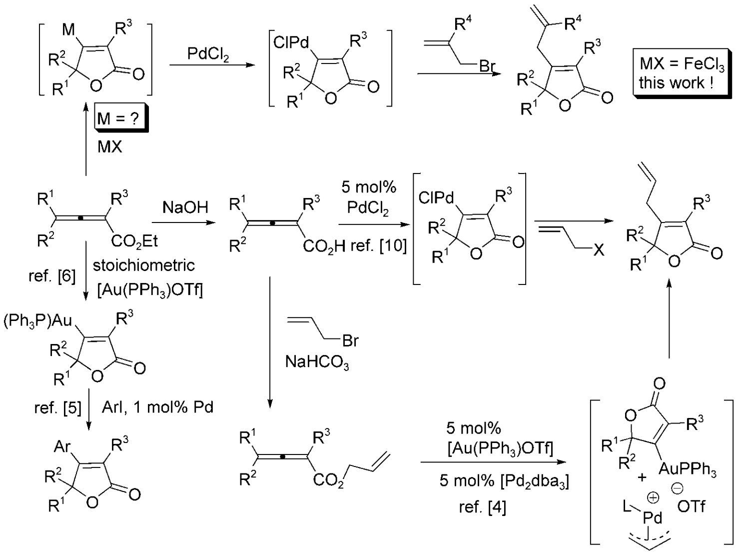
The construction of carbon–carbon bonds is a crucial element in organic synthesis.[1] Among the transition-metal-catalyzed C–C bond formation reactions,[2] palladium-catalyzed cross-couplings of organic halides and their equivalents with organometallic reagents of B (Suzuki), Zn (Negishi), Si (Hiyama) and Sn (Stille), are now most widely used in both academic and industrial synthesis (Scheme 1).[3] Recently, such a coupling reaction with organogold compounds have also been realized by the Blum[4] and Hashmi groups[5] based on Hammond's observation that the stable organogold compounds may be generated from the reaction of 2,3-allenoates with gold(I) complex[6] (Scheme 2).

$$R'X + RM \xrightarrow{\text{Ni or Pd}} RR'$$

X = halide, OTf, etc.
M = B, Sn, Mg, Zn, Si, Au, etc.

Scheme 1. Pd or Ni-catalyzed cross-coupling reactions.

On the other hand, iron compounds have recently emerged as promising catalysts in organic synthesis; they have attractive potentials in industry due to their low cost and low toxicity.[7] As early as 1973 Kochi et al. developed the first example of iron-catalyzed coupling reactions of Grignard reagents with alkenyl and aryl halides.[8] Other examples of iron-catalyzed cross-couplings of alkenyl halides with organometallic compounds (especially Grignard reagents) soon followed.[9] Although many examples on the iron-catalyzed cross-coupling reactions have been reported, the coupling reaction involving the transmetalation of the organo-iron species with palladium is hitherto unknown to the best of our knowledge. In this paper, we wish to report an unprecedented example of allylic coupling involving in situ generated iron species.



Scheme 2. Cyclization of 2,3-allenoic acids or 2,3-allenoates affording substituted butenolides.

Based on our early investigations on the palladium(II)-catalyzed cyclizations of 2,3-allenoic acids in the presence of allylic halides,[10] it's highly desirable to realize the cyclization of 2,3-allenoates in the presence of allyl bromide, since 2,3-allenoic acids are usually prepared from the hydrolysis of 2,3-allenotes in a mixture of allenoic acids and 2-alkynoic acids. In some cases, the hydrolysis fails to produce 2,3-allenoic acids, affording the 2-alkynoic acids as the only products instead. Before we started to develop such a reaction, we knew that the expected very low reactivity of normal

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[a] B. Chen, Prof. Dr. S. Ma
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Lu, Shanghai 200032 (P. R. China)
Fax: (+86)21-6416-7510
E-mail: masm@sioc.ac.cn

[b] Prof. Dr. S. Ma
Shanghai Key Laboratory of Green Chemistry and Chemical Process
Department of Chemistry, East China Normal University
3663 North Zhongshan Lu, Shanghai 200062 (P. R. China)

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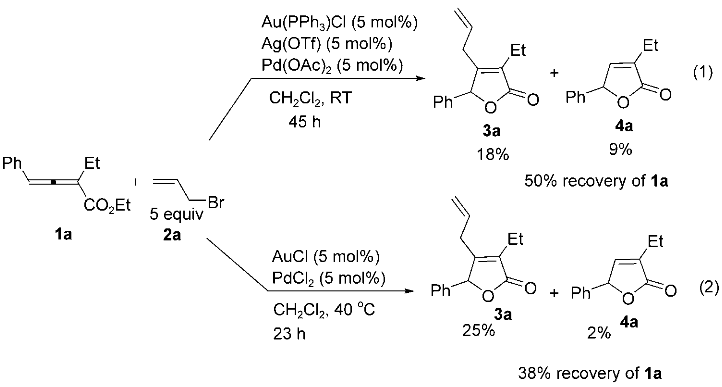
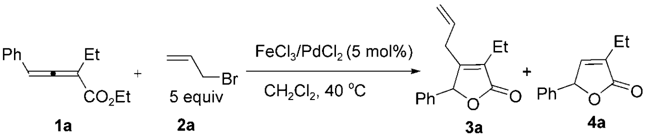
2,3-allenoates for the formation of 2(5*H*)-furanonyl palladium intermediate as compared to that of 2,3-allenoic acids would be a great challenge. Indeed, the in situ formation of 2(5*H*)-furanonyl metal species from 2,3-allenoates is still crucial except Hammond's pioneering contribution by applying a stoichiometric amount of expensive $Au(PPh_3)OTf$.[6] Therefore, Blum et al. cleverly developed the cylization of a special class of esters, that is, allylic 2,3-allenoates, in which the reactive esteric allylic C–O bond was cleaved by applying a palladium(0) catalyst to afford π-allyl palladium and 2(5*H*)-furanonyl Au species, which upon further coupling formed the allylic lactones (Scheme 2).[4] To our delight, after trial and error, we found that the β-allylic butenolide was successfully formed under the catalysis of 5 mol% each of ferric chloride and palladium chloride, which involves the transmetalation of in situ generated 2(5*H*)-furanonyl iron species from the interaction of the routine 2,3-allenoates and $FeCl_3$ (Scheme 2).

At first, we tried the palladium(II)-catalyzed cyclization reaction of ethyl 4-phenyl-2-ethyl-2,3-butandienoate (**1a**) and allyl bromide (**2a**) in the presence of the gold(I) complex used by Hammond, Hashmi, and Blum et al.[4–6] However, after many screenings, under the best conditions the expected product **3a** was formed in very low yields together with the cycloisomerization product **4a** [Eqs. (1) and (2)].



We then switched to $FeCl_3$. First, 1 mmol of allenoate **1a** was treated with 5 equiv of allyl bromide in CH_2Cl_2 (1 mL) using the $Pd(PPh_3)_2Cl_2$ as the catalyst (Table 1, entry 1), though the expected product was not formed; however, we were pleased to note that the $PdCl_2$-catalyzed reaction afforded the expected product **3a** in 58% NMR yield, together with 4% of the cycloisomerization product **4a** (Table 1, entry 2). With $Pd(PhCN)_2Cl_2$, the reaction also smoothly afforded the expected product **3a** in 57% NMR yield, together with 5% of the cycloisomerization product **4a** (Table 1, entry 3). Since the results for $PdCl_2$ and $Pd(PhCN)_2Cl_2$ are almost the same, we chose $PdCl_2$ as the catalyst in further study. Then, we investigated the effects of the substrate concentration and catalyst loading (Table 1, entries 4–8).

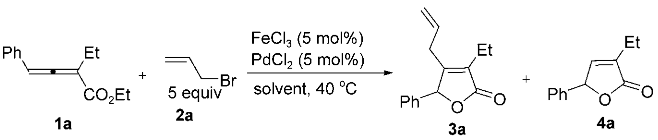
Table 1. Catalyst and concentration effects on the reaction of 2,3-allenoate **1a** with allyl bromide **2a**.



Entry	$FeCl_3$ [mol%]	*c* [M]	*t* [h]	NMR yield of **3a** [%]	NMR yield of **4a** [%]
1[a,b]	5	1	35	0	0
2	5	1	18	58	4
3[c]	5	1	10	57	5
4	5	0.4	33	50	7
5	5	2	12	41	4
6	1	1	45	41	9
7	3	1	20	53	5
8	10	1	11	56	4

[a] $[Pd(PPh_3)_2Cl_2]$ was used as the catalyst. [b] 71% of **1a** was recovered. [c] $[Pd(PhCN)_2Cl_2]$ was used as the catalyst.

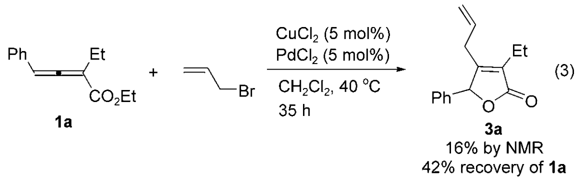
Table 2. Solvent effect on the reaction of 2,3-allenoate **1a** with allyl bromide **2a**.



Entry	Solvent	*t* [h]	NMR yield of **3a** [%]	NMR yield of **4a** [%]	Recovery of **1a** [%]
1	$ClCH_2CH_2Cl$	20	50	4	0
2	CCl_3CH_3	20	45	3	0
3	$CHCl_2CH_3$	20	55	4	0
4	CH_2Cl_2	18	58	4	0
5	$CHCl_2CH_2Cl$	20	54	4	0
6	THF	20	29	10	29
7	toluene	20	41	4	0
8	CH_3CN	20	18	6	32
9	*n*-hexane	20	7	1	55
10	benzene	20	42	2	8
11	1,4-dioxane	20	38	4	12

[a] The reaction was conducted at 1 M of **1a**.

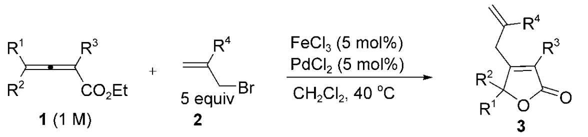
Based on the results presented in entry 2 of Table 1, we subsequently tested the solvent effect on the reaction: chloro solvents gave similar results (Table 2, entries 1–5), while other solvents are less effective (Table 2, entries 6–11). Thus we chose 1 mmol of 2,3-allenoate and 5 equiv of allyl bromide with 5 mol% each of $FeCl_3$ and $PdCl_2$ in CH_2Cl_2 (1 mL) at 40°C as the standard conditions. Before we continued, we also tried the reaction by using 5 mol% of $CuCl_2$ instead of $FeCl_3$ to avoid the mistake made in the iron-catalyzed Buchwald–Hartwig amination.[11] As shown in Equation (3), the yield for **3a** was only 16% by NMR under the



standard conditions for 35 h. In addition, we also noticed that FeCl$_3$ from Aldrich with a purity of 99.99 % provided very similar results. All these facts exclude the possibility of a trace amount of copper or other transition metals in FeCl$_3$ we used as the active catalyst in our current transformations.

With the optimized reaction conditions in hand, we started to investigate the substrate scope of the reaction (Table 3). The reaction gave a good scope affording differently substituted butenolides in moderate to good yields. The substituents of 2,3-allenoates may be aryl, alkyl, cycloalkyl, or benzyl: R^1 could be phenyl or substituted phenyl with electron-donating groups or electron-withdrawing groups (Table 3, entries 1–8). When R^1 is an alkyl group, a higher temperature was necessary for the current protocal (Table 3, entries 9 and 10); R^2 could be H or alkyl (Table 3, entry 11); R^3 could be alkyl, benzyl, phenyl. 2-Methylallyl bromide could also react with 2,3-allenoates affording the corresponding butenolides **3k** and **3l** in 53 and 65 % yield, respectively (Table 3, entries 11 and 12). In addition, it should be noted that the C−Br bond remains untouched due to the nature of the catalytic cycle involving palladium(II) (Table 3, entries 3, 4, and 12).

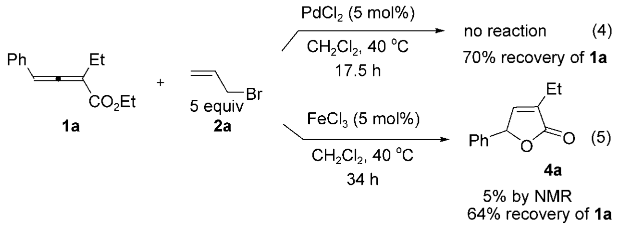
Table 3. Reaction of 2,3-allenoates **1** with allylic bromides **2**.

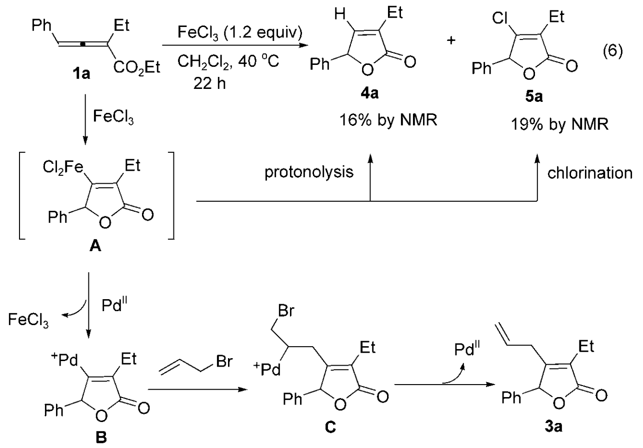


Entry	R^1	R^2	R^3	R^4	t [h]	Yield of **3** [%]
1	Ph	H	Et (**1a**)	H	29	51 (**3a**)
2	Ph	H	nPr (**1b**)	H	15.5	73 (**3b**)
3	p-BrC$_6$H$_4$	H	Et (**1c**)	H	30	59 (**3c**)
4	p-BrC$_6$H$_4$	H	nPr (**1d**)	H	60	53 (**3d**)
5	p-ClC$_6$H$_4$	H	nPr (**1e**)	H	27	64 (**3e**)
6	p-FC$_6$H$_4$	H	nPr (**1f**)	H	68	60 (**3f**)
7	p-MeC$_6$H$_4$	H	nPr (**1g**)	H	71	45 (**3g**)
8	Ph	H	Bn (**1h**)	H	27	65 (**3h**)
9[a]	Et	H	Ph (**1i**)	H	48	40 (**3i**)
10[a,b]	-(CH$_2$)$_5$-		Ph (**1j**)	H	33	50 (**3j**)
11	Ph	H	nPr (**1b**)	Me	67	53 (**3k**)
12	p-BrC$_6$H$_4$	H	nPr (**1d**)	Me	72	65 (**3l**)

[a] The reaction was conducted at 60 °C in 1 mL of DCE. The purity of FeCl$_3$ used is >97 %. [b] Methyl ester was used.

Next, a couple of control experiments were conducted to unveil the mechanism. It should be noted that no reaction was observed with PdCl$_2$ as the only catalyst [Eq. (4)]. In the absence of PdCl$_2$, 5 mol % of the cycloisomerization product **4a** was formed with 5 mol % of FeCl$_3$ [Eq. (5)]; 16 % of 2(5H)-furanone **4a** and 19 % of 3-chloro-2(5H)-furanone **5a** were formed by applying a stoichiometric amount of FeCl$_3$ [Eq. (6)]. All these results indicated the in situ formation of the 2(5H)-furanonyl iron species, which undergo transmetalation with PdCl$_2$ forming 2(5H)-furanonyl Pd species **B** while regenerating FeCl$_3$. Carbopalladation of **B** with allyl bromide followed by dehalopalladation of intermediate **C** afforded product **3a** and regenerated the catalytically active species palladium(II).[10]





In conclusion, we have developed an FeCl$_3$/PdCl$_2$-cocatalyzed[12] coupling cyclization of 2,3-allenoates with allylic bromides. This protocol provides a very concise access to β-allylic substituted butenolides by the direct use of ethyl 2,3-allenoates utilizing the cheap FeCl$_3$ as the cocatalyst of PdCl$_2$. Due to the fact that a variety of different 2,3-allenoates[13] is more readily available than 2,3-allenoic acids, this study has greatly expanded the scope of the reaction reported in reference [10]. In addition, it is the first observation that in situ generated sp^2 carbon iron species may undergo transmetalation process with PdCl$_2$, which will be interesting for the further development of transition-metal-catalyzed coupling reactions involving organic iron species. Further research in this area is ongoing in our laboratory.

Experimental Section

Typical procedure for the synthesis of 4-allyl-3-ethyl-5-phenyl-2(5*H*)-furanone (3a): To a dried Schlenk tube were added FeCl$_3$ (8.1 mg, 0.05 mmol), PdCl$_2$ (8.8 mg, 0.05 mmol), allyl bromide (604.2 mg, 5 mmol), ethyl 4-phenyl-2-ethyl-2,3-butadienoate (217.3 mg, 1 mmol) and CH$_2$Cl$_2$ (1 mL) sequentially under a nitrogen atmosphere at room temperature. Then, the resulting mixture was stirred at 40 °C. When the reaction was complete, as monitored by TLC, the mixture was diluted with Et$_2$O (20 mL) and filtrated. The filtrate was concentrated, and mesitylene (35 μL) was added for the crude ^{1}H NMR analysis. Then evaporation and column chromatography on silica gel (petroleum ether/ethyl acetate 20:1) afforded **3a** (0.117 g, 51 %) as a liquid. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.45–7.31 (m, 3H), 7.24–7.12 (m, 2H), 5.74–5.52 (m, 2H), 5.08 (d, $J = 9.9$ Hz, 1H), 5.0 (d, $J = 17.1$ Hz, 1H), 3.13 (dd, $J_1 = 15.3$, $J_2 = 5.7$ Hz, 1H), 2.70 (dd, $J_1 = 15.3$, $J_2 = 7.5$ Hz, 1H), 2.37 (q, $J = 7.5$ Hz, 2H), 1.16 ppm (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 174.1$, 159.9, 134.6, 132.2, 129.1, 128.8, 126.9, 118.0, 83.5, 30.6, 16.9, 12.9 ppm; IR (neat): $\tilde{\nu} = 3065$, 3033, 2973, 2934, 2878, 1758, 1672, 1638, 1495, 1457, 1376, 1371, 1301, 1257, 1224, 1201, 1158, 1105, 1052, 1009 cm^{-1}; MS: m/z (%): 229 (1.94) $[M+H]^+$, 228 (11.33) $[M]^+$, 199 (6.31) $[M-C_2H_5]^+$, 187 (100) $[M-C_3H_5]^+$; HRMS: m/z: calcd for $C_{15}H_{16}O_2$: 228.1150, found: 228.1149 $[M]^+$.

Acknowledgements

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Keywords: allenes · cross-coupling · cyclization · iron · palladium

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[1] a) R. L. Augustine, *Carbon–Carbon Bond Formation, Vol. 1*, Dekker, New York, **1979**; b) *Comprehensive Carbanion Chemistry Part B* (Eds.: E. Buncel, T. Durst), Elsevier, Amsterdam, **1984**; c) B. M. Trost, I. Fleming, *Comprehensive organic synthesis, Vol. 3*, Pergamon, Oxford, **1991**.

[2] S. M. Roberts, J. L. Xiao, J. Whittall, T. E. Pickett, *Metal-Catalysed Carbon–Carbon Bond-Forming Reactions*, Wiley, New York, **2004**.

[3] F. Diederich, P. J. Stang, *Metal-Catalyzed Cross-coupling Reactions*, Wiley-VCH, Weinheim, **1998**.

[4] Y. L. Shi, K. E. Roth, S. D. Ramgren, S. A. Blum, *J. Am. Chem. Soc.* **2009**, *131*, 18022.

[5] A. S. Hashmi, L. Christian, D. René, R. Matthias, D. R. Tanuja, R. Frank, *Angew. Chem.* **2009**, *121*, 8392; *Angew. Chem. Int. Ed.* **2009**, *48*, 8243.

[6] L. Liu, B. Xu, M. S. Mashuta, G. B. Hammond, *J. Am. Chem. Soc.* **2008**, *130*, 17642.

[7] For reviews on iron-catalyzed reactions, see: a) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217; b) A. Fürstner, R. Martin, *Chem. Lett.* **2005**, *34*, 624; c) A. Correa, O. G. Mancheño, C. Bolm, *Chem. Soc. Rev.* **2008**, *37*, 1108; d) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500; e) A. A. O. Sarhan, C. Bolm, *Chem. Soc. Rev.* **2009**, *38*, 2730. For a recent monograph on the chemistry of iron catalysis, see: f) B. Plietker, *Iron Catalysis in Organic Chemistry: Reactions and Applications*, Wiley-VCH, Weinheim, **2008**.

[8] a) M. Tamura, J. K. Kochi, *J. Am. Chem. Soc.* **1971**, *93*, 1487; b) M. Tamura, J. K. Kochi, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3063; c) M. Tamura, J. K. Kochi, *Synthesis* **1971**, 303; d) S. M. Neumann, J. K. Kochi, *J. Org. Chem.* **1975**, *40*, 599; e) R. S. Smith, J. K. Kochi, *J. Org. Chem.* **1976**, *41*, 502.

[9] For selected examples of iron-catalyzed coupling reactions, see: a) G. A. Molander, B. J. Rahn, D. C. Shubert, S. E. Bonde, *Tetrahedron Lett.* **1983**, *24*, 5449; b) V. Fiandanese, G. Miccoli, F. Naso, L. Ronzini, *J. Organomet. Chem.* **1986**, *312*, 343; c) J. L. Fabre, M. Julia, J. N. Verpeaux, *Bull. Soc. Chim. Fr.* **1985**, 772; d) H. M. Walborsky, R. B. Banks, *J. Org. Chem.* **1981**, *46*, 5074; e) G. Cahiez, H. Avedissian, *Synthesis* **1998**, 1199; f) G. Cahiez, S. Marquais, *Tetrahedron Lett.* **1996**, *37*, 1773; g) A. Fürstner, H. Brunner, *Tetrahedron Lett.* **1996**, *37*, 7009; h) L. K. Ottesen, F. Ek, R. Olsson, *Org. Lett.* **2006**, *8*, 1771; i) B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3943; j) M. Nakamura, K. Matsuo, S. Ito, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 3686; k) A. Fürstner, A. Leitner, M. Méndez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856; l) G. Cahiez, V. Habiak, C. Duplais, A. Moyeux, *Angew. Chem.* **2007**, *119*, 4442; *Angew. Chem. Int. Ed.* **2007**, *46*, 4364; m) R. B. Bedford, M. Betham, D. W. Bruce, A. A. Danopoulos, R. M. Frost, M. Hird, *J. Org. Chem.* **2006**, *71*, 1104; n) T. Nagano, T. Hayashi, *Org. Lett.* **2004**, *6*, 1297.

[10] S. Ma, Z. Yu, *J. Org. Chem.* **2003**, *68*, 6149.

[11] S. L. Buchwald, C. Bolm, *Angew. Chem.* **2009**, *121*, 5694; *Angew. Chem. Int. Ed.* **2009**, *48*, 5586.

[12] For a monograph on dual metal-catalyzed reactions, see: M. Shibasaki, Y. Yamamoto, *Multimetallic Catalysts in Organic Synthesis*, Wiley-VCH, Weinheim, **2004**.

[13] a) R. W. Lang, H.-J. Hansen, *Org. Synth.* **1984**, *62*, 202; b) J. A. Marshall, M. A. Wolf, E. M. Wallace, *J. Org. Chem.* **1997**, *62*, 367; c) J. Tsuji, T. Sugiura, I. Minami, *Tetrahedron Lett.* **1986**, *27*, 731.

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