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Directed Zincation with TMPZnCl·LiCl and Further Functionalization of the Tropolone Scaffold

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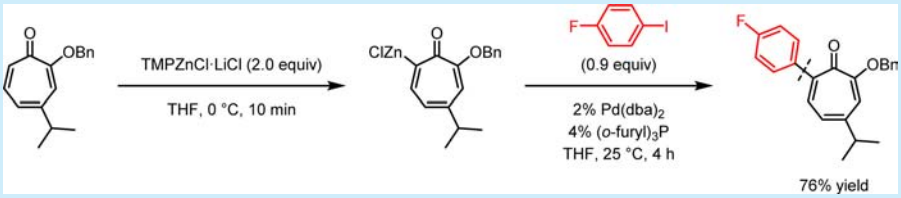
Supporting Information



ABSTRACT: The directed zincation of tropolone derivatives was achieved using TMPZnCl·LiCl. Various functionalizations of the zincated intermediates by halogenation, acylation, allylation, and Negishi cross-coupling were successfully performed. Additionally, 1,8-conjugate addition−elimination reactions with a variety of arylmagnesium and secondary alkylzinc reagents were carried out to further elaborate the tropolone core.

The structures of tropolone (**1**) and the related natural product hinokitiol (*β*-thujaplicin, **2**) were proposed by Dewar[1] and Nozoe.[2] More than 200 natural products are currently reported to contain a troponoloid core.[3] Among them, colchicine (**3**) is used for the treatment of gout and familial Mediterranean fever (Figure 1).[4] These cyclic

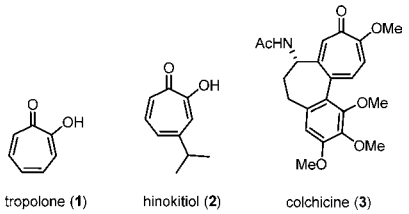
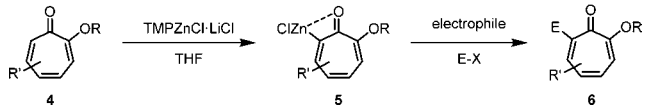


Figure 1. Structures of tropolone derivatives.

molecules are of interest because of their non-benzenoid, planar, seven-membered ring structure showing aromatic-like properties[5] as well as their biological properties.[6]

Nonetheless, the synthesis of highly substituted tropones and tropolones is still a synthetic challenge. The tropolone core was shown to decompose in the presence of strong bases such as LDA.[7] We recently reported the functionalization of an array of aromatic and heteroaromatic substrates using various TMP-derived bases (TMP = 2,2,6,6-tetramethylpiperidyl).[8] However, preliminary studies in our laboratory have shown that TMPLi and TMPMgCl·LiCl[9] lead to decomposition of various protected tropolones even at low temperatures. TMP-Zn bases, such as TMPZnCl·LiCl,[10] $TMP_2Zn·2MgCl_2·2LiCl$,[11] and TMPZnOPiv·LiCl,[12] have proven to be especially efficient for performing metalations of sensitive (hetero)arenes, as these metalations produce organozinc derivatives that tolerate a range of functional groups.[8] As it is known that the tropolonato anion coordinates to the Zn(II) center,[13] we envisioned that coordination to TMPZnCl·LiCl[10] may enable the desired metalation and thus would afford zinc reagents **5** corresponding to tropolone derivatives of type **4** (Scheme 1). Herein we report the functionalization of tropolone derivatives by zincation using TMPZnCl·LiCl followed by reaction with various electrophiles (E−X).

Scheme 1. Zincation of Tropolone Derivatives Using TMPZnCl·LiCl



Treatment of benzyl-protected tropolone derivative **4a** with TMPZnCl·LiCl (2.0 equiv, 10 min, 0 °C) leads to the quantitative formation of the corresponding zincated tropolone **5a**. The intermediate zinc reagent can then be quenched by various electrophiles, furnishing tropolones of type **6** (Table 1). Quenching of **5a** with either iodine or bromine provides the halogenated tropolones **6a** and **6b**, respectively, in 89% and 83% yield (entries 1 and 2). The addition of aryl or alkyl acyl chlorides in the presence of catalytic amounts of $Pd(PPh_3)_4$ (3 mol %) allows the formation of ketones **6c** and **6d** in 68−76% yield (entries 3 and 4). Additionally, Negishi cross-coupling reactions[14] proceed with various aryl iodides containing electron-withdrawing or -donating groups as coupling partners in the presence of 2−3 mol % $Pd(dba)_2$ as the catalyst and 4−6 mol % tris(*o*-furyl)phosphine (Farina's ligand),[15] affording a variety of arylated tropolone derivatives **6e−h** in 77−91% yield (entry 5). Furthermore, 2-iodothiophene undergoes a Negishi

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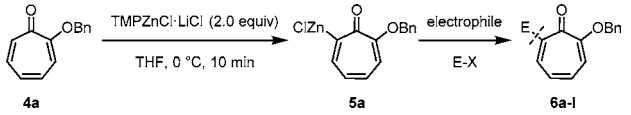
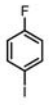
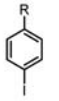
Table 1. Zincation of *O*-Benzyltropolone (4a) and Reactions with Electrophiles



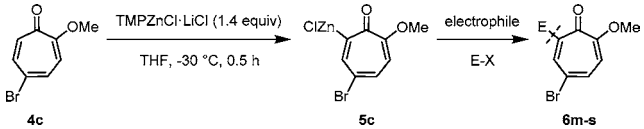
no.	E-X	product/yield	no.	E-X	product/yield
1	I_2	**6a**, 89%	6		**6i**, 80%[b]
2	Br_2	**6b**, 83%	7		**6j**, 75%[b] (*E*:*Z* 97:3)
3		**6c**, 76%[a]	8		**6k**, 94%[c]
4		**6d**, 68%[a]	9		**6l**, 76%[b,d]
5		R = OMe, **6e**, 77%[b] R = NMe_2, **6f**, 77%[b] R = Cl, **6g**, 83%[b] R = CF_3, **6h**, 91%[b]			

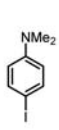
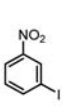
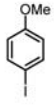
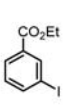
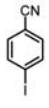
[a]Acylation in the presence of 3 mol % $Pd(PPh_3)_4$. [b]Negishi cross-coupling performed in the presence of 2−3 mol % $Pd(dba)_2$ and 4−6 mol % P(*o*-furyl)$_3$. [c]Allylation performed in the presence of CuCN·2LiCl (1.1 equiv). [d]Starting from *O*-benzyl-4-isopropyltropolone (**4b**); see the Supporting Information.

cross-coupling reaction with zinc species **5a** to afford **6i** in 80% yield (entry 6). The alkenyl iodide (*E*)-1-iodooct-1-ene undergoes cross-coupling with **5a**, giving tropolone **6j** in 75% yield (*E*:*Z* = 97:3; entry 7). Additionally, a Cu-mediated allylation reaction with 3-bromocyclohexene affords the desired tropolone **6k** in 94% yield (entry 8). Also, *O*-benzyl-4-isopropyltropolone (**4b**), derived from the commercially available natural compound *β*-thujaplicin by benzylation,[16] also undergoes smooth metalation with TMPZnCl·LiCl at the position *α* to the keto group (2.0 equiv, 0 °C, 10 min), and in situ Negishi cross-coupling of the corresponding zinc reagent with 1-fluoro-4-iodobenzene affords tropolone **6l** in 76% yield (entry 9).

We further explored the scope of this zincation using TMPZnCl·LiCl on other tropolone derivatives. Bromotropolone **4c**, a precursor to Fitzgerald's compound,[17] which has been shown to have similar biological activities as colchicine, is metalated with TMPZnCl·LiCl at low temperatures (1.4 equiv, 0.5 h, −30 °C; Table 2). Halogenation of the intermediate zinc

Table 2. Zincation of Bromotropolone 4c and Reactions with Electrophiles



no.	E-X	product/yield	no.	E-X	product/yield
1	I_2	**6m**, 98%	5		**6q**, 67%[a]
2	Br_2	**6n**, 74%	6		**6r**, 89%[a]
3		**6o**, 70%[a]	7		**6s**, 73%[a]
4		**6p**, 81%[a]			

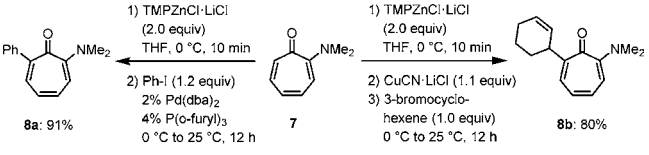
[a]Negishi cross-coupling in the presence of 3 mol % $Pd(dba)_2$ and 6 mol % P(*o*-furyl)$_3$.

reagent **5c** with iodine or bromine provides the corresponding products **6m** and **6n** in 74−98% yield (entries 1 and 2). Negishi cross-coupling reactions of **5c** with aryl iodides containing substituents such as methoxy, cyano, dimethylamino, nitro, or ester afford the desired tropolone derivatives **6o**−**s** in 63−89% yield (entries 3−7).

2-Dimethylaminotropone (**7**) also undergoes metalation with TMPZnCl·LiCl (2.0 equiv, 10 min, 0 °C), providing the corresponding zinc reagent quantitatively. The organozinc reagent reacts in a Cu-mediated allylation with 3-bromocyclohexene as well as a Negishi cross-coupling reaction with phenyl iodide to afford the tropolone derivatives **8a** and **8b**, respectively, in 91% and 80% yield (Scheme 2).

Interestingly, when carbamate **9** was subjected to the optimized metalation conditions using TMPZnCl·LiCl (2.0 equiv, 0 °C, 10 min) followed by addition of bromine as an electrophile, the desired main product **10** was obtained in 81%

Scheme 2. Zincation of 2-Dimethylaminotropone (7) and Reactions with Electrophiles Leading to Tropones 8a and 8b



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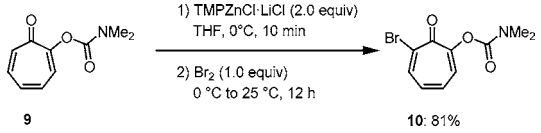
yield, with bromination occurring at the position α to the ketone (Scheme 3).[18]

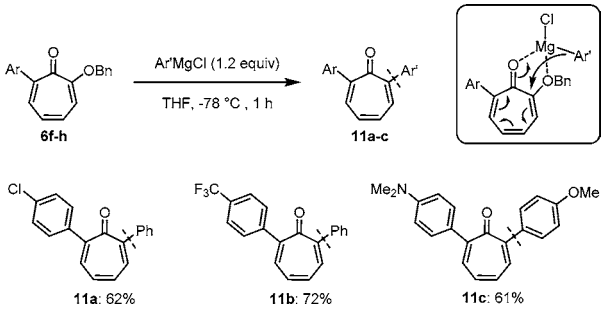
Scheme 3. Zincation of Carbamate 9 and Reaction with Bromine



9 **10**: 81%

In order to further elaborate the tropolone core, we have performed various additions of organomagnesium and -zinc reagents to several tropone derivatives. Reaction of tropolone or its methylated derivative with phenylmagnesium bromide or phenyllithium has been proposed to occur via a 1,8-conjugate addition−elimination mechanism.[19] Thus, the addition of various arylmagnesium chloride reagents to 2-aryltropolones (**6f−h**) provides the diarylated tropones **11a−c** with substitution of the −OBn group, presumably via the 1,8-conjugate addition−elimination mechanism (Scheme 4).

Scheme 4. 1,8-Addition−Elimination of Tropolone Derivatives Using Arylmagnesium Reagents

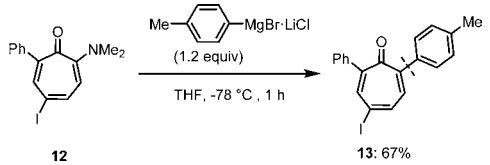


6f-h **11a-c**

11a: 62% **11b**: 72% **11c**: 61%

Surprisingly, even tropone derivative **12** containing an iodide substituent preferentially undergoes a formal substitution of the dimethylamino group with *p*-tolylMgBr·LiCl instead of I/Mg exchange,[20] thus providing the substituted tropone **13** in 67% yield (Scheme 5).[21]

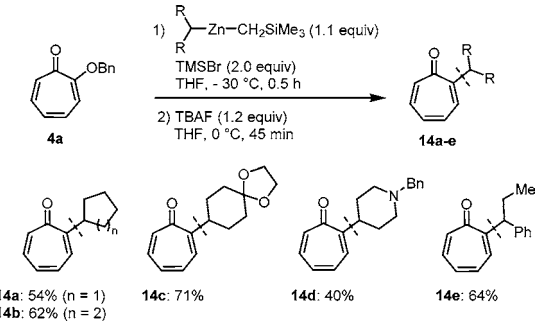
Scheme 5. 1,8-Addition−Elimination of 2-Dimethylaminotropone 12 Using *p*-TolylMgBr·LiCl



12 **13**: 67%

Additionally, we have performed conjugate addition−elimination reactions of various secondary mixed alkylzinc reagents[22] with benzyl-protected tropolone **4a** to obtain numerous α-alkylated tropone derivatives of type **14** (Scheme 6). The reaction of benzylated tropolone **4a** with various cyclic alkylzinc reagents proceeded within 0.5 h at −30 °C in the presence of TMSBr (2.0 equiv), followed by a reaction with TBAF, to afford the alkylated products **14a−c** in 54−71% yield. Surprisingly, even a benzyl-protected 4-piperidinylzinc reagent and a benzylic zinc derivative reacted under our reaction

Scheme 6. 1,8-Conjugate Addition−Elimination Using Secondary Mixed Zinc Reagents



4a **14a-e**

14a: 54% (n = 1)
14b: 62% (n = 2) **14c**: 71% **14d**: 40% **14e**: 64%

conditions to produce the desired 1,8-addition−elimination products **14d** and **14e**, respectively, in 40−64% yield.

In summary, we have developed a new general method for the regioselective zincation of various tropolone derivatives using TMPZnCl·LiCl. The generated organozinc reagents reacted with a variety of electrophiles in Cu-mediated allylation reactions as well as in Pd-catalyzed Negishi cross-coupling and acylation reactions, providing substituted seven-membered tropones. Additionally, to further elaborate the tropolone core, 1,8-conjugate addition−elimination reactions of various tropolone derivatives were carried out using a variety of organometallic reagents, such as arylmagnesium or secondary alkylzinc reagents. Further extension of this method toward the synthesis of biologically active tropolones is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03270.

Full experimental details and ^{1}H and ^{13}C NMR spectra (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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■ REFERENCES

(1) (a) Dewar, M. *Nature* **1945**, *155*, 50. (b) Dewar, M. *Nature* **1945**, *155*, 141.

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Org. Lett. 2016, 18, 6380−6383

(2) (a) Nozoe, T. *Sci. Rep. Tohoku Univ., Ser. 1: Phys., Chem., Astron.* **1950**, *34*, 199. (b) Nozoe, T. *Nature* **1951**, *167*, 1055. (c) Erdtman, H.; Gripenberg, J. *Nature* **1948**, *161*, 719.
(3) Bentley, R. *Nat. Prod. Rep.* **2008**, *25*, 118.
(4) (a) Zemer, D.; Revach, M.; Pras, M.; Modan, B.; Schor, S.; Sohar, E.; Gafni, J. *N. Engl. J. Med.* **1974**, *291*, 932. (b) Pietra, F. *Acc. Chem. Res.* **1979**, *12*, 132. (c) Banwell, M. G.; Onrust, R. *Tetrahedron Lett.* **1985**, *26*, 4543. (d) Banwell, M. G. *Aust. J. Chem.* **1991**, *44*, 1. (e) Graening, T.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3230.
(5) Pauson, P. L. *Chem. Rev.* **1955**, *55*, 9.
(6) (a) Chung, S.; Himmel, D. M.; Jiang, J.-K.; Wojtak, K.; Bauman, J. D.; Rausch, J. W.; Wilson, J. A.; Beutler, J. A.; Thomas, C. J.; Arnold, E.; Le Grice, S. F. J. *J. Med. Chem.* **2011**, *54*, 4462. (b) Piettre, S. R.; André, C.; Chanal, M.-C.; Ducep, J.-B.; Lesur, B.; Piriou, F.; Raboisson, P.; Rondeau, J.-M.; Schelcher, C.; Zimmermann, P.; Ganzhorn, A. J. *J. Med. Chem.* **1997**, *40*, 4208. (c) Fullagar, J. L.; Garner, A. L.; Struss, A. K.; Day, J. A.; Martin, D. P.; Yu, J.; Cai, X.; Janda, K. D.; Cohen, S. M. *Chem. Commun.* **2013**, *49*, 3197. (d) Jacobsen, F. E.; Lewis, J. A.; Heroux, K. J.; Cohen, S. M. *Inorg. Chim. Acta* **2007**, *360*, 264.
(7) Berg, U.; Bladh, H. *Acta Chem. Scand.* **1998**, *52*, 1380.
(8) (a) Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 9794. (b) Martínez-Martínez, A. J.; Kennedy, A. R.; Mulvey, R. E.; O'Hara, C. T. *Science* **2014**, *346*, 834. (c) Chevallier, F.; Mongin, F. *Chem. Soc. Rev.* **2008**, *37*, 595. (d) Klier, L.; Bresser, T.; Nigst, T. A.; Karaghiosoff, K.; Knochel, P. *J. Am. Chem. Soc.* **2012**, *134*, 13584. (e) Hedidi, M.; Erb, W.; Lassagne, F.; Halauko, Y. S.; Ivashkevich, O. A.; Matulis, V. E.; Roisnel, T.; Bentabed-Ababsa, G.; Mongin, F. *RSC Adv.* **2016**, *6*, 63185.
(9) (a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958. (b) Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673. (c) Garcia-Alvarez, P.; Graham, D. V.; Hevia, E.; Kennedy, A. R.; Klett, J.; Mulvey, R. E.; O'Hara, C. T.; Weatherstone, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 8079. (d) Mulvey, R. E. *Organometallics* **2006**, *25*, 1060. (e) Westerhausen, M. *Dalton Trans.* **2006**, 4755. (f) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3802. (g) Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497. (h) Mosrin, M.; Boudet, N.; Knochel, P. *Org. Biomol. Chem.* **2008**, *6*, 3237. (i) Piller, F. M.; Knochel, P. *Synthesis* **2011**, *2011*, 1751.
(10) (a) Mosrin, M.; Bresser, T.; Knochel, P. *Org. Lett.* **2009**, *11*, 3406. (b) Bresser, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 1914. (c) Duez, S.; Steib, A. K.; Manolikakes, S. M.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7686. (d) Unsinn, A.; Ford, M. J.; Knochel, P. *Org. Lett.* **2013**, *15*, 1128. (e) Haas, D.; Mosrin, M.; Knochel, P. *Org. Lett.* **2013**, *15*, 6162. (f) Shen, J.; Wong, B.; Gu, C.; Zhang, H. *Org. Lett.* **2015**, *17*, 4678.
(11) (a) Wunderlich, S.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7685. (b) Mosrin, M.; Knochel, P. *Chem. - Eur. J.* **2009**, *15*, 1468. (c) Wunderlich, S.; Rohbogner, C. J.; Unsinn, A.; Knochel, P. *Org. Process Res. Dev.* **2010**, *14*, 339. (d) Klier, L.; Bresser, T.; Nigst, T. A.; Karaghiosoff, K.; Knochel, P. *J. Am. Chem. Soc.* **2012**, *134*, 13584. (e) Hammann, J. M.; Haas, D.; Knochel, P. *Angew. Chem., Int. Ed.* **2015**, *54*, 4478.
(12) (a) Stathakis, C. I.; Manolikakes, S. M.; Knochel, P. *Org. Lett.* **2013**, *15*, 1302. (b) Manolikakes, S. M.; Ellwart, M.; Stathakis, C. I.; Knochel, P. *Chem. - Eur. J.* **2014**, *20*, 12289.
(13) (a) Muetterties, E. L.; Roesky, H.; Wright, C. M. *J. Am. Chem. Soc.* **1966**, *88*, 4856. (b) Muetterties, E. L.; Alegranti, C. W. *J. Am. Chem. Soc.* **1969**, *91*, 4420. (c) Jacobsen, F. E.; Lewis, J. A.; Heroux, K. J.; Cohen, S. M. *Inorg. Chim. Acta* **2007**, *360*, 264. (d) Morita, Y.; Matsumura, E.; Okabe, T.; Shibata, M.; Sugiura, M.; Ohe, T.; Tsujibo, H.; Ishida, N.; Inamori, Y. *Biol. Pharm. Bull.* **2003**, *26*, 1487.
(14) (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (b) Kobayashi, M.; Negishi, E. *J. Org. Chem.* **1980**, *45*, 5223. (c) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (c1) Haas, D.; Hammann, J. M.; Greiner, R.; Knochel, P. *ACS Catal.* **2016**, *6*, 1540.
(15) (a) Farina, V.; Baker, S. R.; Benigni, D. A.; Sapino, C., Jr. *Tetrahedron Lett.* **1988**, *29*, 5739. (b) Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C., Jr. *J. Org. Chem.* **1990**, *55*, 5833.
(16) Tamburlin-Thumin, I.; Crozet, M. P.; Barrière, J.-C. *Synthesis* **1999**, *1999*, 1149.
(17) Fitzgerald, T. J. *Biochem. Pharmacol.* **1976**, *25*, 1383.
(18) A 7% yield of dibrominated product was also isolated. See the Supporting Information.
(19) (a) Nozoe, T.; Mukai, T.; Minegishi, J. *Proc. Japan Acad.* **1951**, *27*, 419. (b) Mukai, T. *Bull. Chem. Soc. Jpn.* **1958**, *31*, 852.
(20) (a) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302. (b) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701. (c) Tilly, D.; Chevallier, F.; Mongin, F.; Gros, P. C. *Chem. Rev.* **2014**, *114*, 1207.
(21) Reaction with the Grignard reagent *i*-PrMgCl·LiCl also occurs through the 1,8-conjugate addition pathway.
(22) (a) Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, T. A.; Reddy, C. K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1496. (b) Jones, P.; Knochel, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, *1*, 3117. (c) Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 4934. (d) Jones, P.; Reddy, K. C.; Knochel, P. *Tetrahedron* **1998**, *54*, 1471.

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