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Carbon-Based Leaving Group in Substitution Reactions: Functionalization of sp^3-Hybridized Quaternary and Tertiary Benzylic Carbon Centers

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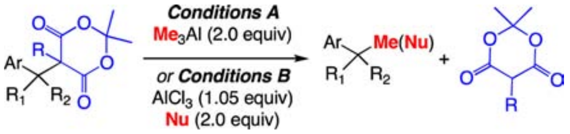
ABSTRACT



Lewis acid promoted substitution reactions employing Meldrum's acid and 5-methyl Meldrum's acid as carbon-based leaving groups are described which transform unstrained quaternary and tertiary benzylic $C_{sp^3}-C_{sp^3}$ bonds into $C_{sp^3}-X$ bonds (X = C, H, N). Importantly, this reaction has a broad scope in terms of both suitable substrates and nucleophiles with good to excellent yields obtained (typically >90%).

The direct modification/functionalization of sp^3-hybridized carbon centers through cleavage of unstrained C–C σ-bonds remains a challenging transformation in organic synthesis.[1–5] In 2009 our group discovered two such reactions in which Meldrum's acid functions as a highly effective and convenient leaving group in the Pd-catalyzed hydrogenolysis of quaternary benzyl Meldrum's acids,[6] replacing an unstrained benzylic $C_{sp^3}-C_{sp^3}$ σ-bond with a $C_{sp^3}-H$ bond with inversion of configuration (Scheme 1) and additionally with tertiary benzylic Meldrum's acids in the presence of Sc(OTf)$_3$ and a nucleophile.[7] Subsequently, Li's group described a related FeCl$_3$-catalyzed substitution at sp^3-hybridized tertiary stabilized (primarily diaryl) carbon centers, with π-nucleophiles, in which 1,3-diphenylpropane-1,3-dione acted as a leaving group.[8]

We postulated that substitution of Meldrum's acid derivatives at sp^3-hybridized benzylic carbon centers with carbon- and heteroatom-based nucleophiles, via C–C σ-bond cleaving/C–X (X = C, N, H) σ-bond forming reactions, would allow for benzylic functionalization.

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(1) For selected general reviews on C–C σ-bond scission, see: (a) Ruhland, K. *Eur. J. Org. Chem.* **2012**, 2683. (b) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100. (c) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (d) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610. (e) Rybtchinski, D.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870. (f) Murakami, M.; Yoshihiko, I. In *Topics in Organometallic Chemistry*; Murai, S., Ed.; Springer-Verlag: Berlin, 1999; Vol. 3, p 97.

(2) For a review on advances in leaving groups, see: Lepore, S. D.; Mondal, D. *Tetrahedron* **2007**, *63*, 5103.

(3) Tsuji–Trost substitutions and related isomerizations with 1,3-diketone, malonate, cyclopentadienyl, and Meldrum's acid as carbon-based leaving groups under palladium or nickel catalysis have been reported; for selected examples, see: (a) Fisher, E. L.; Lambert, T. H. *Org. Lett.* **2009**, *11*, 4108. (b) Trost, B. M.; Simas, A. B. C.; Plietker, B.; Jäkel, C.; Xie, J. *Chem.—Eur. J.* **2005**, *11*, 7075. (c) Vicart, N.; Goré, J.; Cazes, B. *Tetrahedron* **1998**, *54*, 11063. (d) Bricout, H.; Carpentier, J.-F.; Mortreux, A. *Tetrahedron Lett.* **1997**, *38*, 1053. (e) Vicart, N.; Goré, J.; Cazes, B. *Synlett* **1996**, 850. (f) Nilsson, Y. I. M.; Andersson, P. G.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1993**, *115*, 6609.

(4) For an isolated example of a nickel catalyzed substitution employing Meldrum's acid as a leaving group, see: Sumida, Y.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2010**, *12*, 2254.

(5) For other approaches to the cleavage of unstrained C–C σ-bonds, see: (a) He, C.; Guo, S.; Huang, L.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 8273. (b) Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2452. (c) Nečas, D.; Kotora, M. *Org. Lett.* **2008**, *10*, 5261. (d) Tobisu, M.; Chatani, N. *Chem. Soc. Rev.* **2008**, *37*, 300. (e) Gooßen, L. J.; Rodríguez, N.; Gooßen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100. (f) Nečas, D.; Drabina, P.; Sedlák, M.; Kotora, M. *Tetrahedron. Lett.* **2007**, *48*, 4539. (g) Turský, M.; Nečas, D.; Drabina, P.; Sedlák, M.; Kotora, M. *Organometallics* **2006**, *25*, 901. (h) Nečas, D.; Turský, M.; Tišlerová, I; Kotora, M. *New J. Chem.* **2006**, *30*, 671. (i) Nečas, D.; Turský, M.; Kotora, M. *J. Am. Chem. Soc.* **2004**, *126*, 10222. (j) Zhang, N.; Vozzolo, J. *J. Org. Chem.* **2002**, *67*, 1703. (k) Jun, C.-H.; Lee, H.; Lim, S.-G. *J. Am. Chem. Soc.* **2001**, *123*, 751. (l) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1999**, *121*, 8645. (m) Jun, C.-H.; Lee, H. *J. Am. Chem. Soc.* **1999**, *121*, 880.

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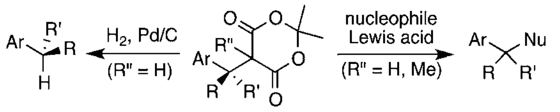
10.1021/ol301442z

Herein, we report a Lewis acid promoted modification/functionalization of sp^3-hybridized quaternary and tertiary benzylic carbon centers through displacement of carbon-based leaving groups, namely Meldrum's acid and 5-methyl Meldrum's acid (Scheme 1).

The substitution reaction was shown to be general with an array of substrate substitutions and nucleophiles, under mild conditions, and proceeding in good to excellent yields.

The ability to substitute Meldrum's acid at quaternary all-carbon sp^3-hybridized centers with a methyl group was first explored. Trimethylaluminum was chosen for its combined Lewis aciditiy and nucleophilic properties upon complexation with a Lewis base.[9] A wide array of readily available benzyl Meldrum's acids **1** effectively reacted with Me_3Al to yield **2** in excellent yields at room temperature. As depicted in Table 1, the process was general as electronics and sterics did not affect the efficiency of the substitution reaction. Both mesomerically and inductively donating groups, electron neutral groups as well as mildly electron withdrawing groups, afforded the desired product with excellent isolated yields.

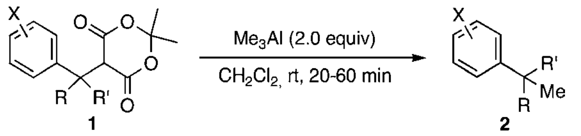
Scheme 1. General Strategy



Having established the substrate scope of the methylation of benzyl Meldrum's acids, we proceeded to explore the range of nucleophiles compatible with this system. After optimization studies,[10] it was found that a combination of Lewis acid, $AlCl_3$, and an external nucleophile furnished substitution products in good yield under mild reaction conditions (Figure 1).[11] From **1c**, the relatively weak nucleophile allyltrimethylsilane and methallyltrimethylsilane led to **2o** and **2p**, respectively, in excellent yields. Allenyl and propargyl compounds **2q** and **2r** were formed from **1c** and propargylTMS and allenylSnBu$_3$, respectively.

The same net result of our hydrogenolysis protocol[6] was achieved by the reaction of **1c** with *i*-Bu$_3$Al, which furnished **2s** in 84% yield (Figure 1). Substitution was also realized with TMSCN, yielding **2t** in quantitative yield. π-Nucleophiles 2-methylfuran and 2-methylthiophene were also effective in the substitution reaction, with complete regioselectivity for the 5-position. Reacting 2-(trimethylsiloxy)furan and **1c** led to a 9:1 mixture of regioisomeric butenolides in an 84% combined yield. Furthermore, the azide functionality was also introduced at the benzylic position via the use of azidotrimethylsilane.

Table 1. Methyl Substitution at Quaternary Centers



entry	X	R; R′	yield[a] (%)
1	H	R–R′ = $(CH_2)_5$ (**1a**)	quant (**2a**)
2	4-*t*-Bu	R = R′ = Me (**1b**)	96 (**2b**)
3	4-(MeO)	R = R′ = Me (**1c**)	93 (**2c**)
4	4-($C_8H_{17}O$)	R = R′ = Me (**1d**)	95 (**2d**)
5	4-Cl	R–R′ = $(CH_2)_5$ (**1e**)	quant (**2e**)
6	4-F	R–R′ = $(CH_2)_5$ (**1f**)	95 (**2f**)
7	2-Et	R = R′ = Me (**1g**)	91 (**2g**)
8	2-($C_8H_{17}O$)	R = R′ = Me (**1h**)	94 (**2h**)
9	2-F	R–R′ = $(CH_2)_5$ (**1i**)	96 (**2i**)
10	3- *t*-Bu	R = R′ = Me (**1j**)	98 (**2j**)
11	3-(C_6H_{13})	R = R′ = Me (**1k**)	97 (**2k**)
12[b]	3-($C_8H_{17}O$)	R = R′ = Me (**1l**)	89 (**2l**)
13	3-TMS	R = R′ = Me (**1m**)	quant (**2m**)
14	3-F	R–R′ = $(CH_2)_5$ (**1n**)	98 (**2n**)

[a] In all cases, conversion was >95%. [b] Reaction time was 5 h.

The generality of the substitution reaction was further established by investigating the reactivity of tertiary

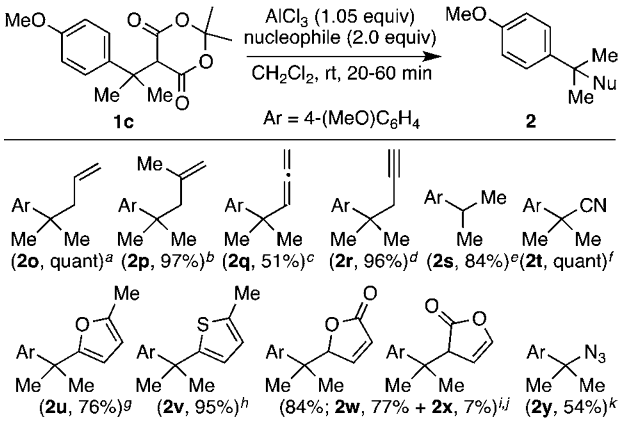


Figure 1. Scope of the nucleophile. In all cases, conversion was >95%. Nucleophile employed: [a]allylTMS; [b]methallylTMS; [c]propargylTMS; [d]allenylSnBu$_3$; [e]*i*-Bu$_3$Al (in the absence of $AlCl_3$); [f]TMSCN; [g]2-methylfuran; [h]2-methylthiophene; [i]2-(trimethylsiloxy)furan; [j]77% of butenolide **2w** plus 7% of minor regioisomer **2x** isolated as individual components; [k]TMSN$_3$.

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(7) Meldrum's acid was reductively cleaved and displaced by acetone (C-alkylation); see: Mahoney, S. J.; Moon, D. T.; Hollinger, J.; Fillion, E. *Tetrahedron Lett.* **2009**, *50*, 4706.

(8) Li, H.; Li, W.; Liu, W.; He, Z.; Li, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 2975.

(9) Related strategies of activation/methylation to afford *tert*-alkyl-substituted aromatics have been demonstrated from tertiary benzylic alcohols and chlorides; for an example, see: Hartsel, J. A.; Craft, D. T.; Chen, Q.-H.; Ma, M.; Carlier, P. R. *J. Org. Chem.* **2012**, *77*, 3127 and references cited therein.

(10) Alternative Lewis acids surveyed in optimization studies were found to deliver inferior yields to $AlCl_3$ with the main side reactions being elimination and indane formation.

(11) In the absence of added nucleophile, from **1c**, the following indane was formed in 80% yield, where Ar = (4-MeO)C_6H_4.

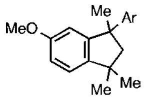
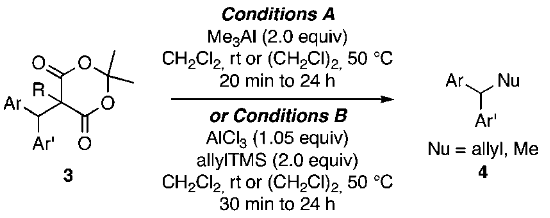


Table 2. Substitutions at Tertiary Benzylic Centers



entry	Ar; Ar′; R	Cond	Nu	yield (%)
1[a]	Ar = Ar′ = C_6H_5; R = H (**3a**)	A	Me	N/A (**4a**)
2[a]	(**3a**)	B	allyl	50 (**4b**)
3	Ar = Ar′ = C_6H_5; R = Me (**3b**)	A	Me	92 (**4a**)
4	(**3b**)	B	allyl	93 (**4b**)
5	Ar = Ar′ = 4-(MeO)C_6H_4; R = H (**3c**)	A	Me	quant (**4c**)
6	(**3c**)	B	allyl	94 (**4d**)
7[a]	Ar = 4-(MeO)C_6H_4; Ar′ = C_6H_5; R = H (**3d**)	A	Me	95 (**4e**)
8	(**3d**)	B	allyl	96 (**4f**)
9[a]	Ar = 4-(MeO)C_6H_4; Ar′ = 4-ClC_6H_4; R = H (**3e**)	A	Me	87 (**4g**)
10[a]	(**3e**)	B	allyl	91 (**4h**)
11	Ar = Ar′ = 4-ClC_6H_4; R = H (**3f**)	A	Me	N/A (**4i**)
12[a]	(**3f**)	B	allyl	42 (**4j**)
13	Ar = Ar′ = 4-ClC_6H_4; R = Me (**3g**)	A	Me	96 (**4i**)
14	(**3g**)	B	allyl	94 (**4j**)
15	Ar = 2-naphthyl; Ar′ = 3,4,5-$(OMe)_3$Ph; Ar′ = 3,4,5-$(OMe)_3C_6H_2$; R = Me (**3h**)	A	Me	99 (**4k**)

[a] Reaction was performed in $(CH_2Cl)_2$ at 50 °C.

benzhydryl Meldrum's acids **3**. Relative to quaternary benzyl Meldrum's acids **1**, benzhydryl Meldrum's acids **3** were shown to be sensitive to the electronics of the rings.[12] To our surprise, substitution product **4a** was not formed when **3a** was reacted with Me_3Al (Table 2, entry 1). Instead, vigorous gas evolution was observed and starting material recovered, suggesting a competing deprotonation of the Meldrum's acid moiety with formation of methane. Similarly, the optimized conditions for allylation furnished compound **4b** in only modest yield (Table 2, entry 2). Gratifyingly, methylation of the 5-position of Meldrum's acid remedied this limitation. Substitution product **4a** was formed in 92% yield when **3b** was treated with Me_3Al (Table 2, entry 3). The allylation of **3b** also proceeded in high yield (Table 2, entry 4). Facile reactions were observed with electron-rich substrates **3c**, **3d**, and **3e** which efficiently afforded the desired methylation and allylation products for both $AlCl_3$ and Me_3Al systems (Table 2, entries 5–10). Substrate **3f** bearing strong inductively withdrawing substituents was inert toward the methylation reaction (Table 2, entry 11, gas evolution also observed), and the allylation proceeded sluggishly (Table 2, entry 12). Remarkably, the methylated analogue **3g** enabled the methyl and allyl substitutions to proceed in excellent yields (Table 2, entries 13 and 14). The utility of this methodology was further demonstrated by applying the methylation conditions to the synthesis of the potent inhibitor of tubulin polymerization **4k** (Table 2, entry 15).[13]

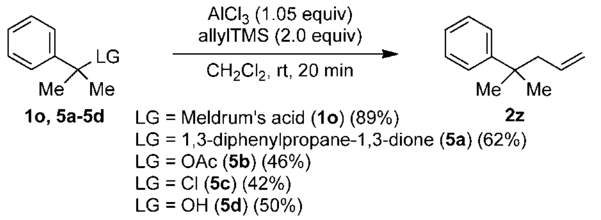


Figure 2. Leaving group comparison in allyl substitutions.

A direct comparison to alternative leaving groups was performed with substrates bearing the challenging quaternary benzylic center motif under our optimized allylation conditions (Figure 2). In analyzing the allyl substitutions of **1o**, **5a–d**, Meldrum's acid as a leaving group was found to be superior to 1,3-diphenylpropane-1,3-dione, acetate, chloride, and hydroxide,[14] as **1o** furnished **2z** in highest yield.[15]

In conclusion, we have described unprecedented substitution reactions through C–C σ-bond cleaving/C–X (X = C, N, H) σ-bond forming reactions that allow for direct modification of sp^3-hybridized tertiary and quaternary carbon centers with good to excellent yields. Notably, a wide range of electronics and substitutions are tolerated on the substrate and a large collection of nucleophiles can be added using this system. Current efforts are directed at broadening the use of Meldrum's acid derivatives as convenient leaving groups.

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(14) For a review of direct substitutions on stabilized alcohols, see: Emer, E.; Sinisi, R.; Capdevila, M. G.; Petruzziello, D.; De Vincentiis, F.; Cozzi, P. G. *Eur. J. Org. Chem.* **2011**, 647–666.

(15) For **5a–d**, the lower yields of **2z** reflected competing pathways: elimination and indane formation.

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Supporting Information Available. Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.