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Room Temperature Hydroalkylation of Electron-Deficient Olefins: sp C–H Functionalization via a Lewis Acid-Catalyzed Intramolecular Redox Event

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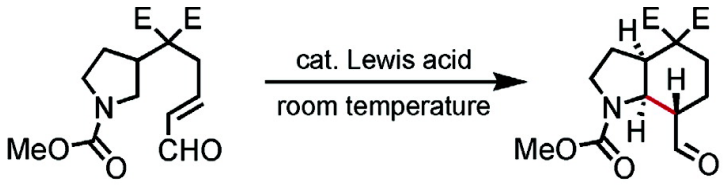

■Functionalization of sterically hindered 2°, 3°, and benzylic C-H bonds

■12 additional examples: 68 99% yield

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Room Temperature Hydroalkylation of Electron-Deficient Olefins: sp^3 C−H Functionalization via a Lewis Acid-Catalyzed Intramolecular Redox Event

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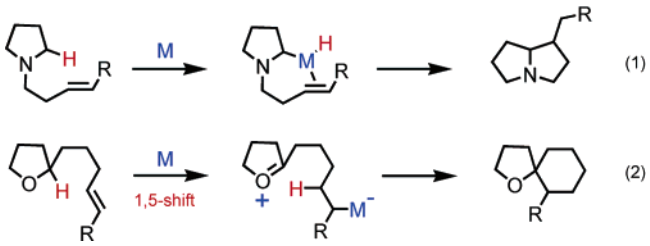
In response to the limited precedence for the catalytic coupling of sp^3 C−H bonds and alkenes,[1] we became interested in developing annulation reactions based on the direct functionalization of sp^3 C−H bonds. Our first approach relied on a sequence initiated by transition metal insertion into the C−H bond of interest (eq 1), which led to the development of an iridium-catalyzed cyclization of pyrrolidine-based amide−alkene substrates.[2] This report demonstrated that C−H activation and olefin insertion can occur in tandem and in preference to β-hydride elimination. However, at the same time, it was recognized that this approach would be unsuitable for C−C bond formation at tertiary and sterically hindered positions.

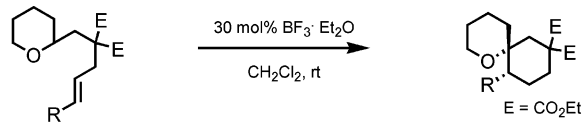


To overcome this limitation, we proposed an alternative approach wherein the unsaturated moiety (alkene, alkyne) is activated by an electrophilic metal, which in turn may induce a selective C−H bond cleavage via a hydride shift (eq 2). Importantly, as the initiation occurs at the point of unsaturation, functionalization of sterically hindered C−H bonds may be possible. Support for this proposal was provided by the cyclization of *N*-,*N*′-dialkyl-2-vinylanilines under Lewis acid-catalyzed[3a] or thermal[3b−d] conditions; however, cyclization of substrates lacking an extended π-system has not been reported (e.g., isolated olefins).

We began our explorations with a tetrahydropyran substrate containing an enal side chain attached to the 2-position (**1a**, Scheme 1); this connectivity sets up the β-position of the enal and the targeted C−H bond in a 1,5-relationship. Selection of substrate **1a** was based on three points: (1) aldehyde/Lewis acid complexes are known to possess a high degree of electrophilicity;[4] (2) hydride transfer from the position adjacent to oxygen would result in an oxonium ion; and (3) the cation-induced through-space hydride shift would most likely proceed via a six-membered transition state.[5] On the basis of this concept, a Lewis acid-catalyzed intramolecular hydroalkylation reaction of isolated electron-deficient olefins was developed. Herein, we disclose the initial exploration of the scope and efficiency of this transformation.

We initiated our studies by subjecting tetrahydropyran substrate **1a** to 30 mol % of $BF_3{\cdot}Et_2O$ in methylene chloride. Gratifyingly, in 12 h, enal **1a** was smoothly converted to the spirocycle **2a** at ambient temperature in 91% isolated yield as a mixture of diastereomers (Scheme 1). $Sc(OTf)_3$, $GaCl_3$, TiF_4, and $PtCl_4$ were more reactive than $BF_3{\cdot}Et_2O$ for this transformation, although these catalysts generated undesired byproducts.[6] In addition to the highly electrophilic α,β-unsaturated aldehyde acceptor component, hydroalkylation of enone acceptors also proceeded smoothly. Specifically, under the action of 30 mol % of $BF_3{\cdot}Et_2O$, both the methyl ketone **1b** and phenyl ketone **1c** substrates were efficiently transformed into spirocycles **2b** and **2c**, respectively (Scheme 1). *These transformations demonstrate the potential power of this approach, whereby a tertiary C−H bond is directly transformed into a heteroatom-substituted quaternary center with concomitant formation of an adjacent tertiary center under catalytic conditions at room temperature.*

Scheme 1



1a, R = CHO
1b, R = COMe
1c, R = COPh
1d, R = CO_2Me

2a, 12 h, 91%, dr = 3.7 : 1
2b, 10 h, 94%, dr = 2 : 1
2c, 36 h, 98%, dr = 3 : 1
2d, no reaction

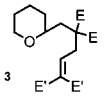
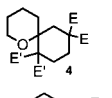
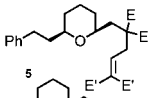
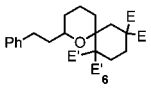
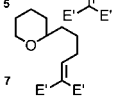
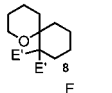
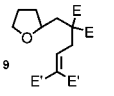
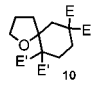
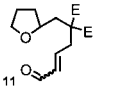
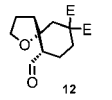
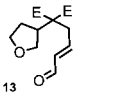
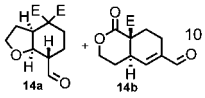
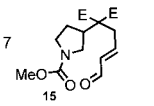
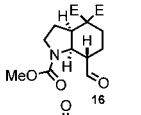
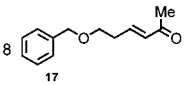
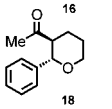
With an exciting lead and a wide range of potential hydroalkylation catalysts in hand, we proceeded to examine the scope of this reaction (Table 1). Although it was found that the α,β-unsaturated ester moiety was not reactive under the reaction conditions (Scheme 1), hydroalkylation of a variety of α,β-unsaturated malonate substrates occurred (entries 1−4, Table 1). In the case of the α,β-unsaturated malonate substrates, $Sc(OTf)_3$ proved to be the catalyst of choice, with near quantitative hydroalkylation occurring in short reaction times with only 5 mol % catalyst loading. Notably, geminal substitution along the olefin tether was not required for efficient annulation (entry 3, Table 1). In addition to tertiary C−H bonds, secondary C−H bonds could also be coupled (entries 6 and 7, Table 1). The tetrahydrofuran-based enal **13** and the pyrrolidine-based enal **15** provided the bicyclic products **14** and **16**, under the action of a substoichiometric amount of $PtCl_4$[7] in moderate to good yield. In the case of **13**, the byproduct **14b** was also isolated, which presumably results from a hydroalkylation/elimination/lactonization sequence.[8] The 2,3-disubstituted tetrahydropyran **18** was obtained in high diastereomeric purity via treatment of acyclic ether **17** with a substoichiometric amount of $BF_3{\cdot}Et_2O$ at elevated temperature (entry 8, Table 1).

We further wanted to examine if substrates lacking the stabilization of an α-heteroatom could be employed. To this end, we prepared aryl substrate **19** and thiophene substrate **21**. Gratifyingly, it was found that at elevated temperatures the hexa-substituted cyclohexanes **20** and **22** could be obtained in moderate to good yield, and in preference to 7-exo-hydroarylation.[9]

From a practical standpoint, this cyclization method is user friendly. Reactions can be performed at ambient temperature in flasks from the drawer and can be carried out in air without the rigorous exclusion of moisture. This is in stark contrast to many transition metal-catalyzed reactions, which typically require high temperature and necessitate air- and moisture-free techniques. Additionally, increasing the catalyst loading enhances the reaction rate without any noticeable decrease in product yield (entry 5, Table 1).

10.1021/ja053337f CCC: $30.25

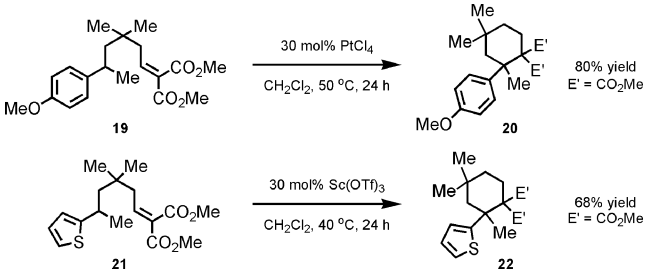
Table 1. Lewis Acid-Catalyzed Hydroalkylation of Olefin Substrates

entry	substrate	product	cat	time (h)	yield(%)[a]
1			5 mol% $Sc(OTf)_3$	2	94
2			5 mol% $Sc(OTf)_3$	4	99 (1:0.8)[b]
3			5 mol% $Sc(OTf)_3$	12	99
4			5 mol% $Sc(OTf)_3$	<1	96
5			5 mol% $BF_3 \cdot Et_2O$ 30 mol% $BF_3 \cdot Et_2O$	12 2	98 (1.5:1)[b] 99 (1.5:1)[b]
6			10 mol% $PtCl_4$	7	40 (**14a**)[c] ; 34 (**14b**)[c]
7			30 mol% $PtCl_4$	38	77 (>15:1)[b]
8			75 mol% $BF_3 \cdot Et_2O$[d]	45	90 (>15:1)[b]

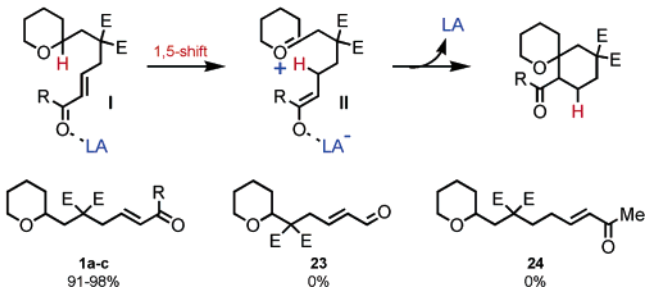
E = CO_2Et E' = CO_2Me

[a] All reactions were performed in CH_2Cl_2 (0.025 M substrate) at room temperature. Isolated yields after flash chromatography. [b] Diastereomeric ratio given in parentheses. [c] Diastereomeric ratio >15:1. [d] Reaction performed at 50 °C.

Scheme 2



Scheme 3. Mechanistic Rationale for Lewis Acid-Catalyzed Hydroalkylation: A 1,5-Relationship Is Required



The mechanistic rationale for this transformation is provided in Scheme 3. Lewis acid complexation with the carbonyl oxygen activates the olefin and triggers the [1,5]-hydride shift, affording the zwitterionic intermediate **II**. This crucial step may be viewed as an intramolecular variant of the Meerwein−Ponndorf−Verley reaction; however, in this case, a metal enolate and a carbocation are generated, which react to furnish a new C−C bond and the desired hydroalkylation product. Thus, no oxidant is required for the overall C−H to C−C transformation.[10] A 1,5-relationship between the electrophilic site and the targeted C−H bond seems to be a requirement for hydroalkylation to proceed. Substrate **23** containing a 1,4-relationship and substrate **24** containing a 1,6-relationship each failed to yield hydroalkylation products (Scheme 3), demonstrating the current limitation of this approach to the formation of six-membered rings.[5]

In summary, we have demonstrated that the hydridic character of C−H bonds can be exploited to promote their direct conversion into C−C bonds. This simple approach has been utilized to efficiently functionalize tertiary and secondary positions α to heteroatoms (ethers and carbamates), as well as tertiary benzylic C−H bonds, under catalytic or substoichiometric conditions. An important finding was that a variety of Lewis acids functioned as catalyst. Studies primarily aimed at expanding the scope of this concept to encompass a variety of acceptor components are ongoing in our laboratory.

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Note Added after ASAP Publication: There were errors in Scheme 2 in the version published on the Internet August 16, 2005. The version published August 23, 2005, is correct.

Supporting Information Available: Experimental procedures and spectroscopic data for starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) DeBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556.
(3) Although the mechanism in these reports is suggested to proceed through a 1,5-sigmatropic hydrogen shift, it is possible that a direct hydride transfer mechanism is operative. Selected examples: (a) Noguchi, M.; Yamada, H.; Sunagawa, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3327. (b) Nijhuis, W. H. N.; Verboom, W.; El-Fadl, A. A.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1989**, *54*, 199. (c) Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1987**, *109*, 3136. (d) Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N. *Synthesis* **1987**, 641.
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(5) The term "through space" is used to differentiate this process from more common hydride shifts that proceed through a σ- or π-framework. The overwhelming majority of these examples proceed through a six-membered transition state. For selected examples, see: (a) Kanischev, M. I.; Schegolev, A. A.; Smit, W. A.; Caple, R.; Kelner, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 5660 and references therein. (b) Schulz, J. G. D.; Onopchenko, A. *J. Org. Chem.* **1978**, *43*, 339. (c) Heathcock, C. H.; Piettre, S.; Ruggeri, R. B.; Ragan, J.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2544. (d) Krohn, K.; Flörke, U.; Höfker, U.; Träubel, M. *Eur. J. Org. Chem.* **1999**, 3495. (e) Wölfling, J.; Frank, E.; Schneider, G.; Tietze, L. F. *Angew. Chem., Int. Ed.* **1998**, *38*, 200. (f) Diaz, D.; Martín, V. S. *Org. Lett.* **2000**, *2*, 335. (g) Diaz, D.; Martín, V. S. *Tetrahedron Lett.* **2000**, *41*, 743. (h) Wölfling, J.; Frank, E.; Schneider, G.; Tietze, L. F. *Eur. J. Org. Chem.* **2004**, 90.
(6) A byproduct stemming from the opening of the spiro-system formed in this reaction (see the Supporting Information).
(7) (a) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055. (b) Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859.
(8) The relative amount of **14a** and **14b** is dependent on the reaction time and the catalyst employed.
(9) Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* **2002**, *67*, 1414.
(10) For oxidative intermolecular C−C bond formation at the α-position of reactive amines, see: (a) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312. (b) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968 and references therein.

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