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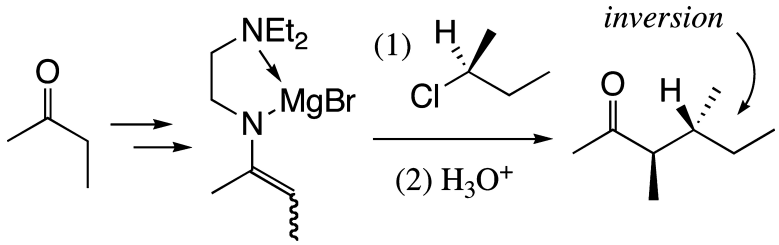

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Alkylation of Magnesium Enamide with Alkyl Chlorides and Fluorides

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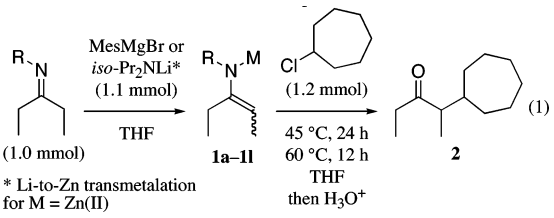
Regioselective alkylation of an enolate anion with an alkyl halide is the fundamental reaction in organic synthesis.[1] Major progress was made in the 1960s and 1970s through development of the chemistry of metalloenamine,[2] lithium enolate,[3] and enol silyl ether,[4] yet problems remained. The metal enolate or enamide derived from a ketone being moderately reactive, the alkylating reagents that give synthetically useful yield and selectivity, have been limited largely to alkyl iodides and bromides, and benzylic and allylic halides. Herein we report that a magnesium enamide bearing an internal nitrogen coordination site, such as **1a**, substantially expands the scope of the Stork metalloenamine chemistry, allowing alkyl chlorides and fluorides to serve as effective alkylating electrophiles. The reaction takes place with inversion of stereochemistry at the electrophilic carbon center.

In our recent studies on α-tertiary alkylation[5] of a zinc enamide with an olefin,[6] we learned that the nitrogen substituent on the enamine exerts a strong impact on the reactivity and the thermal stability of metal enamides, and decided to investigate a variety of combinations of the nitrogen substituent (R) and the metal cation in the S_N2 alkylation reaction (eq 1 and Chart 1). The reaction between a 3-pentanone imine and chlorocycloheptane was used as a benchmark under the conditions shown in eq 1.[7] Mesitylmagnesium bromide (MesMgBr) was eventually found to be the most suitable base for deprotonation of the imine.



The data in Table 1 indicate that the alkylation reaction shows a reactivity profile very different from the one found in a related carbometalation reaction, where the "soft" zinc countercation plays a key role.[6] A magnesium enamide bearing R = 2-(*N*,*N*-diethylamino)ethyl (entry 1; **1a**) is, thus, the best reagent in alkylation,[8] giving the desired secondary alkylated ketone **2** in 88% yield after acidic workup of the reaction mixture. The reaction also produced cycloheptene in 11% yield. The reaction was incomplete after 24 h at 45 °C (69%, entry 2). A 3-(*N*,*N*-dimethylamino)propyl compound **1b** is less reactive and less selective than **1a**, giving 79% of **2** and 17% of cycloheptene (entry 3). A 2-methoxyethyl compound **1c** produced much lower yield (entry 4). An enamide without the heteroatom addend behaves very differently. Stork's original *N*-cyclohexyl compound **1d** (entry 5) gave **2** in 47% yield after 24 h at 45 °C, and heating at 60 °C did not improve the yield much (51%, entry 6), which we ascribe to decomposition of reactive species. An *N*-phenyl compound **1e** (entry 7) reacted very slowly and gave **2** in only 1% yield. A lithium variant **1f** was found to be reactive but far less selective to give a 1:2 mixture of **2** and cycloheptene (entry 8). Zinc variants **1g** and **1h** are inactive under the reaction conditions, reacting very slowly (entries 9 and 10).

Chart 1. Examined Metal Enamides

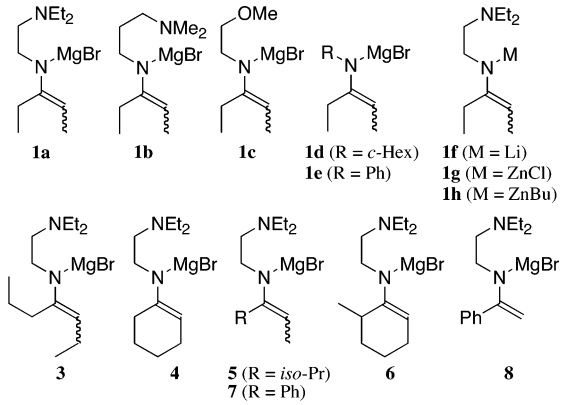


Table 1. Effect of Alkyl Substitution (R) and Metal Countercation

entry[a]	metal enamide	product yield (%)[b] 2	product yield (%)[b] cycloheptene	recovery of c-$C_7H_{13}Cl$ (mmol)
1	**1a**	88	11	0.25
2[c]	**1a**	69	10	0.34
3	**1b**	79	17	0.29
4	**1c**	4	7	0.85
5	**1d**	51	9	0.60
6[c]	**1d**	47	8	0.66
7	**1e**	1	4	1.07
8	**1f**	23	44	0.41
9	**1g**	21	4	0.95
10	**1h**	3	3	1.03

[a] The reaction was carried on a 1.0 mmol scale under the conditions described in eq 1 (at 45 °C for 24 h, and then 60 °C for 12 h) and otherwise noted. [b] Yields of **2** and cycloheptene and recovery of the starting chlorocycloheptane were determined by GC analysis with octane as an internal standard. [c] The reaction was carried out at 45 °C for 24 h.

The synthetic potential of the new method is illustrated by the data in Table 2. The reactions were performed using essentially equimolar amounts of reactants. Examples with alkyl fluorides and chlorides are reported, while bromide and iodides not reported here uneventfully took part in the reaction. Primary alkyl fluoride was found to be an excellent alkylating reagent. An acyclic enamide **3** reacted with 1-fluorodecane to give **9** in 97% isolated yield (entry 1). The reaction of a cyclic enamide **4** and 1-fluorodecane gave **10** in 75% yield (entry 2).

An unsymmetrical enamide **5** prepared from 2-methylpentan-3-one imine reacted with 1-fluorodecane at the less substituted carbon center to give **11** with 91% selectivity (90% yield, entry 3). Either the lack of regioselectivity of the imine deprotonation or in situ enamide regioisomerization may result in the formation of the minor regioisomer. The reaction with 1-chlorodecane gave the product

† PRESTO, Japan Science and Technology Agency (JST).

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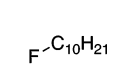
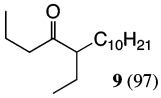
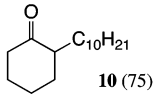
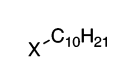
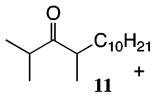
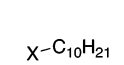
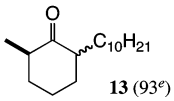
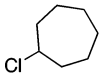
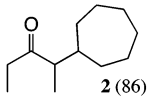
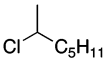
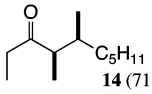
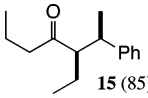
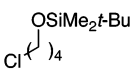
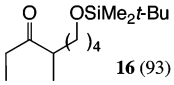
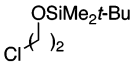
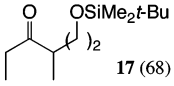
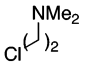
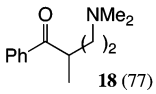
Table 2. α-Alkylation with Primary and Secondary Alkyl Halides

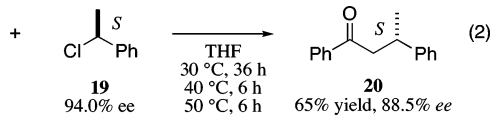
entry[a]	enamide[b]	alkyl halide[c]	conditions temp, time	product (% yield)[d]
1	**3**		65°C, 36 h	 **9** (97)
2	**4**		65°C, 36 h	 **10** (75)
			 **11** + **12**	
3	**5**	X = F	65°C, 36 h	(90) **11**:**12** = 91:9
4	**5**	X = Cl	50°C, 24 h 65°C, 12 h	(94) **11**:**12** = 85:15
				
5	**6**	X = F	65°C, 36 h	**13** (93[e])
6	**6**	X = Cl	50°C, 24 h 65°C, 12 h	**13** (92[f])
7[g]	**1a**		45°C, 24 h 60°C, 12 h	 **2** (86)
8	**1a**		45°C, 24 h 60°C, 12 h	 **14** (71) *syn:anti* = 58:42
9[h]	**3**		30°C, 12 h 50°C, 3 h	 **15** (85) *syn:anti* = 70:30
10	**1a**		50°C, 24 h 65°C, 12 h	 **16** (93)
11	**1a**		50°C, 24 h 65°C, 12 h	 **17** (68)
12[i]	**7**		50°C, 36 h	 **18** (77)

[a] The reaction was carried out in THF (ca. 0.8 M for enamide) on 1.0−2.2 mmol scale unless otherwise noted. [b] Metal enamide was prepared from the corresponding imine and 1.1 equiv of MesMgBr unless otherwise noted. [c] Alkyl halide (1.2 equiv) was used unless otherwise noted. [d] Isolated yield based on imine used. [e] *cis:trans* = 72:28. [f] *cis:trans* = 50:50. [g] The reaction was carried out after THF was mostly removed in vacuo (ca. 2.0 M for enamide). [h] The use of 1.5 equiv of alkyl halide. [i] Alkyl chloride was prepared in situ by treatment of the corresponding hydrochloric acid salt with *t*-BuMgCl. Enamide **7** (1.4 equiv for alkyl chloride) was prepared by using *t*-BuMgCl. Yield was determined by GC analysis on the basis of the alkyl chloride.

in higher yield but with slightly lower regioselectivity (entry 4). In contrast, an enamide **6** prepared from 2-methylcyclohexanone imine showed 100% regioselectivity in the reactions with 1-fluorodecane and 1-chlorodecane to give **13** in 93 and 92% yield, respectively (*cis:trans* = 72:28 and 50:50, respectively, entries 5 and 6).

Entries 7−9 describe the use of secondary alkyl chlorides. The reaction of 2-chloroheptane with **1a** took place in 71% yield to give **14**, where we observed 58:42 *syn:anti* selectivity (entry 8). (1-Chloroethyl)benzene reacted much faster to give **15** in 85% with 70:30 *syn:anti* selectivity (entry 9). The origin of this small *syn* preference is uncertain at this time.

Entries 10−12 show functional group tolerance. A remote siloxy group does not interfere at all with the alkylation reaction (entry 10). Entry 11 indicates that the reaction is feasible even in the presence of a nearby electron-withdrawing siloxy group to give the product in acceptable yield. The neighboring amino function in the chloride does not affect much the reaction as shown for *N*-(2-chloroethyl)dimethylamine in entry 12.



19
94.0% ee

20
65% yield, 88.5% *ee*

The substitution reaction takes place with inversion of stereochemistry at the electrophilic carbon atom (eq 2). For instance, (*S*)-(1-chloroethyl)benzene **19** (94.0% ee) reacted with enamide **8** at 30−50 °C to give (*S*)-1,3-diphenylbutan-1-one **20** in 65% yield with 88.5% ee. We consider that the substitution itself occurred with a very high level of inversion of stereochemistry along with partial racemization of the benzylic chloride substrate.[9] Availability of a variety of chiral alkyl halides and enamides[10] suggests that the reaction offers a new opportunity for asymmetric synthesis.

Supporting Information Available: Details of the experimental procedure, characterization, and physical data of products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Yamamoto, Y.; Sasaki, N. *Stereochemistry of Organometallic and Inorganic Compounds*; Elsevier Science: New York, 1990; Vol. 4, pp 3−92. (b) Caine, D. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.: Pergamon Press: New York, 1991; Vol. 3, pp 1−64.

(2) (a) Stork, G.; Brizzolarra, A.; Laudesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207−222. (b) Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178−2180. (c) Stork, G.; Benaim, J. *J. Am. Chem.* Soc. **1971**, *93*, 5938−5639. (d) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, *17*, 3−6.

(3) (a) Stork, G.; Rosen, P.; Goldman, N. L. *J. Am. Chem. Soc.* **1961**, *83*, 2965−2966. (b) Spencer, T. A.; Britton, R. W.; Watt, D. S. *J. Am. Chem. Soc.* **1967**, *89*, 5727−5729. (c) House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361−2371.

(4) (a) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464−4465. (b) Kuwajima, I.; Nakamura, E. *J. Am. Chem. Soc.* **1975**, *97*, 3257−3258. (c) Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 1025−1030.

(5) (a) Paterson, I. *Tetrahedron Lett.* **1979**, 1519−1520. (b) Reetz, M. T.; Hüttenhain, S. H.; Walz, P.; Löwe, U. *Tetrahedron Lett.* **1979**, 4971−4974. (c) Reetz, M. T.; Walz, P.; Hübner, F.; Hüttenhain, S. H.; Heimbach, H.; Schwellnus, K. *Chem. Ber.* **1984**, *117*, 322−335.

(6) Nakamura, M.; Hatakeyama, T.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 11820−11825.

(7) See Supporting Information for details of the deprotonation and the alkylation procedure.

(8) Some other dialkyl amino derivatives gave comparable results: dimethylamino (87%), piperidyl (88%), pyrrolidyl (72%), and morpholyl (82%).

(9) Heald, K.; Williams, G. *J. Chem. Soc.* **1954**, 362−366.

(10) Nakamura, M.; Hatakeyama, T.; Hara, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 6362−6363.

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