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Soft Enolization of 3-Substituted Cycloalkanones Exhibits Significantly Improved Regiocontrol vs Hard Enolization Conditions

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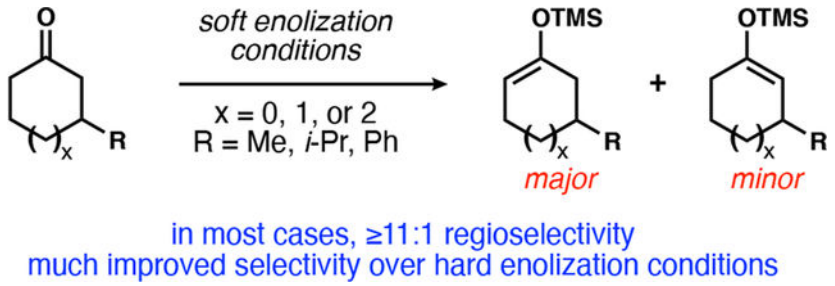
Abstract

Soft enolization conditions are revealed to be markedly better than the typically applied hard enolization protocols for regioselective enoxysilane formation from unsymmetrical 3-substituted cycloalkanones. Five-, six-, and seven-membered cycloalkanones each with either 3-methyl, 3-isopropyl, or 3-phenyl substituents were investigated and, in all but one case, regioselectivities were ≥11:1 for enolization away from the substituent. The selectivities observed are significantly improved over those obtained using strong anionic bases, and are complementary to the regiospecific enoxysilane formation derived from cycloalkenone conjugate addition/enolate silylation.

Graphical Abstract



Enoxysilanes are ubiquitous, high-value intermediates for organic synthesis.[1] They feature in powerful carbon–carbon bond forming reactions such as Mukaiyama aldol[2] or Mukaiyama–Michael[3] additions, and also behave as weak nucleophiles toward strongly electrophilic reagents (e.g. Br_2, *m*-CBPA, PhSCl, etc.).[4] Alternatively, enoxysilanes can be treated with certain nucleophiles, such as MeLi, $LiNH_2$, or fluoride sources to generate at will a reactive enolate species, often the same one from which they were initially

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Supporting Information

All experimental protocols for the synthesis of new compounds and for the synthesis of all enoxysilane products described herein, previously known or unknown. Full characterization data are provided for all new compounds.

The Supporting Information is available free of charge on the ACS Publications website.

formed.[5] Oxidation can also lead to the net dehydrogenation of the parent ketone, with palladium-catalyzed[6] and hypervalent-iodine-mediated[7] processes commonly used to generate enones. Enoxysilanes also undergo productive oxidative couplings to generate new C–C bonds.[8] Another valuable transformation is the direct conversion to alkenyl triflates with preservation of alkene position and geometry, thus permitting a range of cross-coupling reactions.[9] Finally, direct cross-coupling of enoxysilanes can be achieved.[10]

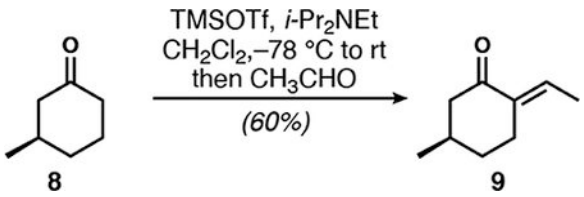
Ketone-derived enoxysilanes are typically prepared via three major reaction types: (1) from the corresponding ketone by enolization; (2) from an α-heteroatom-substituted ketone by reduction; or (3) from an α,β,-unsaturated enone via conjugate reduction/addition. While the latter two processes are regiospecific, the first protocol is the most common, and can have issues of regiochemical control for unsymmetrical ketones with similar substitution patterns on each side of the carbonyl carbon.

It is well-known that regioselectivity of enolization can in some cases be dictated by the choice of reaction conditions and the steric environment of the substrate. For instance, treatment of 2-substituted cycloalkanones under hard enolization conditions (e.g., LDA; TMSCl) selectively generates the kinetic, less substituted enoxysilane product, whereas with treatment under equilibrating conditions (e.g., Et_3N, TMSCl, DMF, heat) the thermodynamic, more substituted, enoxysilane is formed preferentially.[1] These selective methods are limited to unsymmetrical ketones whose substitution levels differ at the α-carbons.

A survey of the literature shows that the protocol most used for the formation of the $\Delta^{1,n}$-enoxysilanes from 3-substituted cycloalkanones is treatment with a strong base (most often LDA or LiTMP) to generate an enolate followed by trapping with a chlorotrialkylsilane (Scheme 1a). Although this procedure typically favors enolization away from the 3-substituent, regioisomeric mixtures of $\Delta^{1,n}$ (**2**) and $\Delta^{1,2}$ (**3**) products are formed, often with low to moderate selectivity, and are typically inseparable by silica gel chromatography.[11,12] It is well known that the $\Delta^{1,2}$ enoxysilane can generally be obtained regiospecifically from the corresponding α,β-unsaturated enone via conjugate addition of an organocuprate/hydride reagent or dissolving metal reduction, with subsequent trapping with chlorotrialkylsilane reagents (Scheme 1b.).[13,14] This communication describes a highly regioselective synthesis of enoxysilanes derived from 3-substituted cyclic ketones, wherein the application of experimentally simple soft enolization conditions vastly improves the regioselectivity "away" from the 3-substituent, compared with the more standard hard enolization conditions (Scheme 1c). As a result, it complements the regiospecific formation of enoxysilanes formed by enone conjugate addition/reduction. We demonstrate that this soft enolization protocol works for varying ring sizes and with substituents of different steric environments at C3. This advance is especially important in light of the difficulty of separation of the regioisomeric enoxysilanes—owing in equal measures to their similar polarities and instabilities—which leads to the formation of isomeric products in the subsequent step.

In the context of recent work in our laboratory toward the synthesis of the pseudopterosins,[15] we learned that (*R*)-3-methylcyclohexanone underwent a highly

regioselective Mukaiyama-type aldol condensation with acetaldehyde when the enoxysilane was formed *in situ* using soft enolization conditions (Eq. 1).



(1)

A careful study of the enolization portion of this reaction (Table 1) was undertaken. Application of the hindered strong base LiTMP with TMSCl was only moderately regioselective (3:1 *rr*, entry 1); this result was consistent with the ratio previously reported using LDA and TMSCl with the same substrate;[11b] more importantly, it served as a benchmark against which to compare future results. The initial enoxysilane formation corresponding to the Mukaiyama aldol condensation in Eq.1 was highly regioselective: the combination of Hünig's base (diisopropylethylamine) and TMSOTf led to a 13.5:1 mixture in favor of the $\Delta^{1,6}$ product (entry 2). The reactivity and selectivity were sensitive to the identity of the amine base. The less bulky triethylamine was not as selective as diisopropylethylamine (7.5:1 *rr*, entry 3); however, the very hindered PMP (1,2,2,6,6-pentamethylpiperidine) proved marginally less selective (entry 4). The amidine base DBU required heating for effective reaction and resulted in a decreased regioselectivity of 2.2:1 (entry 5). Unsurprisingly, the conditions that we identified in entry 2 are just as successful with TBSOTf, thus yielding the TBS alkenyl ether with a 14:1 *rr* (entry 6).[16]

With effective conditions (*i*-Pr_2NEt, 3.5 equiv and TMSOTf, 3.0 equiv at −78 °C in CH_2Cl_2) established, cyclopentanones, cyclohexanones, and cycloheptanones[17] with methyl, phenyl, and isopropyl C3-substituents were evaluated (Table 2). In the cyclopentanone series, an increase in regioselectivity was observed with an increase in the bulk of the substituent.[18,19] For the six- and seven-membered ring ketones, universally high selectivities (≥12:1) were observed. In all cases except for 3-methylcyclopentanone, the chromatographically isolated yields of pure material (as regioisomeric mixtures) were high, and closely mirrored the yields calculated by NMR spectroscopy with integration against an internal standard. To ensure that soft enolization was advantageous with all ring sizes, we also evaluated standard hard enolization conditions for 3-methylcyclopentanone and 3-methylcycloheptanone. The regioselectivity regioselectivity was again greatly enhanced upon switching from hard enolization to soft enolization, (1.5:1 to 5.8:1 and 2.6:1 to >20:1), respectively. The near perfect selectivities in all three cycloheptanone cases is noteworthy.[17]

Of course, in nearly all instances, enoxysilane formation would be coupled with a subsequent synthetically useful transformation.[1] We therefore document the use of these intermediates in (a) Mukaiyama aldol addition (Scheme 2a)[2]; (b) enolate regeneration and alkylation (Scheme 2b)[5]; and dehydrogenation (Scheme 2c)[7]. The products of each of these reactions is obtained in high yield over the two steps, wherein chromatographic purification of the enoxysilane was not required.

The selectivity observed in enoxysilane formation was surprising, given the seemingly small amount of steric differentiation, especially in methyl-substituted cases. However, the simplest explanation for the selectivity is a steric argument, which is consistent with moderate increases in selectivity as the 3-substituent size increases,[18,19] and with the notable increase in selectivity upon going from triethylamine to Hünig's base. Because of the ubiquity of Hünig's base, we opted against evaluating multiple more hindered, less omnipresent bases, given the already quite remarkable selectivities observed.

Given the well-established ability to generate 3-substituted $\Delta^{1,2}$-enoxysilanes regiospecifically from conjugate reactivity of cycloalkenones, it is noteworthy that highly selective access to the other regioisomer of enoxysilanes derived from C3-substituted cycloalkanones has been largely unattainable until now. We have identified operationally trivial conditions for the selective formation of this regioisomer with good scope across five-, six-, and seven-membered cycloalkanones. Further, we know that this reaction works well on a preparative scale, having conducted the reaction sequence shown in Eq. 1 on an 87 mmol scale.[15] The simple soft enolization protocol described here should, as a result, be readily adopted in chemical synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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12. There appears to be a marked preference for regiocontrolled enolization away from fused rings in bicyclic cyclohexanones, as stated by Stork, and originally observed by Sondheimer, even with hard enolization conditions:(a)Stork G; Yamashita A; Hanson RM; Phan L; Phillips E; Dubé D; Bos PH; Clark AJ; Gough M; Greenlee ML; Jiang Y; Jones K; Kitamura M; Leonard J; Liu T; Parsons PJ; Venkatesan AM Synthetic Study toward Total Synthesis of (±)-Germine: Synthesis of (±)-4-Methylenegermine. Org. Lett 2017, 19, 5150–5153. 10.1021/acs.orglett.7b02434. [PubMed: 28876074] (b)Mazur Y; Sondheimer F Synthesis and Reactions of Ring A Methylated Saturated Steroids. J. Am. Chem. Soc 1958, 80, 5220–5229. 10.1021/ja01552a051

13. For a pertinent example, see:Jones TK; Denmark SE A General Method for the Preparation of g-Substituted Cyclohexenals and Cycloheptenals. J. Org. Chem 1985, 50, 4037–4045. 10.1021/jo00221a015

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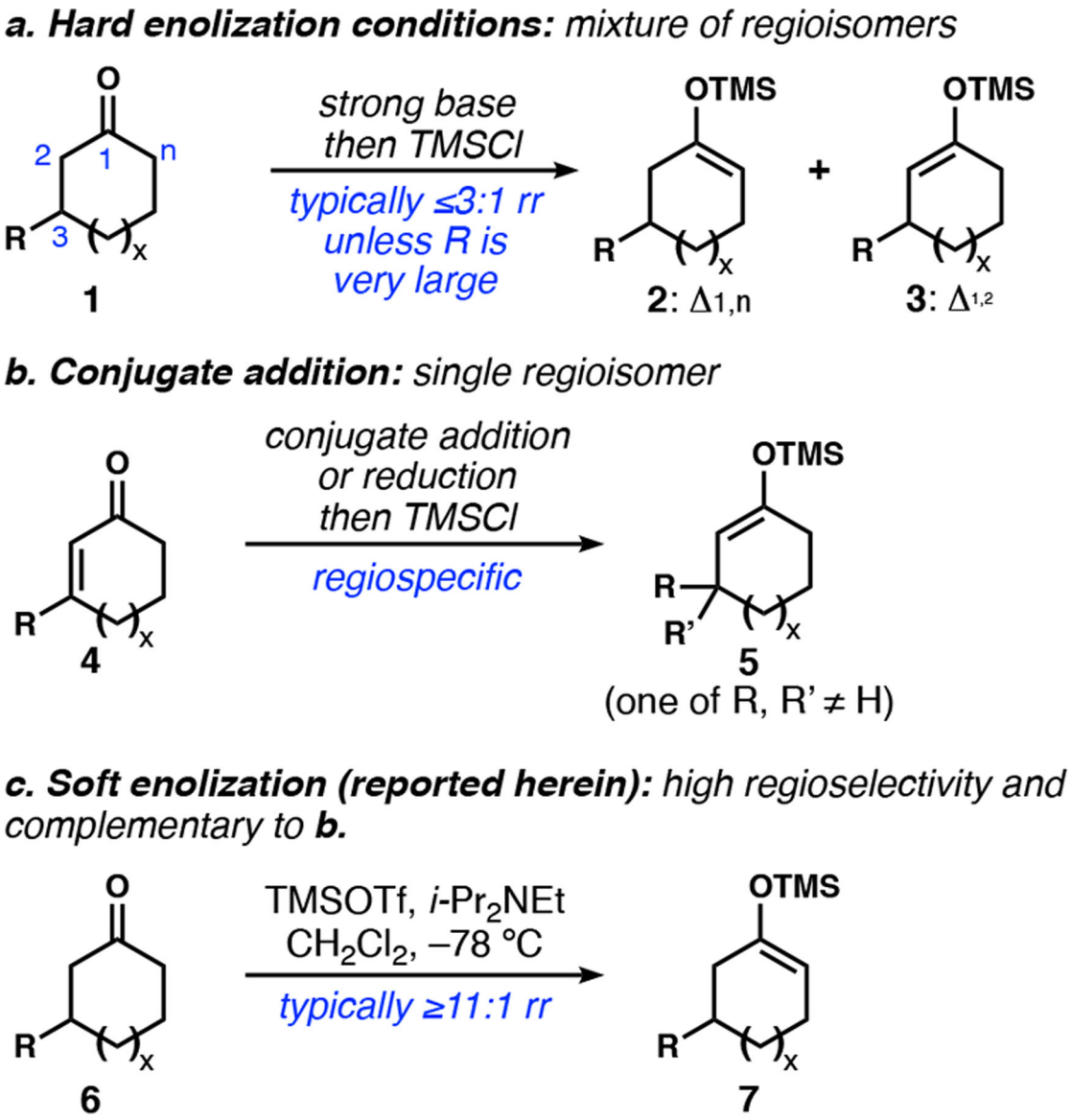
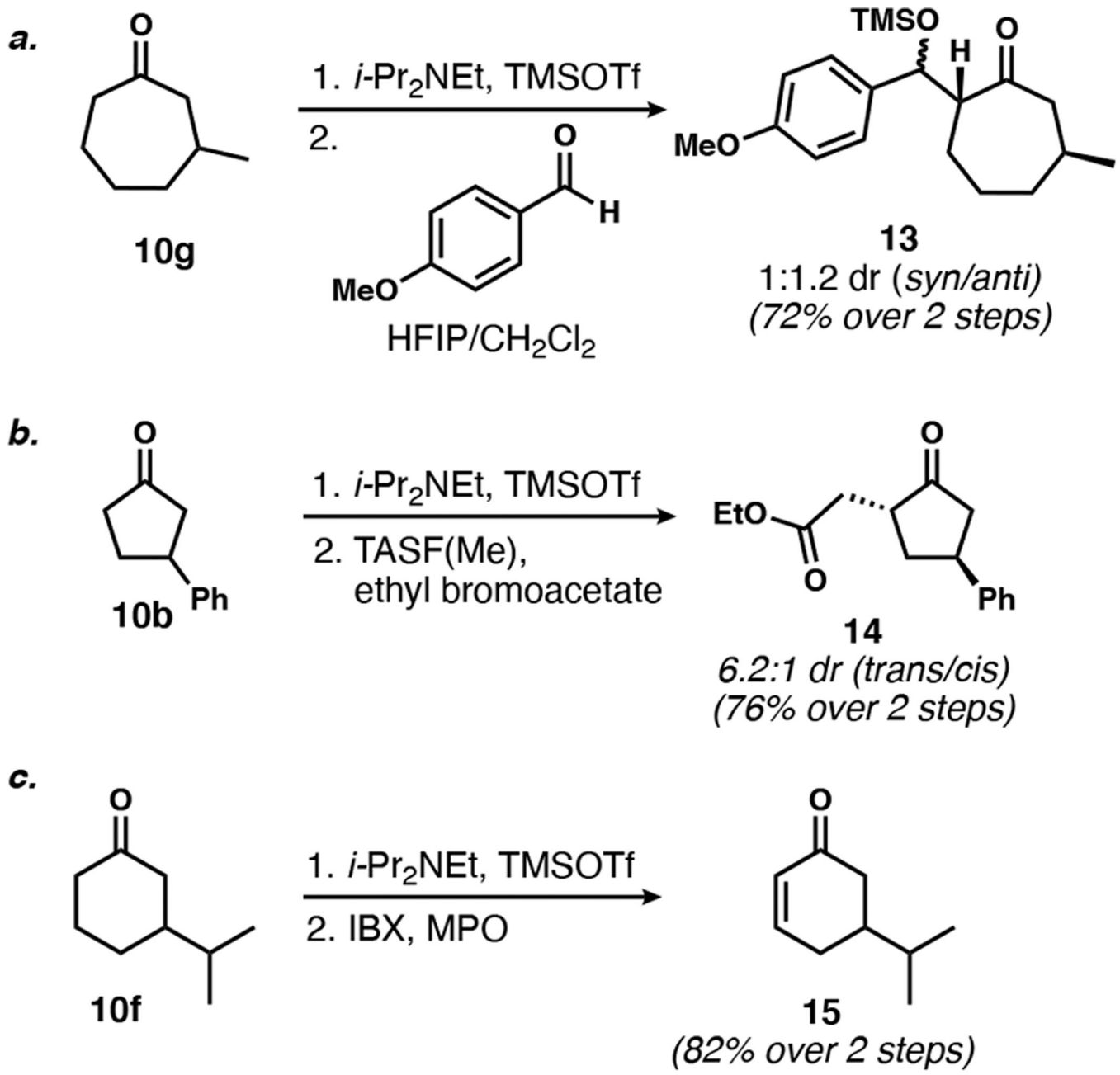
16. In some cases, using soft enolization on 3-substituted cycloalkanones with no other substituents, no regiochemical ratios are provided, and the enoxysilane is carried forward. See, for example:Tsukamoto H; Nakamura S; Tomida A; Doi T; Scalable Total Syntheses and Structure-

Activity Relationships of Haouamines A, B, and Their Derivatives as Stable Formate Salts. Chem. Eur. J 2020, 26, 12528–12532. 10.1002/chem.202001756 [PubMed: 32291830]

17. Surprisingly, we could not find any examples of enoxysilane formation from unsymmetrical 3-substituted cycloheptanones that were particularly relevant to the current study.
18. These results do not exactly track with A values, for which the values for isopropyl and phenyl are 2.15 and 3.00, respectively. While it is possible that A values are simply not the most appropriate measure of “size” in this context, it is also conceivable that the presence of the phenyl ring detracts from selectivity by the mechanism put forth by Posner in ref 13a.
19. Highly selective enolization away from C3 quaternary centers has been documented. See, for example: ref 14b and:Tian X; Huters AD; Douglas CJ; Garg NK Concise Synthesis of the Bicyclic Scaffold of *N*-Methylwelwitindolinone C Isothiocyanate via an Indolyne Cyclization. Org. Lett 2009, 11. 2349–2361. 10.1021/ol9007684. [PubMed: 19432408]



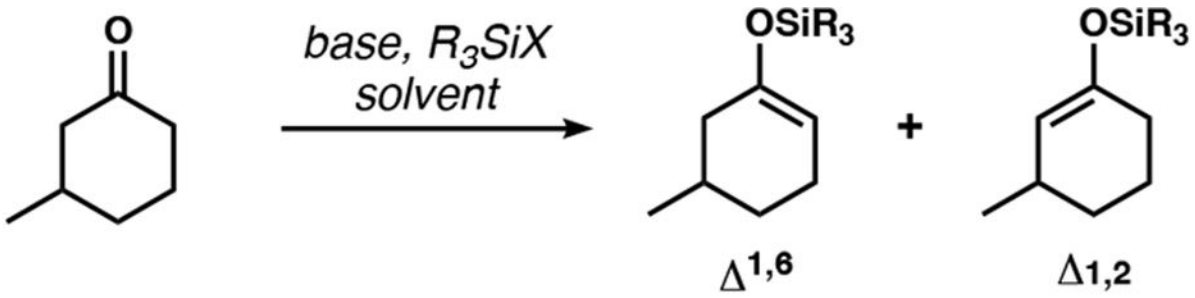
Scheme 1.
Methods for synthesizing TMS-alkenyl ethers from 3-substituted cyclohexanones



Scheme 2.
Synthetic utility of enoxysilane intermediates

Table 1.

Initial studies of the regioselectivity in enoxysilane formation[a]



Entry	Base	R_3SiX	Solvent	$\Delta^{1,6}:\Delta^{1,2}$[b]
1[c]	LiTMP	TMSCl	THF	3:1
2	*i*-Pr_2NEt	TMSOTf	CH_2Cl_2	13.5:1
3	Et_3N	TMSOTf	CH_2Cl_2	7.5:1
4	PMP[d]	TMSOTf	CH_2Cl_2	12:1
5[e]	DBU	TMSCl	CH_2Cl_2	2.2:1
6	*i*-Pr_2NEt	TBSOTf	CH_2Cl_2	14:1

[a] 0.5 mmol ketone, [ketone] = 0.2 M, −78 °C, 1 h, 3.5 equiv. base, 3 equiv. Lewis acid.

[b] Determined by ^1H analysis of unpurified reaction mixture.

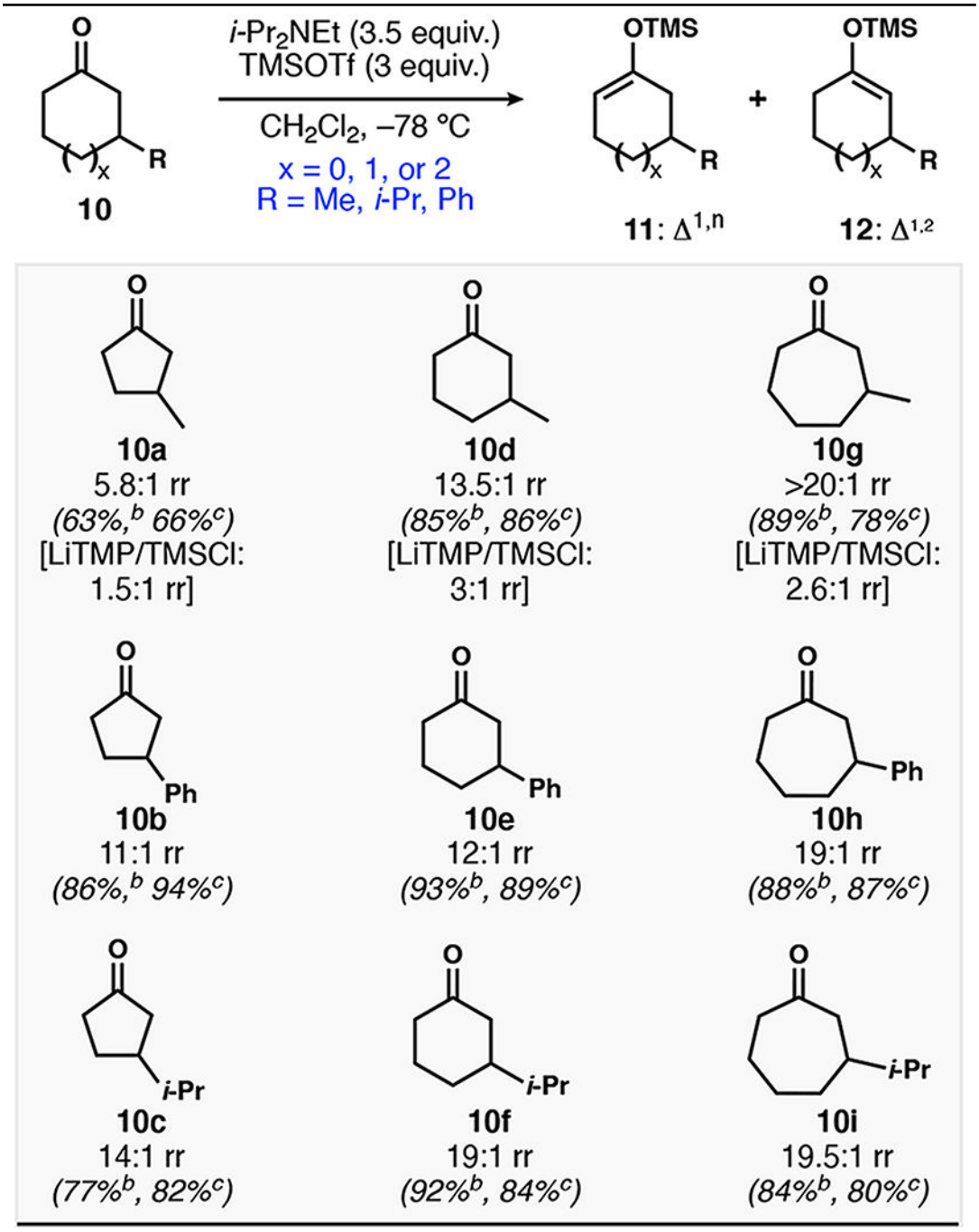
[c] 1.4 equiv. BuLi, 1.5 equiv. TMP, 1.4 equiv. TMSCl.

[d] PMP = 1,2,2,6,6-pentamethylpiperidine.

[e] Heating to 40 °C was required for reactivity, 1.2 equiv. DBU, 1.1 equiv. TMSCl.

Table 2.

Scope of regioselective enoxysilane formation[a]



[a]0.5 mmol scale; [**10**] = 0.2 M; yields reported as a mixture of regioisomers; regioselectivies determined by ^{1}H NMR analysis of unpurified reaction mixtures.

[b]Isolated yield reported after column chromatography on basic alumina.

[c]NMR yield reported using 1,3,5-trimethoxybenzene (20 mol%) as an internal standard.