conversion by removal of ethylene gas,[3] ROIMP gives high conversion under gentle reflux conditions for two reasons. First, ROMP of monomer B is efficient in making the initial homopolycycloalkene chains. Second, the formation of 1,2-disubstituted α,β-unsaturated carbonyl compounds is thermodynamically favored by more than 3 kcal mol^{-1} per bond.[11] These enthalpic factors, combined with the loss of ethylene, drive the reaction to high conversion. Furthermore, the unfavorable oligomerization of diacrylates, in which the intermediate is an unstable enoic carbene, leads to high A,B-alternation.[12] Therefore, ROIMP has benefits of both chain-growth and step-growth polymerization, leading to high molecular weight and high selectivity.

To optimize conversion, other polymerization conditions were investigated. It was found that 0.1–0.5 M solutions in CH_2Cl_2 at 40 °C give the best results. In contrast to ROMP, increasing the concentration beyond 0.5 M resulted in lower conversion. Switching to toluene or 1,2-dichloroethane as solvent also gave lower conversion at either 40 °C or 60 °C. Although there is precedence for CH_2Cl_2 being the best solvent for cross metathesis of functionalized olefins,[12] the concentration dependence for ROIMP is somewhat surprising, since concentrations of 0.1–0.5 M are considered dilute conditions for conventional step-growth-polymerization reactions.

Controlling the molecular weight of polymers is a very important issue since polymers with different molecular weights often exhibit different properties. For alternating copolymers produced by ROIMP, molecular weight can be roughly controlled by changing the relative stoichiometry of the two monomers. For example, using 0.96 equivalents of cyclooctene to 1.0 equivalent of hydroquinone diacrylate gave a copolymer of 17800 g mol^{-1} with 98% A,B-alternation (PDI = 1.64), whereas a copolymer of 45200 g mol^{-1} and 95.5% A,B-alternation (PDI = 1.69) was obtained by increasing the cyclooctene to 1.06 equivalents. These results show that when compared with the 1:1 case (Table 1, entry 7), an excess of hydroquinone diacrylate shortens the polymer chain, but an excess of cyclooctene gives higher molecular weight as a result of the oligomeric blocks of polycyclooctene.

In conclusion, we have demonstrated a new general method for synthesizing highly alternating copolymers by olefin metathesis. The high conversion and degree of alternation arise from the thermodynamically driven selective bond formation between diacrylates and cycloalkenes.

Experimental Section

Full procedures and characterization data are given in the Supporting Information.

Representative procedure (Table 1, entry 1): Catalyst **3** (2.7 mg) and cyclooctene (65 μL, 0.45 mmol) were added to a flask charged with 1,4-butanediol diacrylate (90 mg, 0.45 mmol) in CH_2Cl_2 (2 mL). Quick degassing by dynamic vacuum was conducted and the flask was fitted with a condenser and heated at reflux under argon for 6 h. The product (108 mg, 84%) was precipitated into methanol. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.93 (dt, J = 7.2, 15.9 Hz, 1H), 5.77 (d, J = 15.9 Hz, 1H), 4.13 (br s, 2H), 2.12 (m, 2H), 1.73 (m, 2H), 1.43 (m, 2H), 1.30 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 149.6, 121.3, 64.0, 32.5, 29.3, 28.2, 25.8 ppm.

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Polymerase Recognition of Unnatural Base Pairs**

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The storage and replication of genetic information requires bases that pair stably and selectively in duplex DNA and are also good substrates for DNA polymerases. Though the four natural bases pair by hydrogen bonding, there is no reason to assume that the pairing of two unnatural bases could not be driven by other intermolecular interactions, for example, those based on hydrophobicity.[1,2] To investigate this issue, a wide variety of hydrophobic base pairs has been characterized.[3,4] For example, ICS (see Figure 1) and its derivative PICS, with a propynyl group at C7, form self-pairs in duplex DNA that are as stable as natural base pairs. The unnatural triphosphates are also inserted opposite themselves in the

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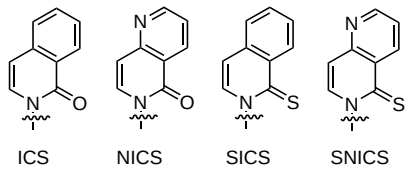


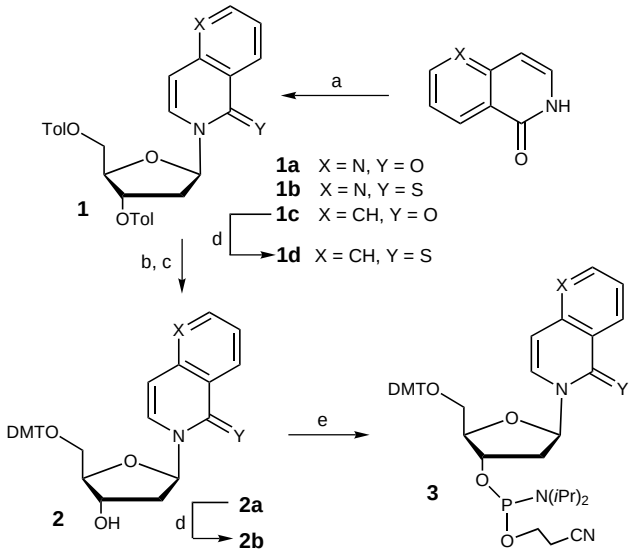
Figure 1. Representation of the unnatural nucleobases used.

template (self-pair synthesis) with reasonable efficiency and selectivity by polymerases.[4] However, with all of the polymerases and nucleobases examined to date, replication has been limited by inefficient continuation of primer extension after synthesis of the unnatural self-pair.[4] One solution to this problem is to use a binary polymerase system where different polymerases mediate incorporation and extension.[3] Alternatively, if nucleobases are to be generated that can be incorporated and extended by a single polymerase, ultimately in vivo, the determinants of efficient base pair incorporation and extension must be better understood. To this end, we have synthesized and analyzed several ICS analogues and herein report three that efficiently form self-pairs and are also more efficiently extended than the ICS self-pair by the exonuclease-deficient Klenow fragment of DNA polymerase I from *E. coli* (KF).

To find an improved substrate for DNA replication, we synthesized three analogues of ICS with heteroatom substitutions (Figure 1). The effects of a permanent dipole oriented along the long axis of the ICS scaffold was examined with NICS. To further vary the polarizability as well as the hydrogen bond acceptor substituent at C10, we synthesized the sulfur-containing analogues SICS and SNICS.

Each nucleoside was synthesized as shown in Scheme 1 (see also the Supporting Information). The starting 1,6-naphthyridin-5(6*H*)-one was synthesized based on a published four-step protocol.[5] For the 6-aza analogues, the Lewis acid catalyzed N-glycosidic bond formation was found to proceed more efficiently with a stoichiometric loading of $SnCl_4$, possibly because of chelation of the catalyst by the N6 atom. Compound **1a** was obtained as a mixture of β and α anomers which were separated by preparative TLC after protection of the hydroxy group at C5 with di(*p*-methoxyphenyl)phenylmethyl chloride (DMT). The analogues SICS and SNICS, which contain a thio group at C10, were synthesized from the corresponding lactams using Lawesson's reagent.[6,7] The synthesis of ICS has already been described.[4] Each DMT-protected nucleoside was converted into the corresponding phosphoramidite and incorporated into oligonucleotides with an ABI 392 DNA/RNA synthesizer. The corresponding triphosphates were synthesized as described.[4]

The thermal stability of the ICS analogues was evaluated by determining the melting temperature (T_m) of duplex DNA containing the SICS:SICS, NICS:NICS, or SNICS:SNICS self-pairs (Table 1). As reported previously, the ICS self-pair is as stable as a dA:dT pair in the same sequence



Scheme 1. Synthesis of the unnatural nucleobases. a) Bis-TMS acetamide, RT, **4**, then chloroglycoside, $SnCl_4$, 0 °C; b) 0.5 M NaOMe, MeOH, RT; c) DMTCl, pyridine, RT; d) Lawesson's reagent, toluene, reflux; e) diisopropylchlorophosphoramidite, Hünig's base, CH_2Cl_2, 0 °C. DMT = di(*p*-methoxyphenyl)phenylmethyl, Tol = *p*-methylbenzoyl, TMS = trimethylsilyl.

context (T_m = 59.3 and 59.2 °C for ICS:ICS and dA:dT, respectively). Thio substitution at C10 results in a 5.5 °C decrease in T_m for the SICS self-pair. Aza-substitution at position 6 of the ICS framework leads to only a 3.2 °C destabilization for the NICS self-pair (relative to the ICS self-pair). Surprisingly, the SNICS analogue containing both heteroatom substitutions forms a self-pair that is more stable than either analogue with a single substitution. The SNICS self-pair was only 2.2 °C less stable than the ICS self-pair. The thermal selectivity of each self-pair is also high.

The ICS, SICS, NICS, and SNICS phosphoramidites were incorporated into a 45-mer oligonucleotide and used with the corresponding triphosphates to investigate the KF-mediated synthesis of the unnatural self-pairs under steady-state conditions (Table 2).[4] The ICS self-pair is synthesized with an efficiency (k_{cat}/K_M) of $2.0 \times 10^4\,M^{-1}min^{-1}$, which agrees well with previously reported data.[4] Relative to ICS, replacement of C6 with nitrogen in NICS resulted in about a twofold decrease in insertion efficiency. However, thio substitution at C10 provided a marked increase in efficiency; the SICS self-pair was synthesized 80-fold more efficiently than ICS. The

Table 1. Denaturation temperatures (T_M) for NICS, SICS, and SNICS.[a]

5′-dGCGTAC**X**CATGCG
3′-dCGCATG**Y**GTACGC

X	Y	T_M [°C]	X	Y	T_M [°C]	X	Y	T_M [°C]
NICS	NICS	56.1 ± 0.14	SICS	SICS	53.8 ± 0.01	SNICS	SNICS	57.1 ± 0.14
NICS	dA	52.4 ± 0.68	SICS	dA	52.0 ± 0.03	SNICS	dA	51.8 ± 0.03
NICS	dT	51.0 ± 0.03	SICS	dT	52.5 ± 0.03	SNICS	dT	52.3 ± 0.14
NICS	dC	47.5 ± 0.52	SICS	dC	48.3 ± 0.04	SNICS	dC	49.4 ± 0.13
NICS	dG	48.6 ± 0.03	SICS	dG	48.6 ± 0.02	SNICS	dG	50.2 ± 0.18

[a] The values for T_M were determined under the following conditions: 10 mM piperazine-*N*,*N*′-bis(2-ethanesulfonic acid) (PIPES), 10 mM $MgCl_2$, 100 mM NaCl, pH 7.

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Table 2. The efficiency of incorporation of unnatural and natural triphosphates opposite unnatural bases in the template.

```
5'-dTAATACGACTCACTATAGGGAGA
3'-dATTATGCTGAGTGATATCCCTCTXGCTAGGTTACGGCAGGATCGC
                           ↓ dYTP
5'-dTAATACGACTCACTATAGGGAGAY
3'-dATTATGCTGAGTGATATCCCTCTXGCTAGGTTACGGCAGGATCGC
```

X	Y	k_{cat} [min^{-1}]	K_M [μM]	k_{cat}/K_M [M^{-1}min^{-1}]
ICS	ICS	1.7 ± 1.1	86 ± 27	2.0×10^4
	A	0.04 ± 0.01	7.7 ± 2.7	5.7×10^3
	C	n.d.[a]	n.d.[a]	5.9×10^1
	G	0.2 ± 0.1	95 ± 32	2.3×10^3
	T	0.5 ± 0.2	147 ± 39	3.5×10^3
NICS	NICS	0.8 ± 0.3	76 ± 3	1.1×10^4
	A	0.20 ± 0.04	26 ± 6	7.7×10^3
	C	0.27 ± 0.01	2.7 ± 1.8	1.0×10^5
	G	0.32 ± 0.08	62 ± 7	5.2×10^3
	T	2.1 ± 0.2	129 ± 56	1.6×10^4
SICS	SICS	5 ± 1	3.2 ± 3.1	1.6×10^6
	A	1.6 ± 0.6	45 ± 2	3.7×10^4
	C	n.d.[a]	n.d.[a]	1.3×10^2
	G	13 ± 3	85 ± 9	1.5×10^5
	T	2.7 ± 1.2	194 ± 66	1.4×10^4
SNICS	SNICS	3.8 ± 1.0	3.4 ± 3.2	1.1×10^6
	A	1.31 ± 0.06	18 ± 10	7.4×10^4
	C	0.11 ± 0.02	72 ± 40	1.5×10^3
	G	0.9 ± 0.1	35 ± 8	2.5×10^4
	T	0.6 ± 0.1	97 ± 40	6.1×10^3

[a] n.d. = not determined. The reaction was too inefficient to obtain accurate measurements.

presence of N6 and thio substitution at C10 together in SNICS resulted in an unnatural base pair that is also efficiently synthesized with $k_{cat}/K_M = 1.1 \times 10^6\,M^{-1}min^{-1}$ (100-fold increase relative to NICS). The SICS and SNICS self-pairs are synthesized 30- to 50-fold less efficiently than a natural base pair in the same sequence context. The enhanced insertion efficiency imparted by thio substitution at C10 in SICS and SNICS resulted from modest increases in k_{cat} (3- to 5-fold) and more substantial decreases in K_M (ca. 25-fold).

The fidelity of unnatural self-pair synthesis was also determined by measuring the efficiency of insertion of each natural triphosphate opposite the unnatural bases in the template. In agreement with previously reported data, the most efficiently synthesized mispair with ICS came from the insertion of dATP ($k_{cat}/K_M = 5.7 \times 10^3\,M^{-1}min^{-1}$), which resulted in a selectivity of only 3.5-fold. The slightly decreased efficiency of NICS self-pair synthesis, along with the efficient insertion of dCTP opposite the base ($k_{cat}/K_M = 1.0 \times 10^5\,M^{-1}min^{-1}$), provided poor selectivity for the NICS self-pair. The triphosphate dGTP was efficiently inserted opposite SICS ($k_{cat}/K_M = 1.5 \times 10^5\,M^{-1}min^{-1}$), but less so than d(SICS)TP ($k_{cat}/K_M = 1.6 \times 10^6\,M^{-1}min^{-1}$), resulting in an 11-fold increase in selectivity for this self-pair. The highest fidelity was found for the SNICS self-pair, which showed an efficiency that was at least 15-fold greater than that of all possible mispairs.

The unnatural phosphoramidites were also incorporated into a 24-mer primer as the 3′-terminal nucleotide (Universal solid support, Glen Research). The primer was used, in conjunction with the 45-mer template, as a substrate for DNA synthesis (Table 3). The efficiency and selectivity of KF-mediated insertion of dCTP opposite dG (correct extension) was determined under steady-state conditions.[4] The ICS self-pair is extended inefficiently ($k_{cat}/K_M = 1.8 \times 10^3\,M^{-1}min^{-1}$, compared to $5.4 \times 10^7\,M^{-1}min^{-1}$ for a dA:dT pair in the same sequence context). Relative to ICS, replacement with N6 and thio substitution at C10 each enhanced extension, resulting in an increase in the efficiency of dCTP insertion of 2.0 and 3.5-fold, respectively, for the NICS and SICS self-pairs. Modification of the ICS scaffold at both positions resulted in a SNICS self-pair that was extended with an efficiency of $2.2 \times 10^4\,M^{-1}min^{-1}$, a 12-fold increase over that for the ICS self-pair. While the SNICS self-pair is extended less efficiently than is a natural base pair, this represents significant progress toward a replicable ICS scaffold.

The origins of the enhanced extension efficiency were different for each heteroatom substitution. Both 6-aza substitution in NICS and C10-thio substitution in SICS resulted in an elevated k_{cat} (7- to 10-fold) relative to the ICS self-pair; however, the K_M for dCTP was also increased (3-fold in each case). The effects of the substitutions were quite different when combined in the SNICS unnatural base. The self-pair was extended with both an increased k_{cat} and a decreased K_M (5- and 2.5-fold, respectively) relative to the ICS self-pair. In all cases, insertion of dGTP, dATP, and dTTP opposite dG was found to be negligible ($k_{cat}/K_M < 5 \times 10^2\,M^{-1}min^{-1}$), demonstrating that extension of unnatural base pairs proceeds with reasonable fidelity.

The SNICS self-pair represents significant progress toward expansion of the genetic alphabet. Moreover, the thermodynamic and kinetic data presented above aid in the determination of unnatural base pair properties that mediate their stability and facilitate their replication. The stability of the self-pairs formed between the ICS derivatives are all reduced relative to that of the ICS self-pair, though only marginally in the case of SNICS. The decreased stability is unlikely to be the result of solvation effects as each position is expected to be fully accessible to solvents in either single-stranded or duplex

Table 3. The efficiency of the correct extension of unnatural self-pairs.[a]

```
5'-dTAATACGACTCACTATAGGGAGAX
3'-dATTATGCTGAGTGATATCCCTCTXGCTAGGTTACGGCAGGATCGC
                           ↓ dCTP
5'-dTAATACGACTCACTATAGGGAGAXC
3'-dATTATGCTGAGTGATATCCCTCTXGCTAGGTTACGGCAGGATCGC
```

Unnatural self-pair	k_{cat} [min^{-1}]	K_M [μM]	k_{cat}/K_M [M^{-1}min^{-1}]
ICS	0.15 ± 0.06	82 ± 22	1.8×10^3
NICS	1.0 ± 0.2	257 ± 155	3.7×10^3
SICS	1.5 ± 0.3	242 ± 78	6.3×10^3
SNICS	0.76 ± 0.04	34 ± 16	2.2×10^4

[a] Incorporation of dCTP opposite dG in the template. The extension with an incorrect natural dNTP was in every case less than $3 \times 10^2\,M^{-1}min^{-1}$.

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DNA (through the duplex major groove or minor groove).[8] Increased polarizability of the nucleobase is also unlikely to result in the destabilization as it is expected to enhance interbase stacking.[8] The observed destabilization may result from unfavorable dipole–dipole interactions with flanking bases in the case of NICS, and increased steric repulsion between the opposing sulfur atoms of the self-pairs of SICS and SNICS.

Sulfur substitution in SICS and SNICS results in self-pairs that are synthesized two orders of magnitude more efficiently than ICS and NICS. As described above, this increase in efficiency resulted from a modest increase in k_{cat} (3- to 5-fold) and a more substantial decrease in unnatural triphosphate binding (25-fold). Speculation about the potential origins of these effects may be based on the available structures of the type I DNA polymerases from *B. stearothermophilus* and *T. aquaticus*.[9,10] These polymerases are highly homologous to KF, both structurally and functionally. In these structures the triphosphate hydrogen bond acceptor, located at a position analogous to that of the C10 sulfur atom in the unnatural bases, interacts with the template base as well as a water molecule. Based on the structures, the aromatic ring of the unnatural triphosphate is also expected to pack with Tyr766. It therefore seems likely that sulfur substitution may increase the binding of the unnatural substrate through favorable sulfur–sulfur interactions or through electronic effects which favor hydrophobic packing.

The crystal structures also reveal information that may be relevant to the extension rates that are increased by an order of magnitude. The nucleobase at the primer terminus packs against the base of the incoming triphosphate, and along with the template base is tightly packed by hydrophobic side chains of the protein, which is thought to exert a geometrical selection against the aberrant structures of mispaired bases. The structures also reveal sequence-independent hydrogen bonds between the polymerase and the purine N3 or pyrimidine O2 atoms of the natural bases at the primer terminus. Failure of the unnatural DNA base pair to suitably engage the protein by any of these interactions may result in a misaligned 3′-OH primer terminus which is unable to act as an efficient nucleophile during the extension step. The higher extension efficiency that results from C10-thio substitution may therefore derive from improved packing interactions, structural or electronic changes owing to interpair sulfur–sulfur interactions, or altered hydrogen bonding with protein side chains in the developing minor groove.

Replication of DNA containing unnatural base pairs requires that the base pairs be stable as well as efficiently synthesized and then extended by a DNA polymerase. We have demonstrated that both of these steps may be optimized by heteroatom substitution. The SNICS self-pair is synthesized 55-fold more efficiently and 5-fold more selectively and is extended 12-fold more efficiently than its parent ICS self-pair. Not only does this represent significant progress towards a replicable unnatural base pair, it implies that further improvement in insertion and extension should be possible with further modification of the bases.

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Hierarchically Ordered Silica Mesophases Using Mixed Surfactant Systems as Templates**

An-Wu Xu,* Yue-Peng Cai, Hua-Xin Zhang, Li-Zhi Zhang, and Jimmy C. Yu

Since the discovery of silica mesophases,[1,2] surfactant-templated syntheses based on the hydrolysis and crosslinking of inorganic precursors (I) at the surfaces of supramolecular surfactant (S) assemblies have been used to prepare a variety of hexagonal, cubic, or lamellar mesophases through five pathways: S^+I^-, S^-I^+, $S^+X^-I^+$, $S^-M^+I^-$, and S^0I^0 (or N^0I^0) (X^- = counterion, M^+ = metal ion, N = polyethylene oxide).[3–16] Several methods are now available for the preparation of ordered structures at different length scales, such as micro-, meso-, and macroporous materials.[17,18] However, the preparation of hierarchically ordered structures in a single body, such as seen in diatoms in nature, has remained an experimental challenge.[17]

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