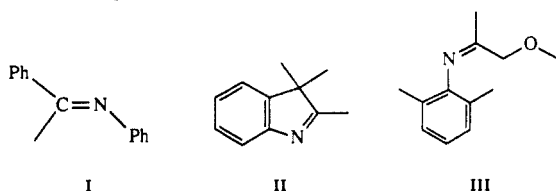


Table I. Hydrogenation of Imines 1-3 Catalyzed by $[\text{Ir}(\text{P-P})\text{H}_2]_2$

entry	S	P-P	S/ $[\text{Ir}_2]$	H_2 (bar), T (°C)	time (h)	ee (%)
1	I	(-)-BDPP	1000	40, 30	2	40 (S)
2	I	(+)-DIOP	1000	28, 30	5	11 (S)
3	II	(-)-BDPP	1000	40, 30	43	80 (+)
4	II	(+)-DIOP	1000	40, 30	21	51 (-)
5	II	(-)-NORPHOS	1000	40, 30	13	47 (-)
6	III	(+)-DIOP	1000	40, 30	8	54 (S)
7	III	(+)-DIOP	4000	100, 20	40	63 (S)
8	III	(-)-BDPP	1000	40, 30	6.5	34 (R)
9	III	(-)-NORPHOS	1000	40, 30	4	25 (S)
10	III	(+)-BINAP	1000	40, 30	145	22 (S)

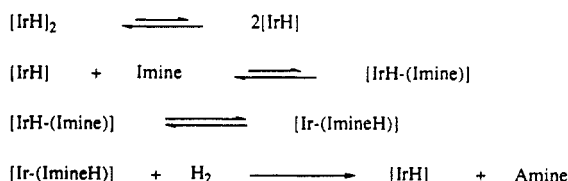
^a All reactions were performed in a stainless steel autoclave using 7.83×10^{-3} mmol of complex in 10 mL of THF/ CH_2Cl_2 (3/1, v/v). Reaction time given above corresponds to 99-100% conversion (GC analysis). The enantiomeric excesses of purified amines are measured by optical activity for reduced I (ref 7) and III (ref 2a) and by ^1H NMR (300 MHz) for reduced II (the absolute configuration of this compound has not been determined) using (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol as chiral shift reagent; the sign of optical rotation ($[\alpha]_D^{20}$ Na, 20 °C) indicated here was measured in hexane.

in both the rate and enantioselectivity of this hydrogenation. **1a** can be recovered unchanged after reduction of III and has been recycled, and further, the catalysts show high chemoselectivity (similar to that found for $\text{Li}[\text{Ir}(\text{P-P})\text{I}_4]_2$), notably not reducing ketones or simple olefins.



When catalytic hydrogenation (40 bar, THF/ CH_2Cl_2) of 200 equiv of III is carried out with a 1/1 catalyst mixture of **1a** and **1a'**, recovery and analysis of the dimers after completion of the reaction shows that extensive but, importantly, *incomplete* scrambling has occurred. Crossed dimer formation also occurs at the same rate in the absence of imine and/or hydrogen and is *first order* in **1a** ($t_{1/2} \approx 11$ h). This observation is concentration independent and thus is only consistent with a dissociative mechanism. However, the initial rate of reduction in the catalytic reaction shows a dependence on $[\text{1a}]^{1/2}$. This indicates that the dimer is equilibrating with a small quantity of monomer and monomer/imine complex, which are the active species on the hydrogenation catalytic cycle, and that this cycle turns more rapidly than the reconversion of monomer back into dimer. However we have been as yet unable to isolate the postulated monomer/imine complexes, perhaps because of their low formation constants, but similar compounds have been synthesized by using chelating imines.⁸

The hydride ligands of **1a** do not directly exchange with D_2 . Further, no discernible isotope effect is observed in deuteration experiments under the catalytic conditions described above, and **1a** is recovered with partial but not total deuteride incorporation. These observations confirm that only a small quantity of monomer is active during catalysis at a given instant. The ^1H and ^2H NMR spectra of deuterated III show that addition has occurred almost exclusively (>95%) on the $\text{C}=\text{N}$ bond, indicating that reduction does not pass by the enamine tautomer.



In summation we note that (1) an equilibrium is established between the dimer, the monomer, and the Ir-imine complex with the dimer predominating; (2) in the catalytic cycle, the hydride transfer⁹ and the heterolytic activation of hydrogen¹⁰ are un-

doubtedly both slow steps, accounting for the fractional kinetic dependence found both on substrate concentration and hydrogen pressure; and (3) the enantioselectivity results from either imine complexation or insertion (or both), the effect of H_2 pressure (>25 bar) not being significant. Attempts to understand the origin of enantioselection in this well-defined catalytic system and further details of the mechanism are under study so that higher chiral discrimination may be achieved.

Acknowledgment. We thank Drs. F. Spindler and H.-U. Blaser (Ciba-Geigy Company) for many helpful discussions. Ciba-Geigy Company is gratefully acknowledged for a graduate fellowship to Y.N.C.C. and financial support of this work.

(9) Slow H/D exchange has been observed when $[\text{Ir}(\text{DIOP})\text{D}_2]_2$ was mixed with benzylideneaniline, which is also a reducible imine; $\text{IrD} + \text{PhCH}=\text{NPh} \rightarrow \text{IrH} + \text{PhCH}=\text{NPh}$.

(10) An Ir(III)-amido 16e complex was found to react with molecular hydrogen to give Ir(III)-H and amine, respectively: Fryzuk, M. D.; MacNeil, P. A.; Rettig, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 2803.

Atom Transfer Addition, Annulation, and Macrocyclization Reactions of Iodomalnonitriles

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Iodomalonic esters are members of a growing class of reagents that can be used as precursors in atom transfer addition,^{2,3} cyclization,⁴ and annulation⁵ reactions. However, a detailed study⁴ revealed at least two significant limitations of iodomalonic esters: (1) they add efficiently only to mono- and 1,1-disubstituted olefins and (2) they are not suitable for simple radical macrocyclizations. The first limitation is especially frustrating because it blocks radical annulations with cyclic alkenes (the addition step fails), and thus fused rings cannot be prepared. We now report preliminary results

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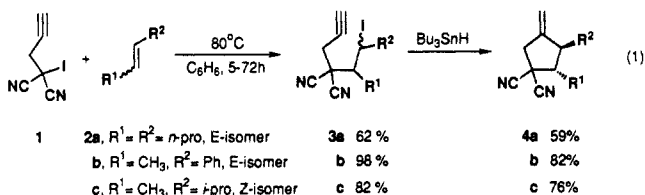
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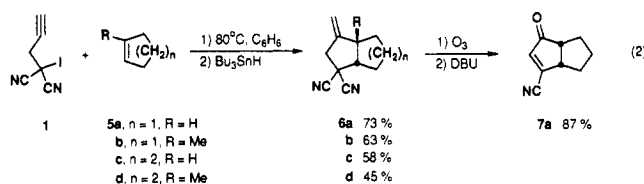
demonstrating that the simple replacement of the ester groups in iodomalones with nitriles⁵ overcomes both of these limitations. Atom transfer reactions of iodomalnonitriles promise to blossom into a general method to form carbon-carbon bonds from unactivated di- and trisubstituted olefins. Beyond that, iodomalnonitriles yield products from atom transfer reactions possessing functionality that facilitates some unusual (often highly stereo-selective) transformations including nitrile elimination, transfer, and abstraction.

Alkyl iodomalnonitriles are a simple yet little-known⁶ class of molecules that can be prepared in yields usually exceeding 90% by deprotonation of an alkyl malononitrile with NaH in the presence of *N*-iodosuccinimide (THF, 25 °C). Although we have tried a wide variety of initiators to promote the atom transfer reactions, the best conditions we have found so far involve simple heating in the dark of an iodomalnonitrile (0.3 M) and an alkene (2 equiv) in benzene.⁷ These thermal reactions (requiring 5–72 h) are slower than the chemically ($\text{Bu}_3\text{SnSnBu}_3$, heat) or photochemically initiated reactions, but they provide much better yields. Annulation reactions with propargyl iodomalnonitrile (**1**) are representative (eqs 1 and 2). The heating of **1** with 1,2-disubstituted olefins generally produces isolable secondary iodides (eq 1). For example, **3a** is isolated in 62% yield from the reaction



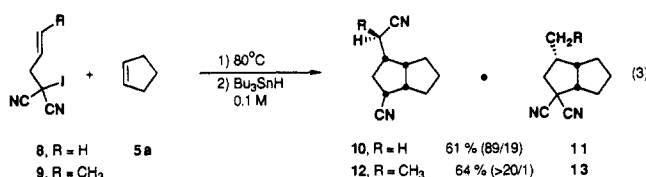
of **1** and *trans*-3-octene (**2a**). Apparently, iodomalnonitriles are such powerful iodine donors that the rate of iodine transfer to the adduct radical exceeds the rate of cyclization.⁸ Standard tin hydride cyclization of **3a** (mixture of isomers) completes the radical annulation and provides the *trans*-substituted methylenecyclopentane **4a** as the only product.⁹ With β -methylstyrene (**2b**) or *cis*-2-methyl-3-pentene (**2c**), two regioisomeric adducts could result, but only a single isomer is formed in each case (**3b**, **3c**).¹⁰ Tin hydride cyclization of **3b** or **3c** produces *trans* products **4b** or **4c**, respectively. The selective formation of **4c** is particularly significant. Starting from an olefin (**2c**) that is devoid of activating functional groups and whose ends are differentiated only by a different level of branching in the substituents, a functionalized carbocyclic ring is annulated in one operation with high selectivity. This is not an easy transformation to accomplish by using existing methods.

Equation 2 illustrates that functionalized, fused rings are readily prepared from unactivated di- and trisubstituted cyclopentenes and cyclohexenes. With the disubstituted alkenes (**5a,c**), intermediate iodides can be isolated if desired, or the annulation can be conducted in one pot by adding tributyltin hydride to the reaction mixture after the addition is complete. With the trisubstituted alkenes (**5b,d**), addition invariably occurs to the less



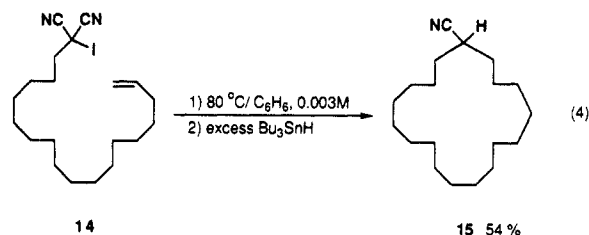
substituted terminus of the alkene, but the intermediate tertiary iodides that are formed are not sufficiently stable to be isolated in good yields. However, direct tin hydride reductions provide the annulation products **6b,d** in 63 and 45% yields. An illustration of the synthetic possibilities of these adducts is provided with **6a**: standard ozonolysis, followed by direct exposure of the crude product to DBU, provides β -cyano enone **7a** in 87% yield. Such a direct transformation of an unactivated cyclopentene (**5a**) to a highly functionalized bicyclooctene (**7a**) is not easily accomplished.

Allyliodomalnonitrile (**8**) also adds to alkenes in yields that are comparable to those obtained with **1**; however, eq 3 illustrates that interesting new transformations occur when the adducts are treated with tributyltin hydride. Heating of **8** and cyclopentene,



followed by addition of tin hydride at 0.1 M, produces a separable mixture of the nitrile-transfer product **10**¹¹ and the simple reductive-cyclization product **11**. When the tin hydride reduction is conducted at 0.03 M, **10** is the only product isolated (80% yield). Even more exciting is the reaction of iodomalnonitrile **9** with **5a**. Here we isolate the nitrile-transfer product **12** as a single stereoisomer in 64% yield,¹² alongside a trace (<5%) of a reductive-cyclization product **13** (configuration of the ethyl group not known). Starting from achiral **9** and **5a**, this reaction assembles one ring, forms three carbon-carbon bonds while breaking one, and selectively creates five stereogenic centers.

The results reported in eqs 1–3 are only representative examples selected from an ongoing study. We have conducted a macrocyclization of one substrate,¹³ and this is shown in eq 4. Heating



of **14** at 0.003 M in benzene provided a mixture of the desired atom-transfer macrocyclization product and oligomers resulting from bimolecular reactions. To facilitate separation and characterization, fractions rich in the macrocyclic product were reduced with 2 equiv of tin hydride at 0.1 M. Much to our surprise, we isolated the macrocyclic mononitrile **15** in 54% overall yield from

(5) We were guided to select malononitriles by studies of the unsubstituted malononitrile radical. (a) Boldt, P.; Schultz, L.; Klinsmann, U.; Köster, H.; Thielecke, W. *Tetrahedron* **1970**, *26*, 3591. (b) Riemenschneider, K.; Bartels, H. M.; Dornow, R.; Drechsel-Grau, E.; Eichel, W.; Luthé, H.; Matter, Y. M.; Michaelis, W.; Boldt, P. *J. Org. Chem.* **1987**, *52*, 205. (c) Gleicher, G. J.; Mahiou, B.; Aretakis, A. *J. Org. Chem.* **1989**, *54*, 308. (d) For hydrogen-transfer reactions of malononitriles, see: Julia, M.; Maumy, M. *Bull. Chim. Soc. Fr.* **1969**, 2415. Calaux, M.; Lalande, R. *Ibid.* **1971**, 461.

(6) Three iodobenzylmalononitriles have been prepared: Sommer, R.; Müller, E.; Neumann, W. P. *Justus Liebigs Ann. Chem.* **1968**, *718*, 11.

(7) An ionic mechanism involving iodonium ions can be envisioned for these reactions, but we believe that a radical mechanism is operating. A subsequent full paper will provide a mechanistic analysis.

(8) Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 1826.

(9) Related, stereoselective cyclizations have just appeared: (a) Kilburn, J. D. *Tetrahedron Lett.* **1990**, *31*, 2193. (b) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4003.

(10) Prolonged heating of **3b** resulted in complete isomerization to an *E/Z* mixture of (iodomethylene)cyclopentanes. See ref 3.

(11) Nitrile transfer to phenyl radicals is the precedent for this reaction: Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565. See also: Watt, D. S. *J. Am. Chem. Soc.* **1976**, *98*, 271. Kalvoda, J.; Heusler, K. *Synthesis* **1971**, 501.

(12) The presence of small amounts of other isomers (<5%) cannot be excluded. The relative stereochemistry of the exocyclic stereocenter is tentatively assigned only from a model (see supplementary material).

(13) Macrocyclizations of nucleophilic radicals have been pioneered by Porter: (a) Porter, N. A.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 2787. (b) Porter, N. A.; Chang, V. H.-T.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1988**, *110*, 3554. (c) Cox, N. J. G.; Pattenden, G.; Mills, S. D. *Tetrahedron Lett.* **1989**, *30*, 621. (d) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4008. (e) Macrocyclizations have recently been observed in the oligomerizations of some electrophilic radicals. See ref 4e.

14. This is the first example of a controlled radical macrocyclization of an electrophilic radical.^{13c} Further, the tin hydride promoted reductive removal of the nitrile group from a malononitrile is an unprecedented reaction of considerable generality. A forthcoming paper will address the scope of this reaction.

Iodomalononitriles are a readily available class of compounds that show great promise as versatile reagents in synthesis. The reactivity profile of substituted malononitrile radicals⁵ goes well beyond that of existing electrophilic radicals. None of the transformations conducted in this paper have yet been accomplished with malonic ester radicals. Indeed, there are precious few bimolecular methods of any kind to form carbon–carbon bonds starting from unactivated di- and trisubstituted alkenes. Full details of the scope of the reactions reported herein and associated mechanistic studies will be reported in the near future.

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Supplementary Material Available: Representative procedures for each type of experiment reported, spectra for all products, and a model to assign the stereochemistry of **12** (9 pages). Ordering information is given on any current masthead page.

Metal Ion Enhanced Helicity in Synthetic Peptides Containing Unnatural, Metal-Ligating Residues

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The α -helical conformation adopted by 40% of all residues in proteins¹ is not, in isolation, energetically favored, as indicated by the existence of most short peptides in aqueous solution as random coils.² Protein helices and rare helical peptides apparently owe their existence to exogenous stabilizing factors.^{3–5} Theory suggests that cross-links⁶ stabilize the folded form of polypeptides by diminishing the entropy of the unfolded form relative to the acyclic counterpart (Figure 1).⁷ We report here the use of metal ions as peptide side chain "cross-linking" agents.⁸ The studies

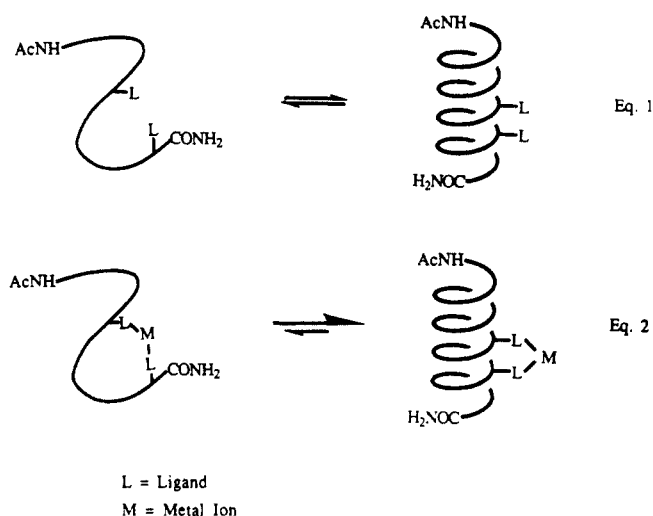


Figure 1. The coil-to-helix equilibrium of a peptide (eq 1) bearing two side chains capable of metal coordination should in theory be shifted to the right by simultaneous coordination to a single metal (eq 2), the result of reduction of entropy of the metal-coordinated coil conformation.

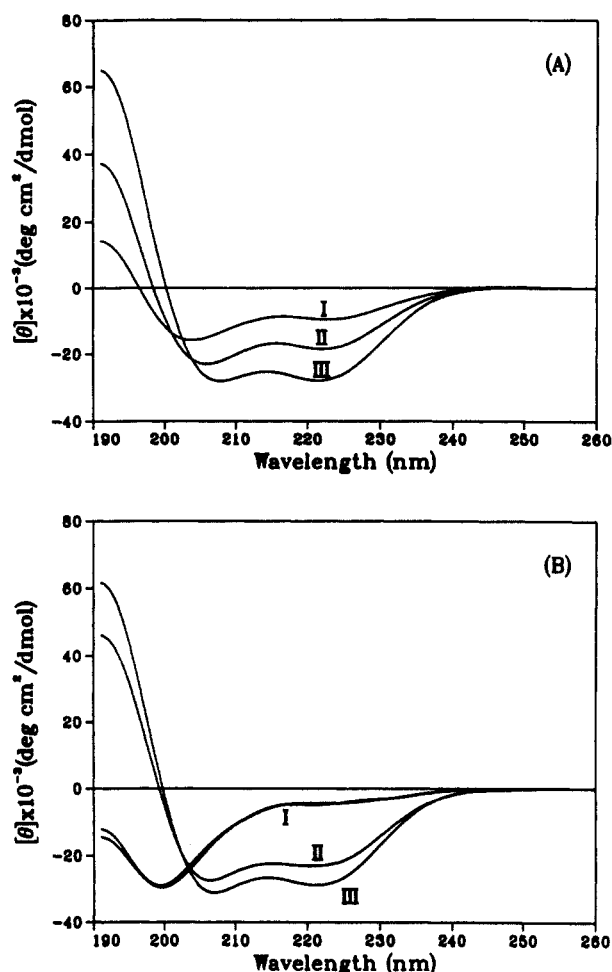


Figure 2. CD spectra of (A) peptide **2a** (12 μ M) in the absence of metal ions (II) and in the presence of Cd^{2+} (III) or Ni^{2+} (I) (200 μ M in metals) at 25 $^{\circ}\text{C}$ and (B) peptide **5a** (36 μ M) in the absence of metals at 4 and 25 $^{\circ}\text{C}$ (I) and in the presence of Cd^{2+} (200 μ M) at 25 (II) and 4 $^{\circ}\text{C}$ (III).

reveal that, for peptides containing metal-ligating residues, the position of the coil-to-helix equilibrium is strongly dependent on the number and spacing of ligating residues, tether length between backbone and ligand, and metal ion. In one remarkable case, an 11-residue peptide is converted from random coil to ca. 80% helix content by addition of Cd^{2+} at 4 $^{\circ}\text{C}$.

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