(62.5 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 76.31, 62.70, 31.84, 31.58, 25.65, 24.17, 22.71, 19.04, 16.37$.

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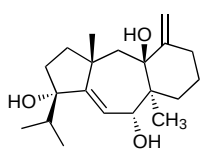
[1] F. J. Evans, C. J. Soper, *Lloydia* **1978**, *41*, 193.
[2] R. Bohm, B. Flaschenträger, L. Lendle, *Arch. Exp. Pathol. Pharmakol.* **1935**, *177*, 212.
[3] a) W. Hoppe, F. Brandl, I. Strell, M. Röhrl, I. Gassman, E. Hecker, H. Bartsch, G. Kreibich, C. V. Szczepanski, *Angew. Chem.* **1967**, *79*, 824; *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 809; b) E. Hecker, H. Bartsch, H. Bresch, M. G. Schmendt, E. Härle, G. Kreibach, H. Kubinyi, H. U. Shairer, C. V. Szczepanski, H. W. Thielman, *Tetrahedron Lett.* **1967**, 3165.
[4] E. Hecker, R. Schmidt, *Fortschr. Chem. Org. Naturst.* **1974**, 377.
[5] J. G. Kidd, P. Rous, *J. Exp. Med.* **1938**, *68*, 529.
[6] M. Castagna, Y. Takai, K. Kaibuchi, S. Komihiko, U. Kikkawa, Y. Nishizuka, *J. Biol. Chem.* **1982**, *257*, 7847.
[7] L. M. Harwood, A. C. Brickwood, V. Morrison, J. Robertson, S. Swallow, *J. Heterocycl. Chem.* **1999**, *36*, 1391, and references therein.
[8] a) L. M. Harwood, G. Jones, J. Pickard, R. M. Thomas, D. Watkin, *J. Chem. Soc. Chem. Commun.* **1990**, 605; b) L. M. Harwood, B. Jackson, G. Jones, K. Prout, R. M. Thomas, F. J. Witt, *J. Chem. Soc. Chem. Commun.* **1990**, 608; c) L. M. Harwood, T. Ishikawa, H. Phillips, D. Watkin, *J. Chem. Soc. Chem. Commun.* **1991**, 527.
[9] A. C. Brickwood, M. G. B. Drew, L. M. Harwood, T. Ishikawa, P. Marais, V. Morisson, *J. Chem. Soc. Perkin Trans. 1* **1999**, 913.
[10] W. Adam, Y.-Y. Chan, D. Cremer, J. Gauss, D. Scheutzow, M. Scindler, *J. Org. Chem.* **1987**, *52*, 2800.
[11] P. A. Krapcho, *Synthesis* **1982**, 893.
[12] L. N. Mander, S. P. Sethi, *Tetrahedron Lett.* **1984**, *25*, 5953.
[13] P. Amice, L. Blanco, J. M. Conia, *Synthesis* **1976**, 196.
[14] A. Speicher, T. Eicher, *Synthesis* **1995**, 998.
[15] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-152923. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
[16] P. Fischer, G. Schaefer, *Angew. Chem.* **1981**, *93*, 895; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 863.
[17] This reaction failed to proceed when it was attempted using Et_2O as a solvent, and only starting material was recovered.
[18] a) Zn-mediated: J. H.-H. Chan, B. Rickborn, *J. Am. Chem. Soc.* **1968**, *90*, 6406; F. Mohamadi, W. C. Still, *Tetrahedron Lett.* **1986**, *27*, 893, and references therein; b) Sm-mediated: G. A. Molander, L. S. Harring, *J. Org. Chem.* **1989**, *54*, 3525; M. Lautens, P. H. M. Delanghe, *J. Org. Chem.* **1992**, *57*, 798; c) Al-mediated: K. Maruoka, Y. Fukutani, H. Yamamoto, *J. Org. Chem.* **1985**, *50*, 4412; d) Mg-mediated: C. Bolm, D. Pupowicz, *Tetrahedron Lett.* **1997**, *38*, 7349.

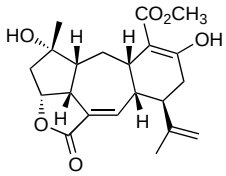
Constructing Tricyclic Compounds Containing a Seven-Membered Ring by Ruthenium-Catalyzed Intramolecular [5+2] Cycloaddition**

Barry M. Trost* and Hong C. Shen

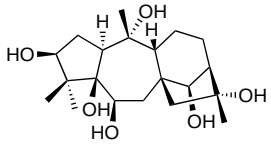
Polycyclic natural products that contain an embedded polyhydroazulene subunit, for example, dilatriol[1a] (**1a**), rameswaralide[1b] (**1b**), grayanotoxin[1c] (**1c**), and phorbol[1d] (**1d**), possess a diversity of biological activities. As such, they



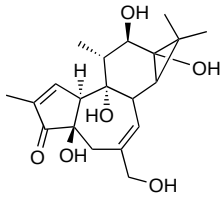
1a



1b



1c



1d

represent interesting yet demanding synthetic challenges and stimulate the development of new methodologies. The ability to increase molecular complexity rapidly by cycloaddition reactions should prove to be particularly interesting in offering short, atom-economical routes to such targets. Among these reactions, Rh-[2] and Ru-catalyzed[3] [5+2] cycloaddition reactions that involve cyclopropyl enynes have been discovered by the Wender group and by our group, respectively. We have shown that the Ru^{II} catalyst **2** can catalyze this process under very mild conditions[3] (room temperature in acetone within a few hours). This fact encouraged us to examine the applicability of this strategy to complex targets represented by **1a**–**d**, which raises a number of reactivity and selectivity issues that are addressed herein.

The sensitivity of the Ru-catalyzed reactions to steric hindrance immediately led us to test the ability of 1,2,3-trisubstituted cyclopropanes to participate in these reactions.

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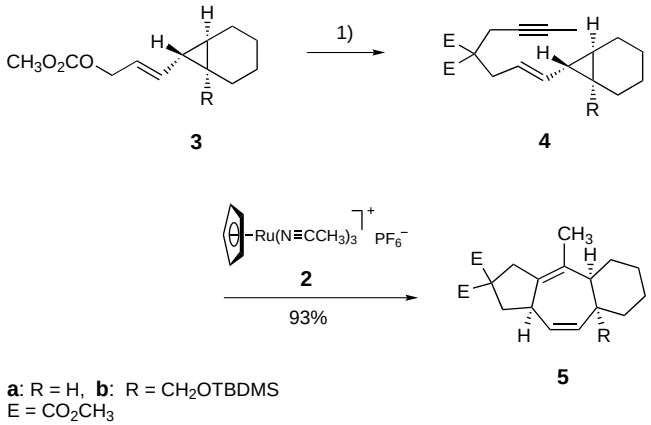
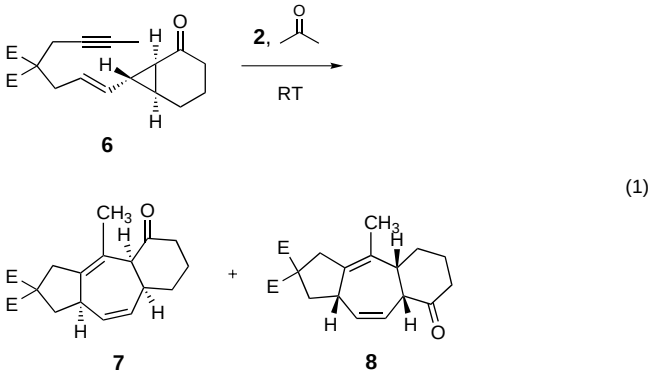
We chose to investigate the norcarane derivative **4a**, which was prepared in 70% yield by a Pd^0-catalyzed allylic alkylation[4] (Scheme 1; Ph_3P, $(C_2H_5)_3N$, CH_2Cl_2, room temperature). The substrate **3a** for the alkylation is easily



Scheme 1. Preparation and Ru-catalyzed intramolecular cycloaddition of cyclopropyl enyne **4**. Reagents and conditions: 1) Ph_3P, $[Pd_2(dba)_3]\cdot CHCl_3$, Et_3N; dba = *trans,trans*-dibenzylideneacetone.

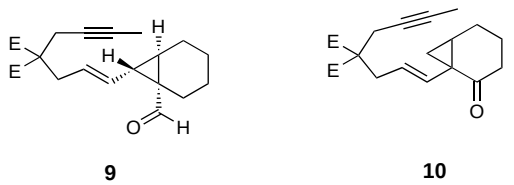
accessed from cyclohexene by typical cyclopropanation[5] and chain-extension protocols. An acetone solution of enyne **4a** was exposed to complex **2** (10 mol%) at ambient temperature for 6 h to ensure complete conversion, since the spots for the product and the starting material overlap on the TLC plate. Tricycle **5a** was isolated as a single stereoisomer in 93% yield. The *syn,syn* stereochemistry was assigned by NOE studies. A further increase in the steric congestion by employing a tetrasubstituted cyclopropyl substrate **4b**, derived in a similar manner from **3b**, also raises the question of the regioselectivity of the ring opening. Interestingly, the reaction proceeded within 3 h at room temperature, to give tricycle **5b** as a single stereoisomer in 85% yield (Scheme 1).

A most interesting regioselectivity question arises with the ketone **6**. Previous work showed that an acetyl substituent in a 1,2-disubstituted cyclopropane produced nearly equal amounts of the two regioisomers.[3b] On the other hand, in the case of **6** [Eq. (1)], both cyclopropyl bonds are disubstituted. In contrast to our earlier study, a selectivity in favor of **7** was observed, but still a small amount of **8** was formed (74% yield, **7**/**8** 6:1). This fact indicates that electronic factors can dominate when steric effects are equivalent, but the electronic effects are not overwhelming. Interestingly, the addition of indium triflate as a cocatalyst increased the selectivity to favor **7** (83% yield) such that none of isomer **8** was detected. Apparently, Lewis acid complexation of the carbonyl group activates the adjacent cyclopropyl bond towards cleavage.

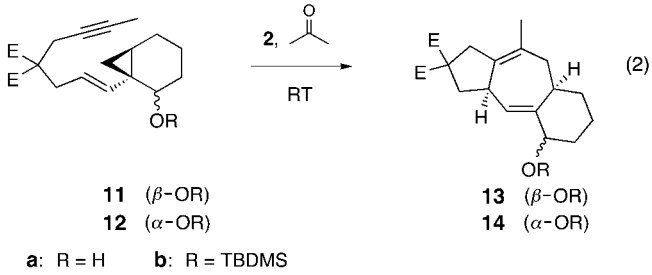


(1)

In contrast to the facile cycloisomerization of Equation (1), which was complete within 4 h, aldehyde **9** and ketone **10** failed to react. Since previous work[3b] clearly establishes that



the functionality is not responsible for this lack of reactivity, we examined the reduced forms of ketone **10**, that is, **11a**,**b** and **12a**,**b** [Eq. (2)].



(2)

Gratifyingly, both epimers of both alcohols **11a** and **12a** reacted normally to give the tricycles **13a** (70% yield) and **14a** (80% yield) in 4–5 h. The sterically bulkier silyl ethers **11b** and **12b** also reacted within 2–3 h to form the desired cycloisomers **13b** (81% yield) and **14b** (69% yield). In every case, excellent diastereoselectivity was observed. In light of these results, the failure of the carbonyl substrates **9** and **10** is quite puzzling. Perhaps the bidentate coordination of the carbonyl group and the double bond that is possible in **9** and **10** but not in **6** accounts for these differences in reactivity.

Varying the placement of the cyclohexyl ring provides an entry to alternative tricycles. For example, dienyne **16** was readily available by means of a Sonogashira coupling[6] of vinyl triflate **15** and the triisopropylsilyl (TIPS) ether of propargyl alcohol. The former was derived from 4-*tert*-butylcyclohexanone by straightforward methodology.[7] Dienyne **16** was exposed to complex **2** (10 mol%) at room temperature in acetone to give a 91% yield of the triene **17** (*dr* 10:1) in 4 h (Scheme 2). The use of a conjugated enyne for the acetylene segment provides an entry to 1,3-dienes and thus sets the stage for further elaboration by means of Diels–Alder reactions.

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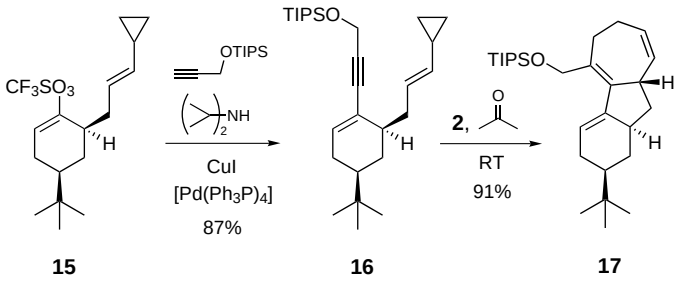
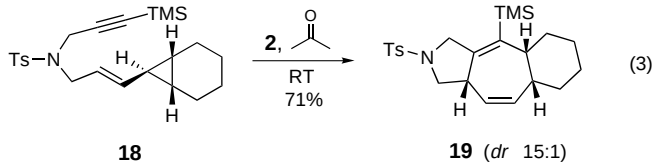


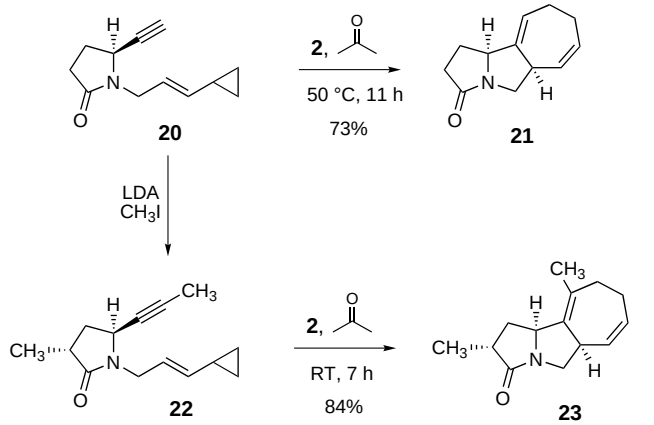
Scheme 2. Formation of alternative tricycles from cyclopropyl enyne **16**.

The incorporation of nonbasic nitrogen in the tether provides an entry to azapolyhydroazulenes. For example, alkyl carbonate **3a** can be converted into sulfonamide **18** by Pd^0-catalyzed alkylation.[4] Intramolecular cycloaddition proceeded under standard conditions in 8 h to produce azatricycle **19** with excellent diastereoselectivity [Eq. (3)]. A lactam



(3)

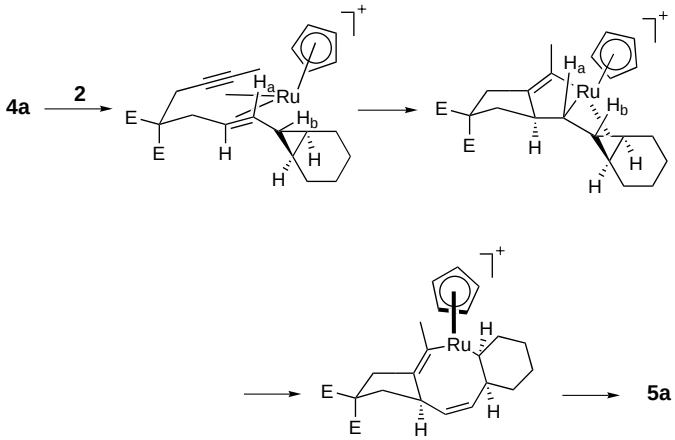
is also a suitable substrate. Thus, ketoglutamic acid was readily converted into enyne **20**. The [5+2] cycloaddition proceeded under standard conditions albeit somewhat more slowly (11 h at 50 °C) but still in excellent yield to give **21** with excellent diastereo- and enantioselectivity (Scheme 3). It



Scheme 3. Effect of terminal versus substituted alkynes on cycloaddition rate. LDA = lithium diisopropylamide

appears that terminal alkynes react more slowly in general in these reactions, presumably because there is a reversible side reaction that involves insertion into the C–H bond by ruthenium.[8] To test this speculation, the terminal alkyne was methylated, a process that was accompanied by simultaneous methylation α to the carbonyl group, to form enyne **22**.[9] The [5+2] cycloaddition reaction to form **23** proceeded at room temperature within 7 h, considerably shorter and milder than required for **21** (Scheme 3).

The diastereoselectivity of all the reactions is outstanding. A mechanism that involves a ruthenacyclopentene[3, 10] accounts nicely for the observed stereochemistry (Scheme 4). Coordination of the double bond results in a dihedral angle of



Scheme 4. Mechanistic rationale for observed diastereoselectivity.

0° between H_a and H_b, since a double bond is formed between the corresponding carbon atoms. This requirement accounts for the propagation of the stereochemistry in a 1,4-manner. It is particularly significant that trisubstituted substrates such as **4** and **6** can be employed, invoking secondary carbon–ruthenium bonds. This type of substitution provides a simple entry to targets represented by **1a–c**. Furthermore, it appears that this methodology extends to these much more complicated substrates with no apparent ill effects—a feature that bodes well for the applicability of this method to complex natural product synthesis.

Experimental Section

General procedure: Distilled acetone (0.5 mL) and then **2** (4 mg, 0.009 mmol) was added to a 5-mL round-bottomed flask containing malonate ester **4a** (30 mg, 0.094 mmol) under argon at room temperature. The resulting brown solution was stirred for an additional 6 h. Without further work-up, flash chromatography of the reaction mixture, eluted with diethyl ether/petroleum ether (5% to 10%), afforded **5a** as yellow oil (28 mg, 0.088 mmol, 93%).

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[1] a) G. R. Pettit, R. H. Ode, C. L. Herald, R. B. Von Dreele, C. Michel, *J. Am. Chem. Soc.* **1976**, *98*, 4677; b) P. Ramesh, N. Srinivasa, Y. Venkateswarlu, M. V. R. Reddy, D. J. Faulkner, *Tetrahedron Lett.* **1998**, *39*, 8217; c) K. Nakanishi, T. Goto, S. Ito, S. Natori, S. Nozoe, *Natural Product Chemistry*, *Vol. 1*, Academic Press, New York, **1974**, p. 285, and references therein; d) *Naturally Occurring Phorbol Esters* (Ed.: F. J. Evans), CRC Press, Boca Raton, FL, **1986**.

[2] a) P. A. Wender, H. Takahashi, B. Witulski, *J. Am. Chem. Soc.* **1995**, *117*, 4720; b) P. A. Wender, D. Sperandio, *J. Org. Chem.* **1998**, *63*, 4164; c) P. A. Wender, H. Rieck, M. Fuji, *J. Am. Chem. Soc.* **1998**, *120*, 10976; d) P. A. Wender, C. O. Husfeld, E. Langkopf, J. A. Love, *J. Am. Chem. Soc.* **1998**, *120*, 1940. e) P. A. Wender, A. J. Dyckman, *Org. Lett.* **1999**, *1*, 2089; f) P. A. Wender, A. J. Dyckman, C. O. Husfeld, D. Kadereit, J. A. Love, H. Rieck, *J. Am. Chem. Soc.* **1999**, *121*, 10442; g) P. A. Wender, F. Glorius, C. O. Husfeld, E. Langkopf, J. A. Love, *J. Am. Chem. Soc.* **1999**, *121*, 5348; h) P. A. Wender, M. Fuji, C. O.

Husfeld, J. A. Love, *Org. Lett.* **1999**, *1*, 137; see also: i) S. R. Gilbertson, G. S. Hoge, *Tetrahedron Lett.* **1998**, *39*, 2075; j) P. Binger, P. Wedemann, S. I. Kozhushkov, A. de Meijere, *Eur. J. Org. Chem.* **1998**, 113.
[3] a) B. M. Trost, F. D. Toste, H. Shen, *J. Am. Chem. Soc.* **2000**, *122*, 2379; b) B. M. Trost, H. C. Shen, *Org. Lett.* **2000**, *2*, 2523.
[4] For a comprehensive review, see: S. A. Godleski in *Comprehensive Organic Synthesis*, *Vol. 4* (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon, Oxford, **1999**, chap. 3.3, pp. 585–662.
[5] M. P. Doyle, K.-L. Loh, K. M. De Vries, M. S. Chinn, *Tetrahedron Lett.* **1987**, *28*, 833.
[6] M. W. Miller, C. R. Johnson, *J. Org. Chem.* **1997**, *62*, 113.
[7] J. d'Angelo, *Tetrahedron* **1976**, *32*, 2979, and references therein.
[8] B. M. Trost, B. Vidal, M. Thommen, *Chem. Eur. J.* **1999**, *5*, 1055, and references therein.
[9] P. A. Jacobi, K. Lee, *J. Am. Chem. Soc.* **2000**, *122*, 4295.
[10] For a similar mechanistic proposal in the Rh-catalyzed reaction, see ref. [2].

Correlating Electron Transport and Molecular Structure in Organic Thin Films**

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Understanding how electrons travel through organic matter is important in designing materials for organic microelectronics[1] and understanding biological electron-transport processes.[2, 3] Herein we describe a simple experimental procedure to measure rates of electron transport across organic thin films having a range of structures, compare the data for several types of films, and outline a theory appropriate for analyzing these rates. We use a junction that is particularly easy to assemble: M-SAM(1)SAM(2)-M′ (Figure 1, "SAM" is a self-assembled monolayer).[4, 5] We have examined two sets of junctions: 1) one in which SAM(1) was formed on Ag from aliphatic or aromatic thiols, and SAM(2) was formed on Hg from hexadecanethiol, and 2) a second in which SAM(1) and SAM(2) have terminal functional groups. In the first, the SAMs contact through van der Waals interactions; in the second, through covalent, hydrogen, or ionic bonds. The current measured across these junctions obeyed the relation $I = I_0 e^{-\beta d}$ (where d is the distance between the electrodes, and β is the structure-dependent attenuation factor for the molecules in SAM(1)); the values of β compare well with those obtained by other experimental methods. The experimental current versus voltage (I-V) curves have been fitted using two theoretical models for electron transport: one

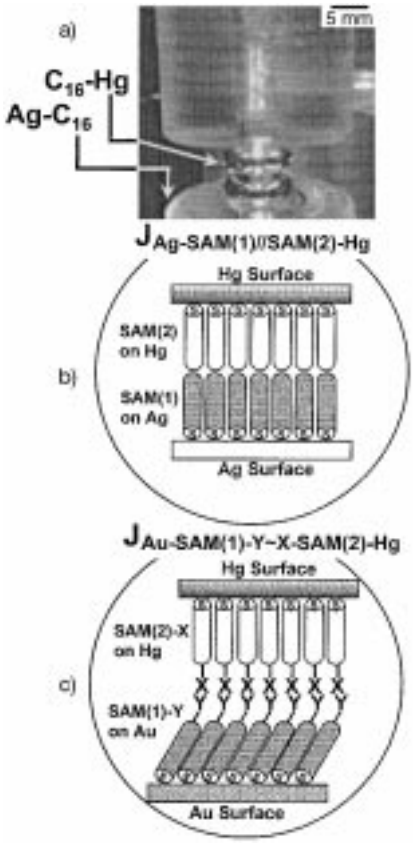

Figure 1. Schematic illustrations of junctions with structures $J_{Ag\text{-}SAM(1)//SAM(2)\text{-}Hg}$ and $J_{Au\text{-}SAM(1)\text{-}X\sim Y\text{-}SAM(2)\text{-}Hg}$ (see text for the nomenclature). The photographic image (a) is that of a $J_{Ag\text{-}C_{16}//C_{16}\text{-}Hg}$ junction; the scale bar represents ~0.5 mm. To assemble $J_{Ag\text{-}SAM(1)//SAM(2)\text{-}Hg}$ junctions (b), a SAM was formed on the surface of a thin evaporated film of silver; we normally used M = Ag, since silver gives highly ordered SAMs.[5] This electrode was covered with a solution of hexadecane containing 1 mM thiol. A small drop of Hg (5 μL) was expressed into a solution of hexadecanethiol (HDT) from a capillary connected to a mercury reservoir, and a SAM of HDT allowed to form on it.[5] The HDT-covered mercury drop (C_{16}-Hg) was then brought into contact with the solid electrode using a micromanipulator. The area of interfacial contact was estimated by using a microscope. With each electrode connected to an electrometer (in two-electrode mode), we applied a potential and recorded the response, and then increased the potential in steps over a range of voltages to generate I–V curves. Junctions of structure $J_{Au\text{-}SAM(1)\text{-}X\sim Y\text{-}SAM(2)\text{-}Hg}$ (c) were made as described for $J_{Ag\text{-}SAM(1)//SAM(2)\text{-}Hg}$ except that one electrode was a thin film of gold, and the thiols used had terminal groups that could react and form covalent bonds (X = carboxylic anhydride, Y = H_2N),[15] or interact strongly but noncovalently (X = CO_2H and Y = HO_2C, or X = CO_2H and Y = H_2N) through hydrogen or ionic bonds.

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