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Discovery of Chemical Reactions through Multidimensional Screening

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Abstract: Multidimensional reaction screening of *ortho*-alkynyl benzaldehydes with a variety of catalysts and reaction partners was conducted in an effort to identify new chemical reactions. Reactions affording unique products were selected for investigation of preliminary scope and limitations.

Introduction

Reaction development has historically been guided by problems in total synthesis or interest in developing chemical transformations of broad scope and utility.[1,2] Chemical methodology development has increasingly relied on systematic evaluation of catalysts[3] and other variables including solvent, temperature, and supporting ligands.[4,5] Screening approaches have increased the efficiency of reaction development[6] with regard to discovery of active catalysts or conditions but have generally been focused on specific transformations of interest.

An emerging but underdeveloped method for chemical reaction discovery involves high-throughput screening. A few examples have been reported in which new reactions were discovered through screening of either multicomponent systems or reaction partners and catalysts. For example, Weber and co-workers reported the discovery of a novel multicomponent, Ugi-type reaction after screening 10,000 reaction mixtures.[7] A more recent example was reported by Liu and co-workers[8] wherein a novel carbon−carbon bond-forming reaction of alkynes and alkenes was discovered using DNA-templated synthesis.

As a part of our overall interest in the synthesis of new chemotypes and structural frameworks, we have initiated a program to identify novel chemical transformations using "multidimensional screening". In this approach, substrates may be reacted with various catalysts and reaction partners in an array format and analyzed for unique reaction processes. Herein, we report our initial studies on this mode of reaction screening and the identification and exploration of several new transformations discovered during initial screening efforts.

Results and Discussion

Significant research has been reported utilizing cycloisomerization of *o*-alkynyl benzaldehydes and related substrates. Yamamoto and others have reported numerous approaches to afford putative metal-"ate" dipolar intermediates (**1a**) that may be reacted further to afford a variety of structures including naphthyl ketones **2** (Scheme 1a). Iwasawa and co-workers have reported group VI transition metal-mediated cycloisomerizations to afford Fischer carbene intermediates (**1b**) which subsequently undergo further reactions to afford polycyclic structures such as **3** (Scheme 1b).[9] Several examples[10] have been reported in

(1) For recent reviews on reaction method development related to natural product synthesis, see: (a) Nicolaou, K. C.; Snyder, S. S. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11929.
(2) For recent reviews on focused reaction method development, see: Taylor, M. S.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5368.
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(6) For examples of automated screening of reaction conditions, see: (a) Harre, M.; Neh, H.; Schulz, C.; Tilstam, U.; Wessa, T.; Weinmann, H. *Org. Process Res. Dev.* **2001**, *5*, 335. (b) von Wangelin, A. J.; Neumann, H.; Gordes, D.; Klaus, S.; Jiao, H.; Spannenberg, A.; Kruger, T.; Wendler, C.; Thurow, K.; Stoll, N.; Beller, M. *Chem.−Eur. J.* **2003**, *9*, 2273. (c) Di, L.; McConnell, O. J.; Kerns, E. H.; Sutherland, A. G. *J. Chromatogr., B* **2004**, *809*, 231. (d) Dinter, C.; Weinmann, H.; Merten, C.; Schutz, A.; Blume, T.; Sander, M.; Harre, M.; Neh, H. *Org. Process Res. Dev.* **2004**, *8*, 482. (e) Rudolph, J.; Lormann, M.; Bolm, C.; Dahmen, S. *Adv. Synth. Catal.* **2005**, *347*, 1361.
(7) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366.
(8) (a) Kana, W. M.; Rosenman, M. M.; Sakurai, K.; Snyder, T. M.; Liu, D. R. *Nature* **2004**, *431*, 545. (b) Miller, S. J. *Nat. Biotechnol.* **2004**, *22*, 1378.
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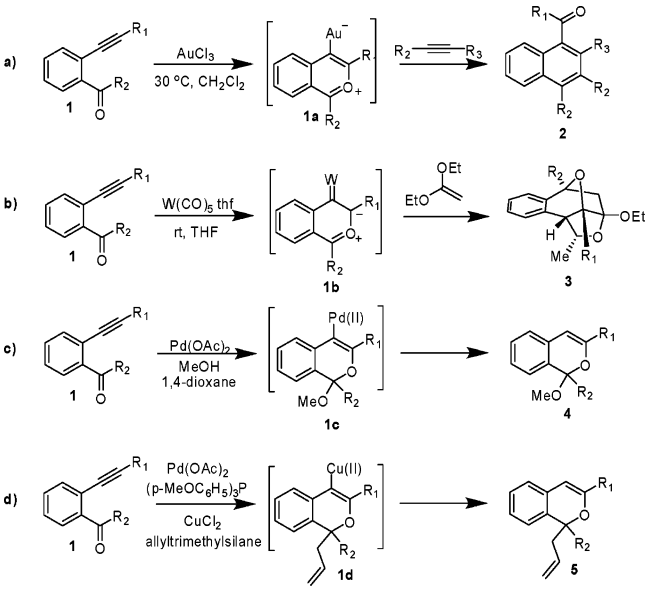
Scheme 1. Cycloisomerization of Alkynyl Benzaldehydes



which transition metal-catalyzed cycloisomerization intermediates sustain nucleophilic attack to afford a variety of isochromenes such as **4** and **5** (Scheme 1c,d).[11,12] These and related processes indicate that the putative intermediates may react with diverse reaction partners in processes that may be metal catalyst-dependent.[13] We therefore considered evaluation of the *o*-alkynyl benzaldehyde system in the context of multidimensional screening of reaction partners, catalysts, and temperature.

Reaction Screen Design and Implementation. In our initial studies, we prepared alkynyl aldehyde **6**[14] for evaluation with a variety of catalysts and reaction partners at two reaction temperatures. We selected reaction partners (Figure 1) for their potential to undergo nucleophilic, electrophilic, and cycloaddition reactions. Catalyst selection was also based on known, reactive catalysts for cycloisomerization[15] as well as other metal catalysts known to interact with alkynes or aldehydes or to form stable Fisher carbenes (Figure 1).[16] An initial reaction screen was performed on an analytical scale (5 μmol), and all reactions were analyzed using LC/MS/ELSD.[17] In this paradigm, reactions that were productive (those affording >20% conversion to a major product based on ELSD area) were subsequently scaled up and purified for further characterization of reaction products (Figure 2). Isolated products were then subjected to a mixture

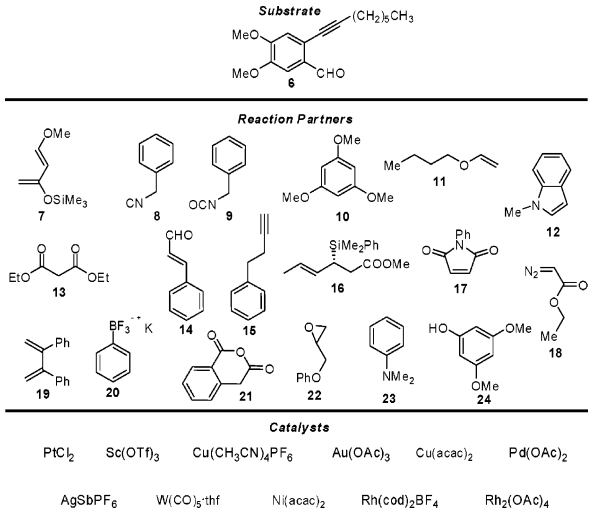


Figure 1. Reaction substrate, partners, and catalysts.

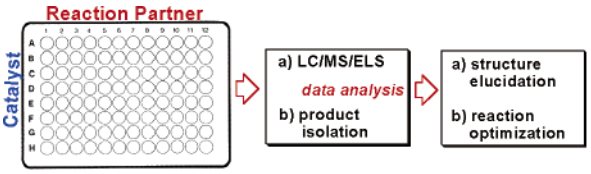


Figure 2. Multidimensional reaction screening workflow.

of traditional structure elucidation[18] and computation-assisted structure elucidation.[19−21] New reaction processes were then investigated to probe optimal reaction conditions, preliminary scope, and plausible reaction pathways.

An analytical reaction screen was conducted in glass deep well 96 well plates[3b] sealed with individual rubber septa. Each catalyst was prepared as a mixture in dried 4 Å molecular sieves (0.2 mmol/g).[14,22] Using molecular sieve mixtures of the catalysts addressed issues of preparing a large number of analytical scale reactions as they were delivered by a resin dispenser. Duplicates of each reaction were made and incubated both at room temperature and at 60 °C. Reactions were incubated for 3 h and subsequently worked up in a 96 well plate format using supported liquid extraction (SLE) cartridges preconditioned with saturated aqueous sodium bicarbonate.[23] Following elution with dichloromethane, solutions were evaporated and analyzed by LC/MS/ELSD. Each reactant was

(11) Asao, N.; Chan, C. S.; Takahashi, K.; Yamamoto, Y. *Tetrahedron* **2005**, *61*, 11322.
(12) For additional examples of nucleophilic addition to cycloisomerization intermediates, see: (a) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553. (b) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 950. (c) Dyker, G.; Hildebrandt, D.; Liu, J.; Merz, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4399. (d) Barluenga, J.; Vaźquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028. (e) Yue, D.; Ca, N.-D.; Larock, R. C. *Org. Lett.* **2004**, *5*, 1581. (f) Patil, N. T. Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 5139. (g) Asao, N.; Chan, C.-S.; Takahashi, K.; Yamamoto, Y. *Tetrahedron* **2005**, *61*, 11322.
(13) Brummond, K. M.; Mitasev, B. *Org. Lett.* **2004**, *6*, 2245.
(14) See the Supporting Information for complete experimental details.
(15) For additional references describing catalytic cycloisomerization of *o*-alkynylbenzaldehydes, see: (a) Zhu, J.; Germain, A. R.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2004**, *43*, 1239. (b) Shin, S.; Gupta, A. K.; Rhim, C. Y.; Oh, C. H. *Chem. Commun.* **2005**, 4429. (c) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 10096.
(16) (a) Ikeda, S.; Cui, D.-M.; Sato, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4712. (b) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227. (c) Meng, J.; Fokin, V. V.; Finn, M. G. *Tetrahedron Lett.* **2005**, *46*, 4543. (d) Padwa, A. *Helv. Chim. Acta* **2005**, *88*, 1357.
(17) Fang, L.; Pan, J.; Yan, B. *Biotechnol. Bioeng.* **2001**, *71*, 162.
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(19) For a discussion of computational NMR analysis and structure elucidation, see: (a) Meiler, J.; Will, M. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 1535. (b) Elyashberg, M. E.; Blinov, K. A.; Williams, A. J.; Molodtsov, S. G.; Martin, G. E.; Martirosian, E. R. *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 771. (c) Steinbeck, C. *Nat. Prod. Rep.* **2004**, *21*, 512.
(20) (a) Marin, G. E.; Hadden, C. E.; Russel, D. J.; Kaluzny, B. D.; Quido, J. E.; Duholke, W. K.; Stiemsma, B. A.; Thamann, T. J. *J. Heterocycl. Chem.* **2002**, *39*, 1241. (b) Sharman, G. J.; Jones, I. C.; Parnell, M. P.; Willis, M. C.; Mahon, M. F.; Carlson, D. V.; Williams, A.; Elyashberg, M.; Blinov, K.; Molodtsov, S. G. *Magn. Reson. Chem.* **2004**, *42*, 567.
(21) Computational structure elucidation was carried out using ACD Labs Structure Elucidator.
(22) For preparation of catalyst-molecular sieve mixtures, see: (a) Ueno, M.; Ishitani, H.; Kobayashi, S. *Org. Lett.* **2002**, *4*, 3395. (b) Kobayashi, S.; Ueno, M.; Saito, S.; Mizuki, Y.; Ishitani, H.; Yamashita, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5476.
(23) For examples of parallel workups employing SLE and liquid−liquid extraction cartridges, see: (a) Johnson, C. R.; Zhang, B.; Fantauzzi, P.; Hocker, M.; Yager, K. M. *Tetrahedron* **1998**, *54*, 4097. (b) Breitenbucher, J. G.; Johnson, C. R.; Haight, M.; Phelan, J. C. *Tetrahedron Lett.* **1998**, *39*, 1295. (c) Johnson, C. R.; Zhang, B.; Fantauzzi, P.; Hocker, M.; Yager, K. *Innovation Perspect. Solid Phase Synth. Comb. Libr., Collect. Pap., Int. Symp. 7th* **1999**, 209−210. (d) Kulkarni, B. A.; Roth, G. P.; Lobkovsky, E.; Porco, J. A., Jr. *J. Comb. Chem.* **2002**, *4*, 56.

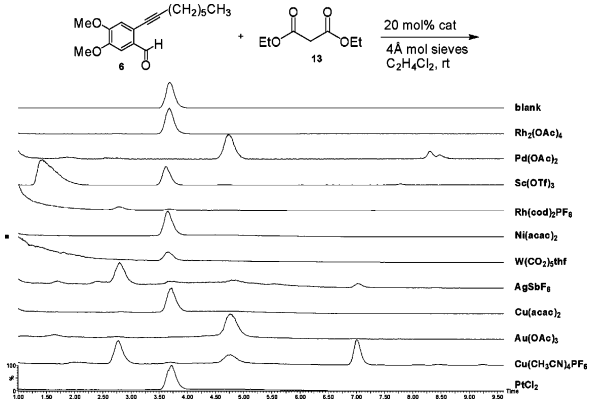
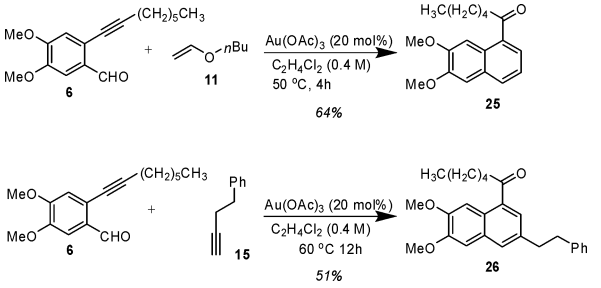


Figure 3. Representative catalyst profile for a single reaction partner.

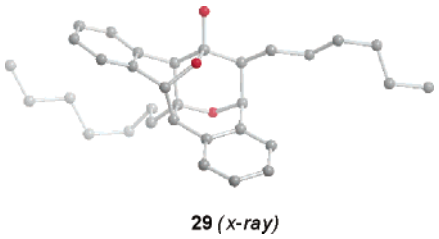
Scheme 2. Products Derived from Known Reaction Processes



subsequently profiled by ELSD signal, and productive reactions were chosen on the basis of this analysis.[14] A representative catalyst profile for a single reaction partner (diethyl malonate **13**) is illustrated in Figure 3. In this example, several products were observed in reactions with $Cu(CH_3CN)_4PF_6$, $Au(OAc)_3$, $AgSbF_6$, and $Pd(OAc)_2$. Reactions identified during the screening process were subsequently repeated, and products were isolated for structure elucidation. Several products were identified that were derived from known reactions.[14] However, we also identified reactions leading to new chemotypes derived from known and novel pathways.

Reaction Products Derived from Known Cycloisomerization Processes. The reaction screen produced a number of products derived from reported reaction processes.[14] In particular, we included reaction partners in which known reactions may occur, such as enol ether **11**[24] and terminal alkyne **15**.[9e,g,12c] Reaction profiles of **11** and **15** revealed the expected reaction products derived from cycloaddition of the putative dipolar intermediate (cf. **1a**, Scheme 1) and subsequent rearrangement to afford naphthyl ketones **25** and **26** (Scheme 2).

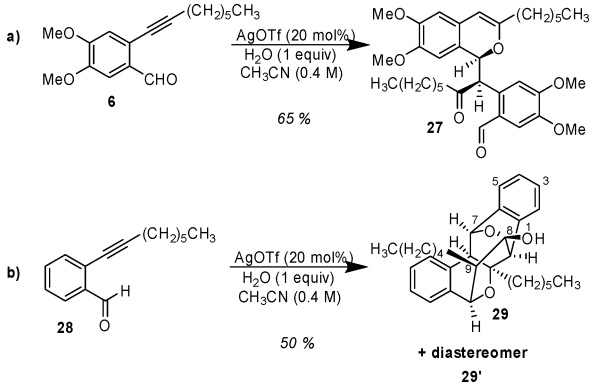
Novel Chemotypes Derived from Homodimerization Processes. Inspection of reaction profiles revealed that a common product was observed in many of the reactions employing $AgSbF_6$, $Au(OAc)_3$, $Rh(cod)_2BF_4$, and $Pd(OAc)_2$ as catalysts. In light of the complexity of the ^1H NMR spectrum obtained, structure elucidation was assisted by computational analysis[21] of the ^{13}C, $^1H-^1H$ COSY, HMQC, and HMBC data[14] resulting in a single suggested structure, homodimerization product **27** (Scheme 3).[25,26] To further probe the requirements for homodimerization, we conducted reactions with alternative substrates. In the event, treatment of *o*-alkynyl benzaldehyde **28** with 2 equiv of AgOTf in CH_3CN led to production of a novel compound (1:1 dr) with a very different ^1H NMR spectrum from dimeric product **37**. X-ray crystal structure analysis (Figure 4)[14] of one diastereomer revealed the product to be polycyclic dimer **29** (Scheme 3b). After reaction optimization, homodimers **27** and **29** were isolated in 65 and 50% yield, respectively (20% AgOTf, 1 equiv of H_2O, CH_3CN).



29 *(x-ray)*

Figure 4. X-ray crystal structure of **29**.

Scheme 3. Homodimerization of *o*-Alkynyl Benzaldehydes



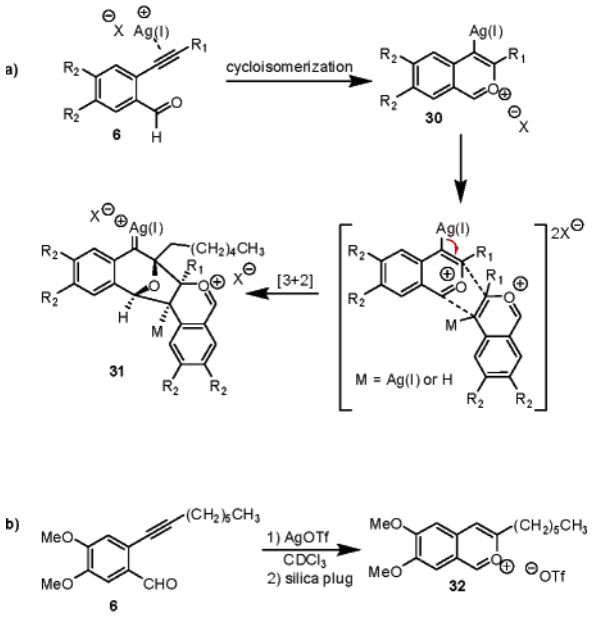
On the basis of the reaction outcomes using substrates **6** and **28**, we propose that both dimerization reactions may be initiated by activation of **6** to afford the vinyl metal pyrylium **30**.[10,11] Dimerization of **30** *via exo* [3 + 2]-cycloaddition affords intermediate **31**[27] (Scheme 4a), although a mechanism in which a single organometallic monomer couples with a benzopyrylium salt (e.g., **32**) cannot be discounted. The requirement of a metallo-benzopyrylium intermediate was further demonstrated by isolation of benzopyrylium species **32** after incubation of **6** in $CDCl_3$ with 1 equiv of AgOTf followed by filtration through silica gel. A dimeric product was not observed after stirring **32** for 24 h, supporting the likely involvement of organo-silver intermediates in the dimerization process.

Scheme 5 outlines a proposed pathway to afford polycyclic dimer **29**. Intermediate **31** may rearrange, through 1,2-migration, to exocyclic enol ether **33**, which subsequently undergoes intramolecular addition to the oxonium[28] to afford **34**. Addition of water and protonation affords **29** and its C9 diastereomer **29′** (50%, dr = 1:1). The C9 stereochemistry of **29** and **29′** was confirmed by 2-D NMR experiments[14] and is seemingly established by the enol ether geometry for intermediate **33**.

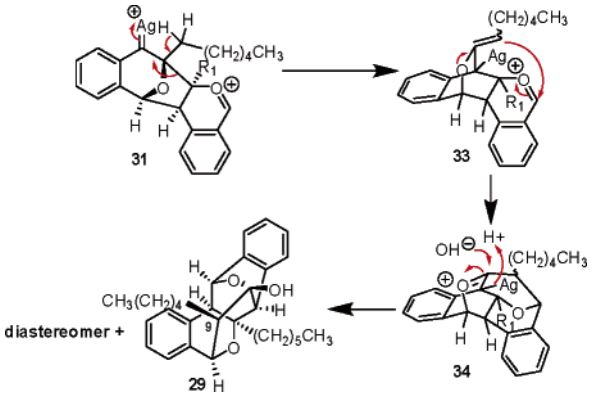
A pathway to afford homodimer **27** then follows from the general process described in Scheme 5. In this case, the

(24) Asao, N.; Aikawa, H. *J. Org. Chem.* **2006**, *71*, 5249.
(25) For examples of related dimers, see: (a) Zhdanov, Yu. A.; Verin, S. V.; Korobka, I. V.; Kuznetsov, E. V. *Khim. Geterotsikl. Soedin.* **1988**, *9*, 1185. (b) Verin, S. V.; Kuznetsov, E. V.; Zhdanov, Yu. A. *Khim. Geterotsikl. Soedin.* **1989**, *6*, 750.
(26) For dimerizations of 1,3-dipoles, see: (a) Hendrickson, J. B.; Farina, J. S. *J. Org. Chem.* **1980**, *45*, 3361. (b) Krishna, U. M.; Deodler, K. D.; Trivedi, G. K.; Mobin, S. M. *J. Org. Chem.* **2004**, *69*, 967.
(27) For a discussion and computational analysis regarding [3 + 2] (Huisgen) versus [4 + 2] cycloaddition of benzopyrylium 1,3-dipoles, see: Straub, B. F. *Chem. Commun.* **2004**, 1726.
(28) Reinhard, R.; Schlegel, J.; Maas, G. *Tetrahedron* **2002**, *58*, 10329.

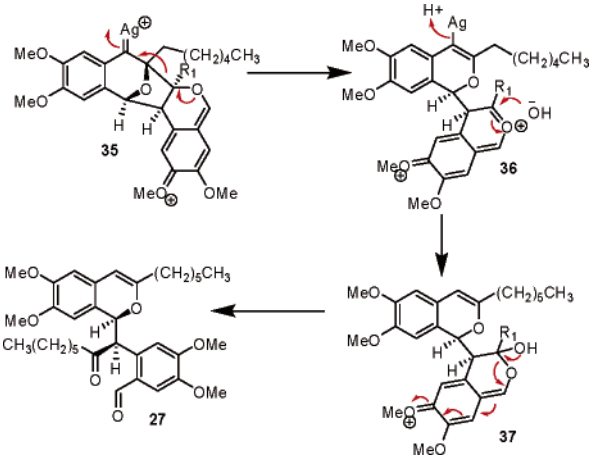
Scheme 4. Cycloisomerization and [3 + 2] Dimerization



Scheme 5. Proposed Reaction Pathway Leading to Polycyclic Dimer **29**



Scheme 6. Proposed Reaction Pathway to Homodimerization Product **27**



additional dimethoxy aryl substitution may lead to oxonium intermediate **35** (Scheme 6). Fragmentation of the pentacyclic framework leads to oxonium species **36**, which may be followed by addition of water to afford hemiketal **37**. Re-aromatization then affords the observed isochromene ketoaldehyde product **27** as a single diastereomer. Assignment of the relative stereochemistry of **27** is based on the *exo* [3 + 2]-cycloaddition mode, which is also evident from the stereochemistry observed for **29**.

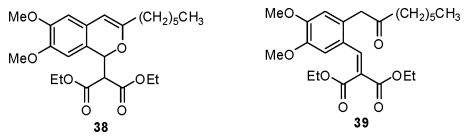
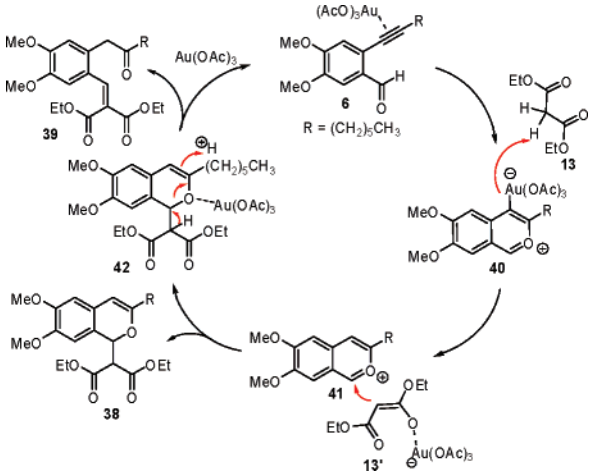


Figure 5. Products derived from cycloisomerization/addition of diethyl malonate.

Scheme 7. Reaction Pathway to Products **38** and **39**



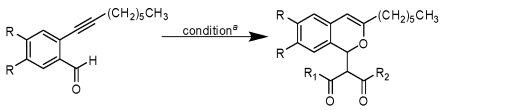
The discovery of a "background" reaction across a number of reaction profiles thus led us to uncover a novel homodimerization process. By altering the aromatic substitution of the starting material, we were able to produce a novel chemotype, polycyclic dimer **29**, which exhibits an extraordinary level of skeletal complexity.

Reaction Products Derived from Addition of 1,3-Dicarbonyls. A promising reaction discovered in the screening process was cycloisomerization/nucleophilic addition using diethyl malonate.[29] Reactions affording new products were detected in the profile employing $Au(OAc)_3$, $AgSbF_6$, $PtCl_2$, and $Rh(cod)_2BF_4$ as catalysts.[14] The structures of the new products were determined to be isochromene **38** and the derived ring-opened product **39** (Figure 5).

Scheme 7 outlines a proposed pathway for cycloisomerization/nucleophilic addition to afford isochromene **38** and benzylidenemalonate **39**. Initial activation of the alkyne through a metal−π complex leads to the putative metallo-benzopyrylium species **40**.[10] Deprotonation of diethyl malonate by the vinyl metal-"ate" species affords gold enolate **13′**, which undergoes nucleophilic addition to the derived benzopyrylium **41**, affording isochromene **38**. Alternatively, coordination of $Au(OAc)_3$ to the isochromene oxygen (**42**) promotes elimination and protonation of the enol ether to afford benzylidenemalonate **39**. Further optimization of the reaction conditions showed that use of 10 mol % of $Au(OAc)_3$ and microwave irradiation (110 °C, 10 min) afforded **38** (62%) along with ring-opened product **39** (20%). Under these conditions, reactions proceeded to full conversion; however, we were not able to fully suppress the pathway leading to **39**. Use of CH_3CN as solvent produced exclusively **39** (90% yield).

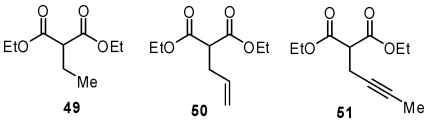
(29) For related additions of 1,3-diketonates, see: (a) Fischer, G. W.; Zimmermann, T.; Weissenfels, M. *Z. Chem.* **1981**, *21*, 446. (b) Asao, N.; Yudha, S. S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526.

Table 1. Scope of Cycloisomerization/Addition Reactions[a]



entry	R	dicarbonyl	product	condition[a]	t	% yield (dr)
1	OMe **6**	**13**	**38**	a	15 m	62%
				b	12 h	58%
2	OMe **6**	**43**	**44**	b	4 h	85% (1:1)
3	OMe **6**	**45**	**46**	b	3 h	70% (2:1)
4	H **28**	**13**	**47**	b	8 h	58%
5	H **28**	**43**	**48**	b	8 h	50% (1:1)

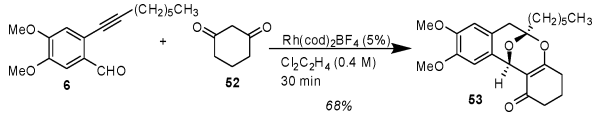
[a] Conditions: (a) $Au(OAc)_3$ (10 mol %), $C_2H_4Cl_2$ (0.4 M), microwave 110 °C (300 W); (b) $Rh(cod)_2BF_4$ (5 mol %), $C_2H_4Cl_2$ (0.4 M).



49 **50** **51**

Figure 6. Unreactive dicarbonyl compounds.

Scheme 8. Unexpected Reactions with 1,3-Dicarbonyls

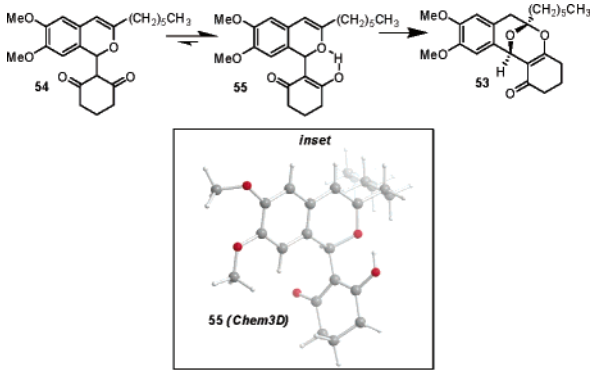


6 **52** **53**

When the dicarbonyl species was changed to β-keto ester **43**, the reaction afforded **44** in 85% yield (Table 1, entry 2) employing 5 mol % of $Rh(cod)_2BF_4$ (25 °C). Cyclic β-ketoester **45** afforded a 70% yield of isochromene **46** (Table 1, entry 3). Furthermore, reaction of alkynyl benzaldehyde **28** afforded the expected addition products in moderate yields (Table 1, entries 4 and 5). Unfortunately, reactions with malonates **49** and **50** were unsuccessful; use of butynyl malonate **51** afforded only trace amounts of the cycloisomerization/addition product. The lack of reactivity of **49**−**51** (Figure 6) is likely due to a higher pK_a (∼18) relative to the successful dicarbonyl substrates in Table 1 (pK_a = 14−16).[30]

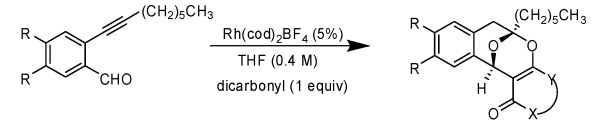
Interestingly, reaction with 1,3-cyclohexanedione **52** afforded an unknown product in moderate yield (68%) (Scheme 8). Computational structure elucidation[14,21] suggested structure **53**, which was further verified by traditional analysis. A proposed pathway to produce tetracyclic ketal **53** proceeded through initial cycloisomerization and nucleophilic addition of the 1,3-cyclohexanedione, affording intermediate **54** (Scheme 9). Tautomerization to enol **54**, likely stabilized through intramolecular hydrogen bonding (cf. inset, Scheme 9),[31] led to internal protonation of the enol ether followed by nucleophilic addition to afford tetracyclic ketal **53**.[32]

Scheme 9. Proposed Reaction Pathway for Addition of 1,3-Cyclohexanedione



54 **55** **53**

Table 2. Reactions with Additional 1,3-Dicarbonyls



entry	R	dicarbonyl	time	product	yield
1	OMe **5**	**56**	4 h	**57**	50%
2	OMe **5**	**58**	12 h	**59**	58%
3	H **28**	**58**	12 h	**60**	48%

Further scope of cyclic 1,3-dicarbonyls was demonstrated with hydroxy pyrone **56** (50% yield of **57**) and hydroxy coumarin **58** (58% yield of **59**) (Table 2). The latter reaction also proceeded in moderate yield with alkynyl aldehyde **28** to afford polycyclic ketal **60** (Table 2, entry 3). X-ray crystal structure analysis[14] of **57** (Figure 7a) further verified initial NMR structural assignments. Notably, a substructure search of the Beilstein natural product database revealed that products **59** and **60** contain the core structural motif found in cyclolycoserone (**61**) and related natural products (Figure 7b).[33]

Reaction Products Derived from Tandem Friedel−Crafts Addition. Analysis of reaction profiles for dimethylaniline **23**

(30) (a) Olmstead, W. N.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299. (b) Arnett, E. M.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 809.

(31) A stochastic conformational search was done using the Molecular Operating Environment (MOE).

(32) For related reactions of 1,3-dicarbonyls, see: (a) Lee, Y. R.; Kim, B. S. *Tetrahedron Lett.* **1997**, *38*, 2095. (b) Lee, Y. R.; Suk, J. Y.; Kim, B. S. *Org. Lett.* **2000**, *2*, 1387. (c) Halland, N.; Velgaard, T.; Jorgensen, K. A. *J. Org. Chem.* **2003**, *68*, 5067. (d) Milan, M.; Viktor, M.; Rudolf, K.; Dusan, I. *Curr. Org. Chem.* **2004**, *8*, 695. (e) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23.

(33) (a) Zdero, C.; Bohlmann, F.; Niemeyer, H. M. *Phytochemistry* **1988**, *27*, 1821. (b) Zderom, C.; Bohlmann, F.; Niemeyer, H. M. *Phytochemistry* **1988**, *27*, 2953.

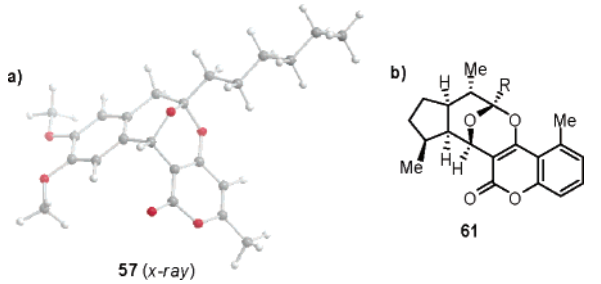
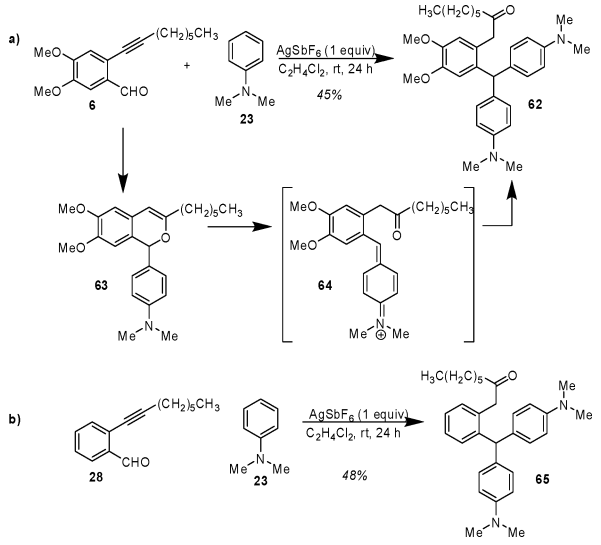
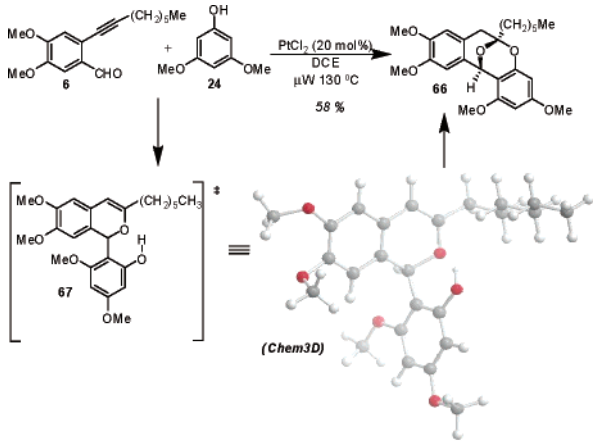


Figure 7. (a) X-ray crystal structure of **57**. (b) Structure of the natural product cyclolycoserone **61**.

Scheme 10. Friedel−Crafts Addition/Annulation of Phenols



Scheme 11. Friedel−Crafts Addition/Annulation of Phenols



revealed production of the unique triarylmethane derivative **62** (Scheme 10). This ketone is apparently derived from cycloisomerization/Friedel−Crafts addition to afford adduct (**63**) followed by ring opening to *para*-quinoid[34] intermediate **64**. A second nucleophilic addition affords the observed ketone **62**.[35] The reaction was also successful when alkynyl benzaldehyde **28** was utilized, affording **65** in moderate yield (48%).

Reaction Products Derived from Friedel−Crafts Addition/Annulation of Phenols. A reaction profile of phenol **24** showed formation of new products catalyzed by $PtCl_2$, AgOTf, $Rh(cod)_2BF_4$, and $Au(OAc)_3$ at 60 °C.[14] Preparative scale reactions using AgOTf and $Au(OAc)_3$ as catalysts failed to provide any isolable products while $Rh(cod)_2BF_4$ afforded dimer **27**. Interestingly, use of $PtCl_2$ uniquely afforded bicyclic ketal **66** (Scheme 11). The reaction likely involves a Friedel−Crafts reaction of phenol **24** with a benzopyrylium intermediate to afford intermediate **67**.[36] The regiochemical outcome (C versus O addition to the oxonium intermediate) of the reaction was determined by HMQC and HMBC analysis.[14] A reaction pathway related to the formation of **66** (cf. Scheme 9) may be proposed in which intermediate **67** exhibits hydrogen bond organization (Chem-3D **67**, Scheme 11) leading to protonation of the isochromene and nucleophilic attack by the phenolic oxygen to afford tetracycle **66**. After reaction optimization, **66** was obtained in 58% yield using microwave irradiation (20% $PtCl_2$, DCE, 130 °C, 300 W).[14] Control reactions excluding $PtCl_2$ under otherwise identical conditions provided only starting materials. Notably, a search of the Beilstein natural product database revealed anthrabenzoxocinone[37] (**68**, Figure 8), which contains the bicyclic ketal motif present in **66**. The unique capability of Pt(II) catalysis for formation of **66** demonstrates the utility of multidimensional screening to identify the appropriate metal catalyst/reaction partner combinations.

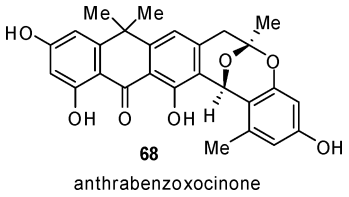


Figure 8. Polycyclic ketal natural product.

Conclusion

Multidimensional reaction screening of *ortho*-alkynyl benzaldehydes with a variety of catalysts and reaction partners was conducted in an effort to identify new chemical reactions. In this initial case study, a screening approach led to the identification of a number of new reaction types including homodimerization, nucleophilic addition of dicarbonyls, addition/oxidation, and Friedel−Crafts addition/annulation, several of which afforded novel molecular frameworks. In a number of cases, a non-intuitive dependence of metal catalyst on the particular reaction process was observed. Computational-assisted structure elucidation was successfully utilized in efforts to ascertain structures of unknown reaction products. Additional applications of multidimensional reaction screening and expansion of the methodologies toward the synthesis of novel chemical libraries are currently underway and will be reported in due course.

Acknowledgment. This work was generously supported by the NIGMS CMLD Initiative (P50 GM067041). We thank Dr. Emil Lobkovsky (Cornell University) for X-ray crystal structure

(34) Tachikawa, T.; Handa, C.; Tokita, S. *J. Photopolym. Sci. Technol*. **2003**, *16*, 187.
(35) For consecutive Friedel−Crafts additions using dimethylaniline, see: Zhu, C. F.; Wu, A. B. *Thermochim. Acta* **2005**, *425*, 7.
(36) A mechanism in which O addition of the phenol is followed by O to C migration may also be possible. For a discussion of O to C glycosylation, see: (a) Matsumoto, T.; Hosoya, T.; Suzuki, K. *Tetrahedron Lett.* **1990**, *31*, 4629. (b) Matsumoto, T.; Hosoya, T.; Suzuki, K. *Synlett* **1991**, 709.
(37) Herath, K. B.; Jayasuriya, H.; Guan, Z.; Schulman, M.; Ruby, C.; Sharma, N.; MacNaul, K.; Menke, J. G.; Kodali, S.; Gaogoci, A.; Wang, J.; Singh, S. B. *J. Nat. Prod.* **2005**, *68*, 1437.

analyses and Professors John Snyder, James Panek, and Scott Schaus for helpful discussions. We also thank Waters Corporation, CEM Corporation, and Zinsser North America for assistance with instrumentation and Advanced Chemistry Development (ACD) Laboratories for assistance with structure elucidation software.

Supporting Information Available: Complete experimental procedures and compound characterization data including X-ray crystal structure data for **29** and **57**. This material is available free of charge via the Internet at http://pubs.acs.org.

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