

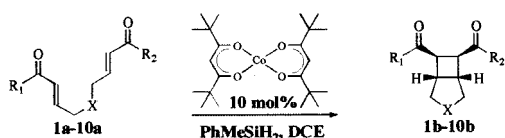
A Diastereoselective Metal-Catalyzed [2 + 2] Cycloaddition of Bis-enones

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While photochemically promoted intramolecular alkene [2 + 2] cycloadditions are routinely used in the synthesis of complex molecular architectures,¹ related metal-catalyzed [2 + 2] cycloadditions of tethered alkenes have not been described.^{2,3} To date, metal-catalyzed alkene [2 + 2] cycloadditions have been restricted to the intermolecular reaction of strained alkene (norbornadienes or methylenecyclopropanes) and electron-deficient alkene partners, typically using zero-valent nickel catalysts.⁴ More recently, chiral Lewis acids have been shown to catalyze the enantioselective intermolecular [2 + 2] cycloaddition between electron deficient alkenes and vinylsulfides or thio ketene acetals.^{2c} In this account, we present the first intramolecular metal-catalyzed [2 + 2] cycloaddition of alkenes. This methodology allows for the facile construction of substituted bicyclo[3.2.0] ring systems in diastereomerically pure form.



Diastereoselective (diketonato)metal-catalyzed aldol and Michael cycloreductions recently were reported from our labs.⁵ In the course of optimizing the Michael cycloreduction of bis-enones **1a** and **2a**, the following observations were made. Whereas Michael cycloreduction represents the exclusive reaction pathway when 2.4 equiv of phenylsilane are used, reactions conducted in the presence of 1.2 equiv of phenylsilane gave comparable amounts of cycloreduction and, remarkably, [2 + 2] cycloaddition products. Attempts were made to optimize the [2 + 2] cycloaddition manifold. Further decreasing the amount of phenylsilane did not substantially alter the product ratio and resulted in diminished yields of both products. In the absence of silane, no reaction was observed. Alternative silane sources were screened for their capacity to induce selection of the [2 + 2] cycloaddition pathway. Optimal yields of the [2 + 2] cycloadducts **1b** and **2b** were obtained with 4.0 equiv of phenylmethylsilane in the

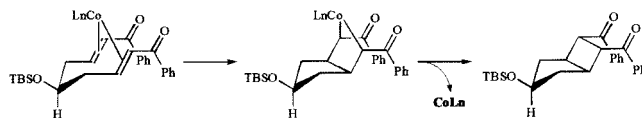
presence of 10 mol % Co(dpm)₂ at 50 °C. Employing the aforementioned conditions, bis-enones **1a** and **2a** were converted to the corresponding [2 + 2] cycloadducts **1b** and **2b** in 72% and 69% yields, respectively, with substantial inhibition of the Michael cycloreduction pathway. Significantly, cycloadducts **1b** and **2b** were obtained as single stereoisomers. The structure of **1b** was corroborated via X-ray diffraction analysis of a single crystal (Table 1).

Table 1. Partitioning [2 + 2] Cycloaddition vs Michael Cycloreduction Manifolds^a

Substrate	Co(dpm) ₂ (equiv.)	Silane (equiv.)	Yield [2+2]	Yield Michael
1a	0.05	PhSiH ₃ , 1.2	38%	41%
1a	0.05	PhSiH ₃ , 2.4	—	73%
1a	0.10	PhMeSiH ₂ , 4.0	72%	11%
2a	0.05	PhSiH ₃ , 1.2	16%	31%
2a	0.05	PhSiH ₃ , 2.4	—	63%
2a	0.10	PhMeSiH ₂ , 4.0	69%	9%

^a See Table 2 for experimental details.

Using these optimized conditions, the cycloaddition of a variety of bis-enones was explored (Table 2). The capacity of the catalyst to tolerate functionality in the tether connecting bis-enones was first examined. Substrates that embody heteroatom-containing linkages, as in oxygen- and nitrogen-bearing bis-enones **2a** and **3a**, smoothly underwent [2 + 2] cycloaddition (Table 2, entries 2 and 3). Tethered bis-enones bearing geminal substitution, as in **4a**, gave increased amounts of Michael cycloreduction (Table 2, entry 4). Substrate-directed diastereoselectivity was probed through the reaction of siloxy-substituted bis-enone **5a** (Table 2, entry 5). The corresponding cycloadduct **5b** was obtained as a single stereoisomer. The siloxy substituent was found to reside on the concave face of the bicyclo[2.3.0] ring system. The stereochemical assignment of **5b** was verified via X-ray diffraction of a single crystal. A general model to account for the observed stereochemistry of all cycloadducts, including **5b**, is indicated below.



Mixed bis-enones containing aliphatic and aromatic enone partners participate in the cycloaddition. Mixed bis-enone **6a** contains a methyl ketone and provides the corresponding cycloadduct **6b** in moderate yield. Finally, heteroaromatic bis-enones **7a–9a**, which contain 2-furyl and 3-indolyl residues, also participate in the cycloaddition reaction.

The stereochemical outcome of the cycloaddition is independent of alkene geometry. Both **1a** and iso-**1a** provide equivalent amounts of **1b** as a single stereoisomer. While π -facial interconversion of an intermediate cobalt enolate might account for this convergent stereochemical outcome, such isomerization should be slow with respect to five-membered ring formation.⁶

The stereochemistry of the [2 + 2] cycloadducts obtained via metal-catalyzed cycloaddition does not reflect the thermodynamic

(1) For selected reviews, see: (a) Bach, T. *Synthesis* **1998**, 683. (b) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, 95, 2003. (c) Crimmins, M. T. *Chem. Rev.* **1988**, 88, 1453. (d) Demuth, M. *Pure Appl. Chem.* **1986**, 58, 1233. (e) De Keukeleire, D.; He, S.-L. *Chem. Rev.* **1993**, 93, 359.

(2) For selected reviews on metal-catalyzed cycloadditions, see: (a) Dzheimilev, U. M.; Khusnutdinov, R. I.; Tolstikov, G. A. *J. Organomet. Chem.* **1991**, 409, 15. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, 96, 49. (c) Hayashi, Y.; Narasaka, K. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Vol. III, Chapter 33.3, p 1255.

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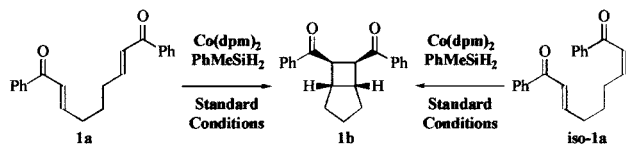
(4) For selected examples of Ni-catalyzed alkene [2 + 2] cycloaddition, see: (a) Kiji, J.; Yoshikawa, S.; Sasakawa, E.; Nishimura, S.; Furukawa, J. *J. Organomet. Chem.* **1974**, 80, 267. (b) Heimbach, P.; Meyer, R. V.; Wilke, G.; *Liebigs Ann. Chem.* **1975**, 743. (c) Takaya, H.; Yamakawa, M.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1982**, 55, 852. (d) Ishii, Y.; Kawahara, M.; Noda, T.; Ishigaki, H.; Ogawa, M. *Bull. Chem. Soc. Jpn.* **1983**, 56, 2181. (e) Saito, S.; Hirayama, K.; Kabuto, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, 122, 10776.

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Table 2. Cobalt(0)Catalyzed [2 + 2] Cycloaddition of Tethered Enones^a

Entry	Substrate	Product	T (°C)	Yield (%) [2+2]	Yield (%) Michael
1			50	72	11
2			50	69	9
3			50	73	—
4			50	50	23
5			50	65	—
6			70	63	5
7			50	48	18
8			50	65	2
9			70	51	—

^a Procedure: Co(dpm)₂ (10 mol %) was added to a solution of phenylmethylsilane (400 mol %) in dichloroethane (0.45 M with respect to substrate) at room temperature. After 30 min, the bis-enone was added as a 0.45 M solution in dichloroethane and the reaction was allowed to stir at 50 °C until complete.



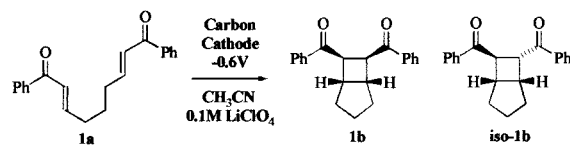
cally preferred configuration. Exposure of **1b** to either Brønsted or Lewis acid catalysts at 30 °C results in clean conversion to the corresponding trans-derivative **iso-1b**, which was characterized via single-crystal X-ray diffraction.

The observed stereochemistry, along with the requirement of at least one aromatic enone partner, suggests organometallic

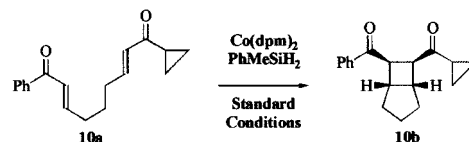
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species en route to the proposed metallobicyclo[3.3.0] intermediate may possess anion radical character. Accordingly, we note that electrochemical reduction of **1a** provides cycloadducts **1b** and **iso-1b** in 32 and 17% yields, respectively.^{7,8}



Cyclopropyl ketones are often used as diagnostic probes for SET. Cobalt catalyzed cycloaddition of mixed enone **10a**, which contains a cyclopropyl ketone, provides cycloadduct **10b** in 42% yield. However, the persistence of the cyclopropyl moiety does not conclusively preclude the anion radical character of reactive intermediates.⁹



In principle, activation of the precatalyst Co(dpm)₂ should require a substoichiometric quantity of silane. However, excess silane is required for complete consumption of starting materials, suggesting the catalyst participates in the competitive dehydrogenative coupling of silane.¹⁰ Indeed, elemental hydrogen is evolved throughout the course of these reactions. Interestingly, mass spectroscopic analysis of Co(dpm)₂ in the presence and absence of PhMeSiH₂ revealed, in the former case, an intense signal at 608(0.72), corresponding to the mass of Co(dpm)₃. Phosphine complexes of Co(II) readily disproportionate.¹¹ It is noteworthy that Co(I), obtained via disproportionation, is iso-electronic with Ni(0), a known alkene [2 + 2] cycloaddition catalyst.⁴

In summary, we have developed a metal-catalyzed [2 + 2] cycloaddition of tethered enones that affords diastereomerically pure substituted bicyclo[3.2.0] ring systems. An important aspect of this methodology resides in the potential to systematically modify the properties of the catalyst to modulate selectivity and broaden substrate scope; a prospect lacking for related photochemical [2 + 2] cycloadditions. Further studies on the mechanism of this process and the development of improved second-generation catalyst systems will be reported in a full account.

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Supporting Information Available: Spectral data for all new compounds (¹H NMR, ¹³C NMR, IR, HRMS); X-ray crystallographic data for **1b**, **iso-1b** and **5b** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(7) Electrochemical experiments were carried out in a divided cell in CH₃CN solution with LiClO₄ as the electrolyte, using reticulated carbon working and counter electrodes and a Ag/AgCl reference electrode.

(8) Anion radical [2 + 2] cycloadditions are uncommon: Janssen, R. G.; Motevalli, M.; Utley, J. H. P. *Chem. Commun.* **1998**, 539.

(9) Tanko, J. M.; Drumright, R. E. *J. Am. Chem. Soc.* **1992**, *114*, 1844.

(10) Rosenberg, L.; Davis, C. W.; Yao, J. *J. Am. Chem. Soc.* **2001**, *123*, 5120.

(11) Socol, S. M.; Verkade, J. G. *Inorg. Chem.* **1986**, *25*, 2658.