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CONTENDO DERIVADO DE
DIBENZOILMETANO PARA PREVENÇÃO E
CONTROLE DE MELANOMA E USO

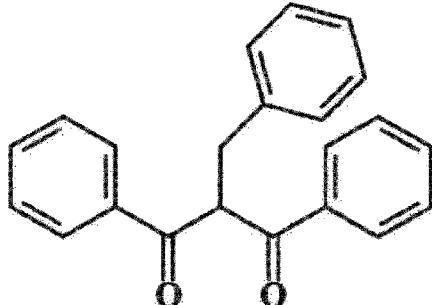
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(57) Resumo: COMPOSIÇÃO FARMACÊUTICA
CONTENDO DERIVADO DE
DIBENZOILMETANO PARA PREVENÇÃO E
CONTROLE DE MELANOMA E USO. A
presente invenção refere a uma composição
farmacêutica contendo 1,3- 5 Difenil-2-benzil-
1,3-propanodiona (DBM2) derivado de
dibenzoilmetano. Tal composição é utilizada na
prevenção e controle de células de melanoma,
sendo de aplicação na indústria farmacêutica
como agente antitumoral no tratamento do
melanoma.



RELATÓRIO DESCRIPTIVO

COMPOSIÇÃO FARMACÊUTICA CONTENDO DERIVADO DE DIBENZOILMETANO PARA PREVENÇÃO E CONTROLE DE MELANOMA E USO

5 CAMPO DA INVENÇÃO

O presente pedido de patente de invenção refere-se a uma composição farmacêutica contendo derivado de dibenzoilmetano (DMB2) utilizado na prevenção e controle de células de melanoma, podendo ser usado na indústria farmacêutica como agente antitumoral, no tratamento do melanoma.

10 Estado da Técnica

Em 2012 no Brasil, foram registrados cerca de 62.680 casos de câncer de pele do tipo não melanoma em homens e 71.490 em mulheres, com cerca de 65 casos a cada 100 mil para os homens e 71 casos em cada 100 mil mulheres. Este tipo de câncer apresenta maior incidência em homens nas regiões Centro-Oeste (124/100 mil), Sul (80/100 mil) e norte (38/100 mil), ficando em segundo lugar as regiões Sudeste (73/100 mil) e o nordeste (31/100 mil). Enquanto nas mulheres ocorre com maior frequência em todas as regiões, na região Centro-Oeste (109/100 mil), sudeste (91/100 mil), sul (68/100 mil), norte (43/100 mil) e região nordeste (42/100 mil) (INSTITUTO NACIONAL DO CÂNCER. ABC do câncer: abordagens básicas para o controle do câncer. Rio de Janeiro: INCA, 2012).

As pessoas que estão mais propensas ao desenvolvimento ao câncer de pele são aquelas portadoras do xeroderma pigmentoso, deficiência genética que vai impedir a reparação dos provocados pela exposição dos raios ultravioletas. Pessoas mulatas ou negras raramente desenvolvem este tipo de câncer, e quando ocorre o tumor, este se desenvolve em locais com ausência de pigmentação como a palma da mão e a planta do pé. Pessoas albinas, que não produzem melanina, de maneira geral, acabam desenvolvendo o câncer de pele (SOUZA, S.R.P.; FISHER, F.M.; SOUZA, J.M.P. Bronzeamento e risco de

melanoma cutâneo: revisão da literatura. Rev. Saúde Pública. 38, 588-98. 2004).

O câncer de pele pode ser de dois tipos principais: melanoma e o não melanoma, sendo este, ainda, encontrado em dois subtipos, o carcinoma basocelular e o carcinoma epidermoide ou espinocelular. O tipo não melanoma, apesar de ser o de maior incidência, possui um nível alto de cura, por ser fácil de diagnosticar no início do seu desenvolvimento (INSTITUTO NACIONAL DO CÂNCER. ABC do câncer: abordagens básicas para o controle do câncer. Rio de Janeiro: INCA, 2011).

O carcinoma basocelular tem a sua origem a partir de células basais da epiderme e aparelho folicular, sendo um tumor de baixa malignidade e seu potencial de formar metástases é restrito. Por ser de fácil diagnóstico, a taxa de óbitos é baixa (MANTESE, S. A. O. Carcinoma basocelular - Análise de 300 casos observados em Uberlândia - MG. Anais Brasileiros de Dermatologia, Rio de Janeiro, 81, 136-142, 2006). Geralmente aparece na face, como ferida isolada, sendo observado com maior frequência em pessoas adultas que possuem a pele com pouca pigmentação, ou ainda devido a outros fatores como a radiação e o papiloma vírus (HPV) que aumentam a chance de desenvolvimento desse tipo de carcinoma (RIBEIRO, R.Y.M.A. Metaloproteinases 2 e 9: expressão, inibidores teciduais e inibição por extratos naturais no carcinoma de células basais e carcinoma espinocelular. Tese (Doutorado em Patologia), Programa de Pós-graduação em Patologia, Universidade Federal de Minas Gerais, Belo Horizonte, 2007). O câncer de pele do tipo melanoma possui menor incidência do que os carcinomas basocelular e escamoso, mas, apesar disso, leva a um maior número de óbitos, representando a causa de 79% dos óbitos por câncer de pele (DIMATOS, D.C.; DUARTE, F.O.; MACHADO, R.S.; VIEIRA, V.J.; VASCONCELLOS, Z. A.A.; BINS-ELY, J.; NEVES, R.D.; Melanoma Cutâneo no Brasil. Arquivos Catarinenses de Medicina. 38, 14-19. 2009; INSTITUTO NACIONAL DO CÂNCER, 2007).

Na última década, o câncer de pele do tipo melanoma apresentou um decréscimo ou estabilidade no número de óbitos em alguns países como os Estados Unidos e Austrália. Já no Brasil, o número de mortes causadas por melanoma ainda está crescendo (SOUZA, S.R.P.; FISHER, F.M.; SOUZA,

- 5 J.M.P. Bronzeamento e risco de melanoma cutâneo: revisão da literatura. Rev. Saúde Pública. 38, 588-98. 2004). Nos países desenvolvidos, a média da expectativa de vida ao melanoma em cinco anos é de 73%, enquanto nos países em desenvolvimento, a expectativa média de vida ao melanoma no mesmo período é de 56%, sendo que a média mundial é 69% (INSTITUTO
 10 NACIONAL DO CÂNCER. ABC do câncer: abordagens básicas para o controle do câncer. Rio de Janeiro: INCA, 2011).

Em média o tempo de sobrevivência de um paciente com melanoma metastático varia de 7 a 9 meses. Menos de 15% desses pacientes conseguem sobreviver por 3 anos (SANTOS, I. Melanoma cutâneo. In: Forones NM. Guia de oncologia (guias de medicina ambulatorial e hospitalar). São Paulo: Manole; 2005. p.191-205; NIKOLAOU, Melanoma: new insights and new therapies. The Journal of investigative dermatology, 132, 854-63, 2012).

- O melanoma surge a partir dos melanócitos, células de origem mesenquimal produtoras de melanina, substância responsável por dar pigmentação à pele (INSTITUTO NACIONAL DO CÂNCER. ABC do câncer: abordagens básicas para o controle do câncer. Rio de Janeiro: INCA, 2011). Existem algumas características gerais morfológicas do melanoma, que são usadas para o seu diagnóstico como: tamanho, ulceração, necrose, simetria, delimitação lateral, melanização (VERONESE, L.A.; MARQUES, M.E.A. Critérios
 20 anatomo-patológicos para melanoma maligno cutâneo: análise qualitativa de sua eficácia e revisão da literatura. J. Bras. Patol. Med. Lab. v. 40, 99-112, 2004). O seu crescimento ocorre em duas fases: a primeira é a fase *radial*, em que o melanoma cresce no interior da epiderme e derme superficial, sendo característica dessa fase a não formação de metástases das células; a segunda
 25 é a etapa de crescimento *vertical*, em que o melanoma se expande em direção às camadas mais internas da derme (KUMAR, V.; ABBAS, A.K. FAUSTO, N.

Robbins e Cotran – Bases Patológicas das Doenças. 7^a edição. Elsevier, 2005.
Cap. 7 e 25).

Apesar de agrupamentos de casos de melanoma sucederem em uma família devido a padrões comuns de exposição solar, até o presente já foram identificados alguns fatores genéticos associados. Estima-se que, em média, 10% dos melanomas são causados por mutações germinativas em genes de suscetibilidade, sendo hereditárias. Até o momento os dois principais genes associados ao melanoma familiar são CDKN2A e CDK4 (CARVALHO, C., GIUGLIANI, B., ASHTON P. Melanoma hereditário: prevalência de fatores de risco em um grupo de pacientes no Sul do Brasil. Anais Brasileiros de Dermatologia 79, 53-60, 2004; LAW, M.H.; MACGREGOR, S.; HAYWARD, N.K. Melanoma genetics: recent findings take us beyond well-traveled pathways. The Journal of investigative dermatology 132, 1763-74, 2012). O primeiro gene codifica dois tipos diferentes de supressores de tumor, o p16INK4a e p14ARF. As mutações nesse gene são encontradas em 10% das famílias que apresentam dois casos de melanoma e em até 40% das famílias com três ou mais casos. As mutações no gene CDK4 são raras e menos significativas (LAW, M.H.; MACGREGOR, S.; HAYWARD, N.K. Melanoma genetics: recent findings take us beyond well-traveled pathways. The Journal of investigative dermatology 132, 1763-74, 2012).

Existem quatro tipos diferentes de melanoma. O *melanoma expansivo superficial* ocorre no tronco e nos membros inferiores, e pode apresentar colorações variadas, como rósea, castanho, preto entre outras. Este tipo se desenvolve depois de anos, podendo aparecer nódulos elevados e sangramento na fase mais avançada do crescimento vertical. O *melanoma nodular* ocorre de forma elevada, apresentando lesão papulosa de cores castanha, azulada ou preta, geralmente acompanhado de sangramentos ou ulcerações. O *melanoma lentigioso acral* representa de 35% a 60% dos casos e ocorre em maior frequência em pessoas não brancas, sendo encontrado nas regiões palmoplantares, extremidades digitais mucosas e semimucosas. O *melanoma lentigo maligno* aparece em regiões de fotoexposição crônica, possuindo limites nítidos e formas não regulares, sendo encontrado principalmente na face, mãos

e membros inferiores, podendo ocorrer ulcerações e sangramentos (FERNANDES, N.C., CALMON, R., MACEIRA, J.P., CUZZI, T., SILVA, C.S.C. Melanoma cutâneo: estudo prospectivo de 65 casos. Anais Brasileiros de Dermatologia 80, 25-34. 2005; DIMATOS, D.C.; DUARTE, F.O.; MACHADO, 5 R.S.; VIEIRA, V.J.; VASCONCELLOS, Z. A.A.; BINS-ELY, J.; NEVES, R.D., Melanoma Cutâneo no Brasil Arquivos Catarinenses de Medicina 38, 14-19. 2009).

O diagnóstico do melanoma pode ser feito pela observação da coloração da pele, que varia de cor castanho-claro até cor negra, podendo ainda ter uma 10 região sem pigmentação. A neoplasia, após seu crescimento superficial se infiltra na epiderme, atingindo ou não a derme papilar. Seu crescimento vertical é rápido através da espessura da pele formando nódulos palpáveis e visíveis (INSTITUTO NACIONAL DO CÂNCER. ABC do câncer: abordagens básicas para o controle do câncer. Rio de Janeiro: INCA 2007). Para auxiliar no 15 diagnóstico observa-se a assimetria da lesão, bordas irregulares e mal definidas, mudança de cor e diâmetro maior de 6 milímetros (DIMATOS, D.C.; DUARTE, F.O.; MACHADO, R.S.; VIEIRA, V.J.; VASCONCELLOS, Z. A.A.; BINS-ELY, J.; NEVES, R.D.; Melanoma Cutâneo no Brasil. Arquivos Catarinenses de Medicina 38, 14-19. 2009). No estadiamento clínico, é realizada 20 uma análise cautelosa da lesão primária, pele adjacente, cadeias linfonodais e órgãos que em maior frequência apresentam metástases (pulmão, cérebro, fígado e ossos) (WAINSTEIN, A.J.A.; BELFORT, F.A. Conduta para o melanoma cutâneo. Rev Col Bras Cir. 31, 204-14. 2004). A biópsia pode ser realizada de duas maneiras: retirando-se completamente a lesão para diagnóstico (biópsia 25 excisional); ou removendo-se apenas parte da lesão (biópsia incisional), que só deve ser feita, quando a lesão for muito grande, estiver distante e não for possível removê-la por meio da biópsia excisional. Estudos vêm sugerindo que o raio x do tórax e dosagem sérica de desidrogenase lática (DHL) auxiliariam nas descobertas das metástases (DIMATOS, D.C.; DUARTE, F.O.; MACHADO, 30 R.S.; VIEIRA, V.J.; VASCONCELLOS, Z. A.A.; BINS-ELY, J.; NEVES, R.D.; Melanoma Cutâneo no Brasil. Arquivos Catarinenses de Medicina 38, 14-19. 2009).

A radiação ultravioleta é uma pequena parcela do espectro das radiações eletromagnéticas e pode ser produzida a partir de fontes artificiais. Estudos propõem que a exposição aos raios ultravioletas seja responsável pela maior parte dos cânceres cutâneo do tipo não-melanomas e possivelmente dos melanomas (BAKOS, L. Tratamento cirúrgico de metástase a distância. Grupo brasileiro de melanoma. Boletim Informativo do GBM - Ano IX - N° 32. Janeiro, Fevereiro e Março, 2006). Além da exposição em excesso a radiação solar, a utilização de fontes artificiais de radiação aumentaram ainda mais o risco de desenvolvimento do melanoma, como no bronzeamento artificial utilizando as câmaras de bronzeamento. Tem-se argumentado que essa seria uma opção segura, pois as lâmpadas que são utilizadas só emitem os raios ultravioletas A, que são os de comprimento longo, mas recentes estudos mostram que os raios ultravioletas A são os principais causadores do melanoma, agindo simultaneamente com os raios ultravioletas B. Estudos recentes mostram um "paradoxo do filtro solar" em que as pessoas que utilizam o bronzeamento artificial são as que mais apresentam queimaduras (SOUZA, S.R.P.; FISHER, F.M.; SOUZA, J.M.P. Bronzeamento e risco de melanoma cutâneo: revisão da literatura. Rev. Saúde Pública 38, 588-98. 2004).

O bronzeamento artificial (bronzeado com lâmpada ultravioleta) tem aumentado nos últimos 20 anos, sendo utilizado com frequência entre adolescentes e adultos de pele mais clara, sendo que estudos vêm demonstrando, nos últimos 15 anos, um maior risco do desenvolvimento do melanoma pelas pessoas que utilizam a cama de bronzeamento, sendo que há evidências que esse risco aumenta ainda mais quando o uso se inicia antes dos 30 anos de idade (BAKOS, L. Tratamento cirúrgico de metástase a distância. Grupo brasileiro de melanoma. Boletim Informativo do GBM - Ano IX - N° 32. Janeiro, Fevereiro e Março, 2006).

Sabe-se atualmente que até 90% dos melanomas e neoplasmas melanocíticos benignos apresentam mutações ativadoras em um dos dois genes principais da via MAPK (Mitogen-activated protein kinase), *NRAS* ou *BRAF* (FLAHERTY, K.T.; HODI, F.S.; FISHER, D.E. From genes to drugs: targeted strategies for melanoma. Nature reviews. Cancer, 12, 349-61, 2012; HOCKER,

T.L.; SINGH, M.K.; TSAO, H. Melanoma Genetics and Therapeutic Approaches in the 21st Century: Moving from the Benchside to the Bedside. *Journal of Investigative Dermatology*, n. April, 2008). Esta via regula processos celulares essenciais, como crescimento, sobrevivência, diferenciação e senescência
 5 (HUANG, P. H.; MARAIS, R. Melanoma troops massed. *Nature*, 459, May, 2009).

As mutações mais frequentes associadas a melanoma (50 a 60% dos casos) são mutações ativadoras de *BRAF*, em associação à inativação da via da proteína de retinoblastoma 1 (Rb1), por exemplo, por meio da inativação de
 10 Andressa INK4a ou por mutações no gene CDK4, que impedem a inibição da CDK4 por p16INK4a, prevenindo a senescência (GODING, C.R. Melanocytes: the new Black. *The international journal of biochemistry & cell biology* 39, 275-9, j2007; NIKOLAOU, V. Melanoma: new insights and new therapies. *The Journal of investigative dermatology* 132, 854-63, 2012). Mutações em NRAS são
 15 identificadas em 15 a 30% dos casos de melanoma cutâneo (FLAHERTY, K.T.; HODI, F.S.; FISHER, D.E. From genes to drugs: targeted strategies for melanoma. *Nature reviews. Cancer* 12, 349-61, 2012; HOCKER, T.L.; SINGH, M.K.; TSAO, H. Melanoma Genetics and Therapeutic Approaches in the 21st
 20 Century: Moving from the Benchside to the Bedside. *Journal of Investigative Dermatology*, n. April, 2008).

Embora sejam menos comuns, melanomas que não apresentam mutações em um dos dois genes da via MAPK citados acima, NRAS e BRAF, podem apresentar algum tipo de alteração genética em outros componentes downstream da via MAPK. Ademais, também podem ocorrer alterações na via PI3K em até 60% dos melanomas (HOCKER, T.L.; SINGH, M.K.; TSAO, H. Melanoma Genetics and Therapeutic Approaches in the 21st Century: Moving from the Benchside to the Bedside. *Journal of Investigative Dermatology*, n. April, 2008). Quando Ras é ativado, há a indução da translocação da membrana e ativação de PI3K. PI3K fosforila o fosfatidilinositol-4,5-bifosfato a
 25 fosfatidilinositol-3,4,5-trifosfato, que leva à ativação de Akt, que é o principal efeito desta via de sinalização, que promove a proliferação, sobrevivência e invasão (SHARMA, A.; TRIVEDI, N.R.; ZIMMERMAN, M.A.; TUVESON, D.A.;

SMITH, C.D.; ROBERTSON, G.P. Mutant V599EB-Raf regulates growth and vascular development of malignant melanoma tumors. *Cancer Res.* 65, 2412-21, 2005).

Derivados de dibenzoilmetanos

5 Os derivados de dibenzoilmetanos (1,3-difenil-propano-1,3-diona, DBM-figura 1) são flavonóides raros e foram isolados pela primeira vez em 1996, pelo grupo da Prof^a Eva Magalhães do Instituto de Química da UNICAMP (MAGALHÃES, A., NOGUEIRA, M. A. Three dibenzoylmethane derivatives from Lonchocarpus species. *Phytochemistry* 46, 1029-1033, 1997).

10 De acordo com levantamentos bibliográficos foram descritos apenas treze derivados de dibenzoilmetanos na natureza e todos encontrados apenas na família Leguminosa nos gênero *Lonchocarpus*.

15 O presente pedido de patente de invenção refere-se a síntese de uma composição farmacêutica contendo o derivado, DBM2, do dibenzoilmetano ativo contra o B16F10, podendo ser utilizado na indústria farmacêutica na produção de medicamentos antitumorais, no tratamento do câncer.

Em busca realizada nos bancos de patentes nacionais e internacionais foi encontrado apenas um documento de patente que apresentou tecnologia similar à apresentada no atual pedido de patente que é apresentada a seguir.

20 O documento de patente PI0006583-8 refere-se à obtenção de novos derivados de dibenzoilmetano que apresentam atividade antineoplásica e de aplicação potencial como protetores solares. Sendo as referidas substâncias caracterizadas pelo fato de apresentar atividade contra as linhagens de células neoplásicas de melanoma, mama, mama resistente.

25 Nesse documento de patente foi pedido a proteção de nove compostos derivados de dibenzoilmetano com atividade antitumoral para quatro linhagens de células tumorais: NCI 460: câncer de pulmão; UACC62: câncer melanoma; MCF7: câncer de mama e NCIADR: câncer mama resistente, diferindo do pedido atual, que trata se de uma formulação farmacêutica de um derivado de

dibenoilmetano utilizado na prevenção, controle e tratamento de células de melanoma.

As outras se referem ao uso de dibenoilmetanos em cosméticos como fotoprotetores, a título de exemplificação e diferenciação, algumas delas são 5 apresentadas a seguir.

O documento de patente PI0202314-8 refere-se a composições de filtro solares contendo um derivado de dibenoilmetano. Tal invenção refere-se a um método para fotoestabilizar uma composição contendo um ou mais agentes de absorção de UV-A de derivado de dibenoilmetano, um ou mais derivados de 10 benzofenona e um diéster ou poliéster de um ácido naftaleno dicarboxílico e a um método de proteção da pele ou cabelo de mamífero contra a radiação UV que consiste em aplicar topicalmente tal composição à pele ou ao cabelo. Essa invenção se trata do uso de derivado de dibenoilmetano como fotoprotetor em formulação cosmética.

15 O documento de patente PI0205475-2 refere-se à composição cosmética ou dermatológica de uso tópico, contendo um derivado de 2-hidroxibenzofenona amino-substituído e processo para melhorar a estabilidade de um derivado de 1,3,5 triazina fotossensível em presença de um derivado de dibenoilmetano. Essa invenção trata do uso do dibenoilmetano como agente fotoprotetor em 20 formulação cosmética.

O documento de patente PI0008044-6 refere-se a composições fotoestáveis adequadas para conferir proteção contra os efeitos prejudiciais da radiação ultravioleta. As composições proporcionam excelente eficiência e eficácia contra UV de amplo espectro, exibindo, ao mesmo tempo, melhor 25 fotoestabilidade. Também são apresentados processos de uso para essas composições. Tais composições compreendem, uma quantidade eficaz de uma substância ativa de filtro solar de dibenoilmetano absorvedora de UVA, um sistema fotoestabilizador consistindo essencialmente em uma quantidade eficaz de p-metoxicinamato de 2-etylhexila e um veículo adequado. Essa invenção trata 30 do uso do dibenoilmetano como agente fotoprotetor em formulação cosmética.

O documento de patente PI0904906-1 refere-se à composição cosmética e processo para melhorar a estabilidade química de pelo menos um derivado de dibenzoilmetano e uso de pelo menos um composto éster de 2-pirrolidinona 4-carbóxi. A presente invenção trata de uma composição que comprehende em um suporte cosmeticamente aceitável pelo menos um sistema que comprehende o derivado de dibenzoilmetano como fotoptotetor. Essa invenção trata do uso do dibenzoilmetano como agente fotoprotetor em formulação cosmética.

O documento de patente PI0205473-6 refere-se a composição cosmética ou dermatológica de uso tópico e processo para melhorar a estabilidade de pelo menos um derivado do dibenzoilmetano e uso de um derivado de 2-hidroxibenzofenona amino-substituído. Tal invenção trata de uma composição cosmética ou dermatológica, que usa o derivado do dibenzoilmetano como agente fotoprotetor. Essa invenção trata do uso do dibenzoilmetano como agente fotoprotetor em formulação cosmética

O documento de patente PI9917231-3 refere-se a processo de composições contendo derivados de dibenzoilmetano, adequadas para uso como filtros solares, que apresentam excelente estabilidade, eficiência e eficácia de proteção contra UV, de maneira segura, económica e esteticamente agradável. Essa invenção trata do uso do dibenzoilmetano como agente fotoprotetor em formulação cosmética.

O documento de patente PI0100691-6 refere-se a um método para fotoestabilizar pelo menos um derivado de dibenzoilmetano contra a radiação UV que utiliza pelo menos uma 5-triazina que contém silicone substituída por dois grupos aminobenzoato ou aminobenzamida com uma fórmula dada. Tal invenção também trata de uma composição que comprehende pelo menos um sistema que filtra as radiações UV em um suporte fisiologicamente aceitável, caracterizado pelo fato de compreender pelo menos um filtro UV do tipo derivado de dibenzoilmetano e pelo menos um composto de 5-triazina que contém silicone substituído por dois grupos aminobenzoato ou aminobenzamida com uma fórmula dada. Essa invenção se trata do uso de derivado de dibenzoilmetano como fotoprotetor em formulação cosmética.

O documentos de patentes US 7,413,730, US 7,368,105, US 7,364,721, ES 2389906, ES 2385223 e ES 2382358 tratam se do uso de derivado de dibenzoilmetano como fotoprotetor em formulação cosmética.

As patentes citadas acima se diferem do atual pedido de patente, pois se referem ao uso de derivados de dibenzoilmetano para uso somente cosmético, já o atual pedido de patente refere-se a um medicamento utilizado na prevenção, controle e tratamento de câncer.

DESCRIÇÃO DAS FIGURAS

As figuras apresentadas neste pedido de patente são descritas a seguir:

10 **Figura 1:** 1,3-Difenil-2-benzil-1,3-propanodiona (DBM₂).

Figura 2: Teste in vivo - Efeito do tratamento com dibenzoilmetano sobre o volume tumoral (cm³), nos diferentes grupos experimentais. O grupo controle (branco) recebeu um placebo como tratamento.

15 **Figura 3:** Quantificação de VEGF pelo teste de ELISA, a partir das amostras de soro coletadas dos camundongos tratados e não tratados (pg/mL).

DESCRÍÇÃO DETALHADA DA INVENÇÃO

PROCEDIMENTO GERAL DE ALQUILAÇÃO

Em um balão de duas bocas de fundo redondo (100 mL), acoplado a um funil de adição contendo o composto dibenzoilmetano a ser alquilado (1,34 mmol) adicionou-se K₂CO₃ (4,02 mmol) e acetona (20 mL) deixou-se sob agitação durante cerca de 30 minutos. Após este tempo, adicionou-se lentamente uma solução de brometo de alquila (1,34 mmol) em acetona (10 mL). A mistura reacional foi agitada vigorosamente por 24 h e, então, filtrada para remoção dos sólidos em suspensão. O filtrado foi concentrado sob pressão reduzida e o resíduo obtido foi purificado por cromatografia em camada

preparativa (CCP, hexano/AcOEt 80:20) levando à obtenção do produto alquilado desejado (Figura 1) com 80 % de rendimento.

PREPARAÇÃO DAS FORMULAÇÕES CONTENDO O COMPOSTO

Foi utilizado um gel transdérmico contendo o composto ativo DMB2 em concentrações de 1 mg/ml a 3 mg/ml. As concentrações utilizadas neste trabalho foram pré-determinadas com base e em comparação aos protocolos utilizados em outros trabalhos. Este tipo de formulação foi escolhido a partir de testes prévios, por apresentar melhor espalhamento e absorção pela pele com maior resistência a água, suor e secreção sebácea. Foram utilizados, agente gelificante, propilenoglicol (umectante), DMSO (promotor de absorção) e álcool 70% (coadjuvante microbiano).

A composição farmacêutica contendo derivado de dibenzoilmetano também pode ser apresentada na forma de pomada e creme.

TABELA 1. Substâncias utilizadas nas composições farmacêuticas de uso tópico.

Substâncias	Quantidades
Dibenzoilmetanos	1 a 3%
DMSO	5 a 10%
Agente gelificante	0,5 a 2%
Propilenoglicol	2 a 5%
Álcool 70 %	qsp

Todos os ingredientes foram previamente pesados ou medidos antes de iniciar o processo de manipulação.

O composto nas concentrações de 1 a 3mg foi dissolvido em 2,5 mL DMSO. Em seguida foram pesados 500 mg de agente gelificante e medidos 20 1,25 mL de propilenoglicol. O agente gelificante e o propilenoglicol foram vertidos em um gral de massa e misturados com auxílio de uma espátula, logo em seguida foi adicionado o composto dissolvido em DMSO, estes foram

novamente misturados com auxílio de uma espátula e o volume foi completado com álcool 70 % até 25 mL. Após, a formulação foi deixada em repouso para completa hidratação do gel na presença da solução hidro alcoólica. Os frascos contendo as formulações foram armazenados herméticamente até o momento 5 do uso.

EXPERIMENTOS DE DEMONSTRAÇÃO

CULTURA DE CÉLULAS

O presente estudo utilizou às linhagens celulares Melan-A (estabelecida a partir de melanócitos normais) e B16F10 (estabelecida a partir de células de melanoma murino). As células da linhagem B16F10 são altamente metastáticas, tendo sido consideradas mais resistentes a drogas e mais instáveis geneticamente do que outras linhagens das células B16 (CILLO et al., 1987).

As células foram rotineiramente cultivadas em meio de cultura completo ("Dulbecco's Modified Eagles Medium" - DMEM - suplementado com 10 % de soro fetal bovino e glutamina 2mM/mL), em frascos de cultura de 25 ou 75 cm², de poliestireno, em incubadora a 37°C, 5% de CO₂ e 95% de umidade relativa. Quando as culturas atingem a semiconfluência, as células são tripsinizadas, replaqueadas e mantidas nas condições acima descritas. As culturas foram periodicamente observadas em microscópio de luz invertido, e alíquotas, 20 congeladas e descongeladas de acordo com a necessidade do experimento.

TRIPSINIZAÇÃO

Culturas de células subconfluentes, após o descarte do meio de cultura, eram lavadas três vezes com PBS e incubadas a 37°C com solução de tripsina a 0,25% e 0,05% de EDTA até que, sob observação microscópica, fosse 25 detectada a dissociação das células entre si, e delas com o substrato. A reação de tripsinização era interrompida pela adição de 5,0 mL de meio completo. A suspensão celular era coletada em tubo de centrífuga e centrifugada a 1500 r.p.m., por 5 minutos, à temperatura ambiente. O meio sobrenadante era cuidadosamente descartado e as células ressuspendidas em meio completo 30 livre de tripsina. Após efetuar a contagem celular, com teste de viabilidade,

volumes da suspensão celular foram subcultivados contendo o número desejado de células.

CONTAGEM DO NÚMERO DE CÉLULAS VIÁVEIS

As contagens das células viáveis são efetuadas em hemocitômetro de Neubauer após o carregamento de ambas as câmaras com a suspensão celular, obtida por meio da tripsinização da cultura celular desejada. Para a determinação do número de células viáveis é utilizado o teste de exclusão de corante, que consiste na incubação de uma alíquota de células com solução de Azul de Tripan a 0,1 % (diluição 1:1), por dez minutos a 37°C. Células hígidas excluem o corante. Para o cálculo da percentagem de células viáveis utiliza-se a fórmula:

$$\% \text{ de células viáveis} = \frac{\text{Número de células viáveis}}{\text{Número total de células}} \times 100$$

Para determinação da quantidade de células viáveis por cm^3 ou mililitro, deve-se calcular a média aritmética entre o número de células vivas das duas câmaras. O número encontrado deve ser multiplicado por 10^4 e pelo valor de diluição (se houver). São contadas somente as células que se encontram ao menos parcialmente na parte central da câmara de Neubauer.

CRIOPRESERVAÇÃO

Quando necessário, alíquotas de células são congeladas após tripsinização rotineira de culturas semiconfluentes. A interrupção da reação de tripsinização é realizada com adição de meio completo e lavagem das células por centrifugação a 1500 r.p.m.. As células são, então, ressuspensas em meio completo contendo 10% de dimetilsulfóxido (DMSO), e as suspensões celulares acondicionadas em criotubos de até 1,8 mL, que permanecem durante a noite a - 80°C e são posteriormente transferidos para o nitrogênio líquido (-196° C), onde são armazenados até que seja necessário seu descongelamento.

DESCONGELAMENTO

Para o descongelamento, criotubos com células da linhagem celular de interesse são mantidos a 37°C, durante 5 minutos. A suspensão celular é então lavada com 10 mL de meio completo por centrifugação a 1500 r.p.m. durante 3
5 minutos, à temperatura ambiente, para a remoção do DMSO utilizado no congelamento. As células são ressuspensas em meio completo, após descarte do sobrenadante, e subcultivadas em frasco de cultura de 25 cm².

ATIVIDADE CITOTÓXICA MEDIDA PELO ENSAIO DO MTT

De acordo com experimentos pilotos realizados previamente, as células
10 em crescimento exponencial foram tripsinizadas e plaqueadas em microplacas de 96 wells, na densidade de 3×10^3 células por poço. Após 24 horas, o meio foi substituído por meio de cultura adicionado do composto ativo, em diferentes concentrações (250 µg/mL, 25 µg/mL, 2,5 µg/mL e 0,25 µg/mL), sendo as células incubadas por outras 48 e 72 horas em uma atmosfera de 5% de CO₂ a
15 37 °C. Quatro horas antes do término de cada período teste (48 e 72 horas), o meio contendo o tratamento foi removido, as células foram lavadas com PBS, e 100 µL de meio de cultura contendo 10 µL m de sal de tetrazolium (MTT, 3-[4,5-dimetiltiazol-2-il]-2,5-difeniltetrazolium bromido: 5mg/mL) foram adicionados às células em cultura, que foram incubadas por 4 h, protegidas da luz. Após esse
20 período de exposição das células ao MTT, o meio de cultura foi removido, e foram adicionados 100 µL de dimetilsulfóxido (DMSO) a cada poço, e as placas incubadas por mais 30 minutos. Sob essas condições, o MTT é reduzido pelo NADH e NADPH em um produto insolúvel azul, o formazam, determinando assim, a viabilidade celular. A leitura foi feita em espectrofotômetro a 570 nm e a
25 concentração inibitória de 50% calculada (IC₅₀). O índice de seletividade (SI) do composto é calculado com base nos valores obtidos para IC₅₀ das duas linhagens celulares utilizadas, considerando-se que ambas são derivadas do mesmo tipo celular da mesma espécie, sendo uma derivada de células normais (melan-A) e a outra derivada de células tumorais (B16F10), a fim de se destacar

o papel do composto ativo sobre as células tumorais, em relação às células normais.

MODELO DE MELANOMA MURINO

Camundongos machos da linhagem C57Bl/6, de 7-8 semanas de idade pesando 20 ± 5 g, provenientes do Biotério Central da Universidade Federal de Viçosa, foram mantidos em biotério ventilado do laboratório de Biofármacos, do Departamento de Bioquímica e Biologia Molecular, também na UFV. Todos os animais foram mantidos em gaiolas de acrílico translúcido, de 24 x 37 x 19 cm, forrada com maravalha, em ambiente com condições controladas (22 ± 2 °C, 10 $60 \pm 5\%$ umidade), com ciclo claro/escuro de 12h, separados por grupos. Receberam dieta padrão e água *ad libitum*. Os experimentos foram realizados de acordo com as normas da Comissão de Ética no Uso de Animais (CEUA) da UFV, e foram aprovados pelo referido órgão, através do processo nº 11/2013.

Os animais foram contidos e tricotomizados na região da nuca, para facilitar a inoculação das células, e para a aplicação do tratamento tópico no local. Para a indução do tumor, 1×10^5 células da linhagem B16F10 foram inoculadas subcutaneamente no flanco dos camundongos C57Bl/6 machos (HAMANO, Y. et al. Physiological levels of tumstatin, a fragment of collagen IV alpha3 chain, are generated by MMP-9 proteolysis and suppress angiogenesis via alphaV beta3 integrin. *Cancer cell* 3, 589–601, 2003; ZEISBERG, E. M. et al. Discovery of endothelial to mesenchymal transition as a source for carcinoma-associated fibroblasts. *Cancer Res.* 67, 10123–10128, 2007). Após 24 horas, os animais começaram a receber o tratamento tópico, realizado durante o período de 21 dias, conforme descrição abaixo. O número de dias de tratamento foi pré-estabelecido por meio de testes prévios.

Após o período do tratamento, os animais foram eutanasiados em câmara de CO₂, com posterior incisão dorsal, para excisão do tumor e análise da presença e medição de possíveis focos de metástase, e incisão ventral, na linha média, para excisão das amostras de fígado, pulmão e rim, além da retirada das amostras de sangue por punção cardíaca.

TRATAMENTO

O experimento *in vivo* foi realizado utilizando como veículo para o composto ativo um gel transdérmico, para fins de otimização da penetração na pele. Foram utilizados 5 grupos no total, conforme descrição abaixo (n = número de animais por grupo), totalizando 27 animais. Os animais receberam o tratamento tópico por 21 dias, começando 24 horas após a indução do tumor, de acordo com os grupos listados abaixo.

- Grupo 0: Controle – animais saudáveis (n = 3)
- Grupo 1: Controle – animais doentes sem tratamento (n = 6)
- 10 • Grupo 2: Animais doentes tratados com o Gel transdérmico com composto ativo – concentração 3 mg/mL (n = 6)
- Grupo 3: Animais doentes tratados com o Gel transdérmico com composto ativo – concentração 1 mg/mL (n = 6)
- 15 • Grupo 4: Controle – Animais doentes tratados com o gel transdérmico sem composto (branco) (n = 6)

O tratamento foi aplicado de forma tópica, na pele dos animais, no mesmo local onde foi induzido o tumor (região tricotomizada).

ANÁLISE DAS AMOSTRAS DE TECIDO COLETADAS

As amostras de tecido (tumor, pulmões, fígado e rins) coletadas foram fixadas em formol 10%, e processadas no Laboratório de Histopatologia, do Departamento de Medicina Veterinária, da Universidade Federal de Viçosa. As lâminas utilizadas para análise histológica foram coradas em hematoxilina-eosina.

As amostras de sangue foram acondicionadas em eppendorfs devidamente identificados, e após a separação do soro, foram congeladas a – 20°C, para posterior realização do ensaio de ELISA (Enzyme-Linked Immunosorbent Assay)

AVALIAÇÃO DE PARÂMETRO SANGUÍNEO

Após a coleta, as amostras de sangue foram centrifugadas para separação do soro, e o soro congelado a - 20°C, conforme orientações do fabricante do kit utilizado para realização do ELISA do tipo sanduíche. As 5 amostras de soro serão avaliadas para presença de VEGF-A, com kit Invitrogen™ KMG0111, seguindo as instruções do manual que acompanha o kit.

HISTOMORFOMETRIA DO TUMOR

Após a excisão do tumor, foram registradas três medidas para estimativa do volume tumoral, para fins de comparação entre controles e tratamento, além 10 da contagem e medição de possíveis focos de metástase que se apresentaram subcutaneamente (KAKUMANU, S. et al. A nanoemulsion formulation of dacarbazine reduces tumor size in a xenograft mouse epidermoid carcinoma model compared to dacarbazine suspension. Nanomedicine: nanotechnology, biology, and medicine 7, 277-83. 2011).

15 Foram feitas lâminas histológicas dos tumores obtidos após a eutanásia dos animais, e nas amostras de melanoma, foram analisados, histologicamente, o número de vasos sanguíneos e presença de áreas de hemorragia, usando-se o software Image-Pro Plus, comparando-se os grupos tratados ao grupo controle. As lâminas foram avaliadas qualitativamente.

20 ANÁLISE DAS AMOSTRAS DE FÍGADO E RIM

Nas amostras de fígado e rim, foi avaliada a presença de alterações 25 histológicas indicativas de citotoxicidade do tratamento sobre o tecido em questão. Assim, buscaram-se, principalmente, alterações da arquitetura normal do tecido, e indicativos de morte celular, como núcleos picnóticos, usando o software Image-Pro Plus.

ANÁLISE DAS AMOSTRAS DE PULMÃO

Nas amostras de pulmão, foi analisada histologicamente a presença de possíveis focos de metástase usando o software Image Pro Plus.

ANÁLISE ESTATÍSTICA

Os dados foram avaliados estatisticamente por análise de variância (ANOVA) e aplicado o teste de Bonferroni, para a verificação da existência de diferenças estatísticas entre as médias dos tratamentos em relação aos 5 controles utilizados, com nível de significância mínimo de 0,05 para os valores analisados. Para a análise dos dados foi utilizado o programa GraphPad Prism®

RESULTADO *IN VITRO*

Após o teste de citotoxicidade realizado com MTT, a concentração inibitória de 50% das células pelo composto foi calculada, utilizando-se os 10 resultados das leituras de absorbância obtidas. Os resultados foram analisados no programa GraphPad Prism®. Com base nas duas linhagens celulares testadas, os valores de IC₅₀ obtidos foram de 225,5 µg/mL para as células da linhagem melan-A (Figura 2) e 53,05 µg/mL para as células da linhagem B16F10 (Figura 3).

15 A partir dos valores de IC₅₀ supramencionados, foi calculado o índice de seletividade (IS) do composto, que é um dos possíveis parâmetros utilizados como indicativo do potencial terapêutico de medicamentos. Valores de IS acima de 2,0 ou 3,0 têm sido considerados significativos (BADISA, R. B. et al. Selective cytotoxic activities of two novel synthetic drugs on human breast 20 carcinoma MCF-7 cells. Anticancer research, 29, 2993-6, 2009; BÉZIVIN, C., TOMASI, F., LOHÉZIE-LE, D., BOUSTIE, J. Cytotoxic activity of some lichen extracts on murine and human cancer cell lines. Phytomedicine 10, 499-503, 2003), ou seja, este valor indica que o composto é duas ou três vezes mais ativo na linhagem de células neoplásicas do que em células normais, o que tornaria 25 um composto adequado para testes clínicos.

No presente estudo, de acordo com a fórmula IS = IC₅₀ melan-A / IC₅₀ B16F10, obteve-se o valor de 4,25 (Tabela 2) como índice de seletividade, o que indica que o composto é 4,25 vezes seletivo para as células do melanoma em 30 relação às células derivadas de melanócitos normais, apresentando potencial terapêutico para ser testado *in vivo*.

Tabela 2 - Valores de IC₅₀ obtidos para as duas linhagens celulares utilizadas, e o índice de seletividade obtido.

Linhagem celular	IC ₅₀ (µg/mL)	IS
Melan-A	225,5	
B16F10	53,05	4,250707

Pode-se calcular, ainda, a porcentagem de proliferação celular em relação aos controles negativos utilizando meio de cultura (Tabela), e a inibição de crescimento das células sob os tratamentos utilizados, e identificou-se que a concentração mais alta (250 µg/mL) promoveu inibição de crescimento de 53,81% nas células melan-A e de 80,95% nas células B16F10.

Tabela 3 - Proliferação celular das células tratadas com o composto ativo, em relação aos controles negativos.

TRATAMENTO	PROLIFERAÇÃO MÉDIA (%)	
	melan-A	B16F10
250 µg/mL	46,19	19,05
25 µg/mL	105,32	83,01
2,5 µg/mL	104,36	99,8
0,25 µg/mL	95,52	86,2

As imagens obtidas a partir das células utilizadas no ensaio de citotoxicidade indicam que a maior concentração testada, 250 µg/mL, inibiu significativamente o crescimento celular, em comparação aos controles utilizados, com meio de cultura e meio de cultura acrescido de 1% de DMSO, que foi a concentração máxima de DMSO utilizada nas células que receberam tratamento com o composto ativo, derivado de dibenzoilmetano.

É interessante observar que, juntamente com a redução do número de células em relação aos controles, a morfologia das células B16F10 tratadas à concentração de 250 µg/mL mudou significativamente, passando a um formato

mais alongado (fusiforme), e apresentando menor adesividade entre as células e também com a placa, características consistentes com a transição epitelial mesenquimal (EMT), em que células tumorais podem adquirir fenótipo mesenquimal, apresentando maior capacidade migratória e infiltrativa

5 (KALLURI, R.; WEINBERG, R. A. The basics of epithelial-mesenchymal transition. *The Journal of Clinical Investigation*, v. 119, n. 6, p. 1420–1428, 2009). Deve-se ressaltar, no entanto, que esta alteração somente foi observada nas células B16F10 tratadas com a maior concentração utilizada do composto, 250 µg/mL. Esta observação coincide com o relato de Mitrus e colaboradores.

10 (MITRUS, I. et al. Properties of B16-F10 murine melanoma cells subjected to metabolic stress conditions. *Acta Biochimica Polonica* 59, 363–366, 2012), que avaliou diferentes parâmetros de células da linhagem B16F10 sob condições de estresse, e relatou a ocorrência de EMT sob privação de oxigênio. Considerando-se que células mais internas de massas tumorais constantemente

15 precisam se adaptar a situações adversas e extremas, como de depleção de nutrientes e hipóxia, é esperado que células derivadas de linhagens tumorais, em cultura, sob situações adversas, também exibam plasticidade (MITRUS, I. et al. Properties of B16-F10 murine melanoma cells subjected to metabolic stress conditions. *Acta Biochimica Polonica* 59, 363–366, 2012). Além disso, células de

20 melanoma, *in vivo*, também passam por um processo semelhante a uma EMT durante a mudança de sua fase de crescimento horizontal, para a fase de crescimento vertical infiltrativo (HSU, M.Y.; MEIER, F.E.; NESBIT, M.; HSU, J.Y.; VAN BELLE, P. E-cadherin expression in melanoma cells restores keratinocyte-mediated growth control and down-regulates expression of invasion-related

25 adhesion receptors. *Am. J. Pathol.*, 156, 1515–1525, 2000).

Em relação ao ensaio realizado com as células da linhagem melan-A, derivadas de melanócitos murinos normais, pode-se observar uma redução significativa do número de células também na concentração mais alta, entretanto, a morfologia das células não se apresentou alterada sob nenhum

30 dos tratamentos aqui utilizados. Assim, o resultado encontrado para IC₅₀ (mesmo conceito básico de CC₅₀) no presente estudo para as células B16F10 (53,05 µg/mL) ficou pouco acima dos valores obtidos por Nakano e

colaboradores (NAKANO, K. et al. *Induction of Apoptosis by , -Diketones in Human Tumor Cells.* v. 718, p. 711-717, 2004) nas linhagens de células tumorais, e dentro da mesma faixa, nas linhagens de células normais (225,5 µg/mL para as células melan-A, nesta pesquisa).

5 RESULTADO *IN VIVO*

No experimento *in vivo*, cerca de 7 a 10 dias após a inoculação das células na região dorso-cervical dos animais, os tumores se tornaram palpáveis. Ao final do período experimental de 21 dias, alguns animais chegaram a óbito, com volume do tumor chegando a causar ulceração na pele.

- 10 Após o período de tratamento dos camundongos, os animais foram eutanasiados e as amostras de fígado, rim, pulmão e o tumor foram removidos. A análise histológica dos tumores excisados demonstrou figuras típicas de melanócitos, com presença de pigmento escurecido, característico de melanina, e presença de vascularização, caracterizando o desenvolvimento de tumor do tipo melanoma, além do aspecto macroscópico enegrecido fornecido pelo pigmento presente. Os resultados da avaliação do volume tumoral dos animais tratados e dos animais não tratados indicam um significativo papel quimiopreventivo ou quimioterápico do composto utilizado na supressão da progressão tumoral, como pode ser visto na figura 2. As análises do volume tumoral dos animais que receberam tratamento tópico com 1,3-Difenil-2-benzil-1,3-propanodiona nas concentrações de 3 mg/mL e 1 mg/mL, em comparação aos grupos controles (o primeiro, que não recebeu tratamento, e o segundo, tratado com uma formulação-placebo), indicaram diferenças significativas em relação aos controles, com volume tumoral menor nos grupos de tratamento.
- 15 20 25 30
- Assim, pode-se identificar que ambas as concentrações do composto utilizadas no ensaio *in vivo* (3 mg/mL e 1 mg/mL) se mostraram eficazes como agentes quimioterápicos ou quimiopreventivos, com volume do tumor do tipo melanoma induzido no flanco dos camundongos cerca de 55% menor nos grupos tratados do que nos grupos não tratados, apresentando, portanto, potencial terapêutico para utilização em formulação tópica.

Durante a avaliação histológica das amostras de tumor, pode-se observar que o aspecto do tecido coletado a partir dos animais tratados diferiu do material dos grupos controle. Nos animais controle (tratados com formulação placebo e sem tratamento), o material apresentou uma arquitetura mais compacta, mais 5 próxima de um tecido organizado do que nos animais tratados, com o tecido mostrando células viáveis preservadas e de aspecto mais homogêneo e vascularizado, apesar da presença de pleomorfismo nuclear, com atipias grosseiras, figuras de mitoses atípicas e diversas áreas de necrose tecidual, concentradas, principalmente, na região mais central do tumor.

10 Nas amostras dos tumores de animais tratados, além das áreas necróticas mais extensas, foi identificada a presença de núcleos picnóticos e corpos apoptóticos, indicativos de morte celular, além da presença de edema celular (ou alteração vacuolar) e inclusões nucleares eosinofílicas.

15 Na avaliação histológica do fígado, pode-se comparar a arquitetura normal do tecido, a partir das amostras do grupo saudável (sem tumor), com os demais grupos, e também os grupos controle (doentes sem tratamento, e tratados com branco) e os grupos tratados (1 e 3 mg/mL). As alterações teciduais visualizadas nos grupos controle (espaços sinusóide aumentados, e vacuolização citoplasmática nos hepatócitos) e o infiltrado inflamatório foram 20 atenuados com o tratamento, caracterizando o efeito hepatoprotetor do composto.

25 Com base na avaliação histológica das amostras do pulmão. Nao foram encontrados sinais de metastase em nenhum dos grupos experimentais. Em relação as amostras de rim também não se encontrou nenhuma alteração presente nas lâminas observadas.

RESULTADOS DA AVALIAÇÃO DE PARÂMETRO SANGUÍNEO

A análise quantitativa realizada para VEGF no soro obtido do sangue dos camundongos mostrou uma redução significativa, em picogramas de VEGF por mL de sangue, dos animais tratados em comparação aos animais controle. A 30 quantidade média de VEGF dos animais tratados com 1 mg/mL do composto não diferiu do valor obtido para os animais saudáveis, ao passo que o grupo

tratado com 3 mg/mL diferiu dos animais saudáveis, e também dos animais controle (tratados com placebo e doentes sem tratamento). A quantidade de VEGF de ambos os grupos tratados diferiu significativamente dos grupos controle, caracterizando o efeito do composto. Estes dados corroboram os 5 números obtidos para volume tumoral, identificando uma possível relação entre a redução do volume tumoral e a redução de VEGF nos animais tratados em relação aos controles.

Além de favorecer a proliferação e migração de células endoteliais, alguns estudos recentes têm indicado que o VEGF desempenha importante 10 papel autócrino e intrácrino sobre células tumorais que expressam o receptor para VEGF (VEGFR) (CALVANI, M.; TRISCIUOGLIO, D.; BERGAMASCHI, C.; SHOEMAKER, R. H.; MELILLO, G. Differential involvement of vascular endothelial growth factor in the survival of hypoxic colon cancer cells. *Cancer Res.*, 68, 285–291, 2008; SAMUEL, S. et al. Intracrine Vascular Endothelial 15 Growth Factor Signaling in Survival and Chemoresistance of Human Colorectal Cancer Cells. *Oncogene*, 30, 1205-1212, 2011). XU, C.; WU, X.; ZHU, J. VEGF Promotes Proliferation of Human Glioblastoma Multiforme Stem-Like Cells through VEGF Receptor 2. *The Scientific World Journal*, 1-8, 2013) por exemplo, relacionaram a proliferação de células-tronco formadoras de glioblastoma 20 multiforme, isoladas a partir de espécimes cirúrgicas de glioblastoma, à estimulação por VEGF exógeno, via VEGFR2, e não via VEGFR1. Esse efeito demonstrou ser, ainda, dose-dependente. PERROT-APPLANAT, M.; BENEDETTO, M. DI. Autocrine functions of VEGF in breast tumor cells - Adhesion, survival, migration and invasion. *Cell Adhe.* 6, 547–553, 2012, 25 revisaram os efeitos do VEGF sobre a proliferação, sobrevivência, adesão, migração e invasão em células de tumor de mama, dando destaque à importância desta área de pesquisa emergente.

Tendo como objetivo a busca por um mecanismo que relate os efeitos do DBM e seus derivados sobre a expressão de VEGF e a morte celular, 30 podemos considerar os resultados obtidos por Anand e seus colaboradores (ANAND, P. et al. Suppression of pro-inflammatory and proliferative pathways by diferuloylmethane (curcumin) and its analogues dibenzoylmethane,

dibenzoylpropane, and dibenzylideneacetone. *Biochem. Pharmacol.*, 82, 1901-1909, 2011), que analisaram os efeitos do dibenzoilmetano e outros compostos análogos, como a curcumina, sobre a ativação do fator de transcrição NF-κB (fator nuclear kappa B) pelo fator de necrose tumoral (TNF), e também sobre produtos gênicos regulados pelo NF-κB e a proliferação celular. A importância do fator de transcrição NF-κB se deve a seu papel na regulação de mais de 500 genes relacionados à inflamação, sobrevivência e proliferação celular, invasão, angiogênese e metástase (SUNG, B. et al. *Cancer Cell Signaling Pathways Targeted by Spice-Derived Nutraceuticals*. *Nutrition and Cancer* 64, 173-197, 2012). DBM e seus derivados suprimiram a expressão de COX-2, ciclina D1, e VEGF, (produtos gênicos regulados pelo NF-κB induzidos por TNF), afetando, assim, vias de sinalização celular da inflamação, proliferação celular, e angiogênese, respectivamente (ANAND, P. et al. *Suppression of pro-inflammatory and proliferative pathways by diferuloylmethane (curcumin) and its analogues dibenzoylmethane, dibenzoylpropane, and dibenzylideneacetone*. *Biochem. Pharmacol.*, 82, 1901-1909, 2011.). O trabalho de SUNG e colaboradores (SUNG, B. et al. *Cancer Cell Signaling Pathways Targeted by Spice-Derived Nutraceuticals*. *Nutrition and Cancer* 64, 173-197, 2012) revisou as vias de sinalização celular que normalmente são alvo de nutracêuticos relacionados a condimentos, incluindo o DBM, e também deram ênfase a seu papel sobre o NF-κB.

Samuel e colaboradores (SAMUEL, S. et al. *Intracrine Vascular Endothelial Growth Factor Signaling in Survival and Chemoresistance of Human Colorectal Cancer Cells*. *Oncogene*, 30, 1205-1212, 2011), identificaram que a inibição da expressão de VEGF em linhagens celulares de câncer colorretal (CRC) humano levou à redução de crescimento celular (arraste do ciclo celular) e a aumento da morte celular por apoptose, e demonstraram os efeitos intrácrinos pró-sobrevivência do VEGF sobre as células pelo uso de anticorpos monoclonais específicos para o VEGF secretado (extracelular). A atividade do VEGF sobre as células não era bloqueada pelo uso do anticorpo monoclonal, de modo que o fator de crescimento parece atuar de forma intracelular. Utilizando, ainda, um inibidor intracelular da função tirosina quinase do VEGFR, puderam

verificar que a atividade de VEGF sobre as células CRC independe da fração tirosina quinase do receptor. Além disso, os resultados relacionados à inibição de crescimento celular e aumento de apoptose foram mediados pelo aumento de mediadores pró-apoptóticos (caspase 3, PARP clivado e Bax), e redução da 5 survivina, um fator pró-sobrevivência.

A apoptose em células tumorais causadas pelo bloqueio da expressão de VEGF também foi demonstrada por Lee e colaboradores (LEE, E.; YIM, S.; LEE, S.K.; PARK, H. Two transactivation domains of hypoxia-inducible factor-1alpha regulated by the MEK-1/p42/p44 MAPK pathway. *Mol. Cells*, 14, 9 - 15, 2002), 10 em células de tumor de mama dependentes de estrógeno e não-dependentes de estrógeno. A inibição de expressão de VEGFR1 também reduziu, significativamente, a sobrevivência celular, através da inibição da quinase Akt. Como a utilização de um ligante específico para VEGFR1 não reverteu a 15 apoptose induzida, os autores analisaram a localização do VEGFR1, e identificaram sua presença no envelope nuclear, constatada por imunofluorescência, tanto em linhagens celulares já estabelecidas de mama humano, quanto em culturas primárias de células de tumor de mama e de células normais da mama.

Com base nos trabalhos supramencionados e nos resultados 20 apresentados até aqui, verificou-se que a composição farmacêutica contendo derivado de DBM utilizado no presente estudo causou algum tipo de bloqueio da expressão de VEGF, através da inibição de NF- κ B, favorecendo, consequentemente, a morte das células tumorais, seja ela por necrose ou por 25 apoptose, visto que ambas são relacionadas a cascatas de sinalização (PI3K/Akt ou PLC- γ) reguladas por VEGF e seus receptores tirosina quinase.

Em relação ao modelo in vivo utilizado, o modelo se mostrou eficiente, uma vez que foram obtidos resultados significativos utilizando-se a via transdérmica de distribuição da droga, e não houve reações adversas observadas. Deve-se considerar, ainda, que esta via de distribuição apresenta 30 vantagens em relação às demais rotas utilizadas. Além de ser menos dolorosa e onerosa, não-invasiva e poder ser aplicada pelo próprio paciente, pode

promover a liberação da droga por períodos prolongados e não produz lixo contaminado, como a aplicação intravenosa.

CONCLUSÕES

A Composição Farmacêutica Contendo Derivado de Dibenzoilmetano 5 objeto de pedido de patente confirmou sua atividade antimelanoma *in vitro*, com destaque para seus efeitos sobre a transição epitelial-mesenquimal sofrida pelas células da linhagem B16F10, e para sua seletividade para as células tumorais, em relação à linhagem derivada de células normais.

In vivo, os testes realizados, neste estudo, reforçam o papel 10 antiproliferativo da composição farmacêutica sobre as células de melanoma, com significativa diferença do volume tumoral de camundongos tratados em relação aos camundongos não tratados. Como a redução do volume tumoral foi associada à redução dos níveis de VEGF sorológicos, este fator de crescimento parece representar umas das peças relacionadas ao mecanismo pelo qual o 15 composto agiu sobre o tumor.

Além disso, há de se considerar o efeito hepatoprotetor exercido pela composição, e também o fato de que os demais tecidos avaliados não apresentaram alterações. E também, o fato de que não foram localizadas metástases pulmonares, principal sítio de metastatização desse tipo de tumor.

20 Assim, os indicativos são de uma opção terapêutica inovadora, com perspectivas futuras de comercialização.

REIVINDICAÇÕES

1- COMPOSIÇÃO FARMACÊUTICA CONTENDO DERIVADO DE DIBENZOILMETANO PARA PREVENÇÃO E CONTROLE DE MELANOMA

caracterizada por compreender composto ativo derivado de dibenzoilmentano associado a um ou mais ingredientes farmaceuticamente aceitáveis;

2- COMPOSIÇÃO FARMACÊUTICA CONTENDO DERIVADO DE DIBENZOILMETANO PARA PREVENÇÃO E CONTROLE DE MELANOMA,

de acordo com a reivindicação 1, caracterizada por compreender o composto ativo 1,3-Difenil-2-benzil-1,3-propanodiona (DBM2);

3- COMPOSIÇÃO FARMACÊUTICA CONTENDO DERIVADO DE DIBENZOILMETANO PARA PREVENÇÃO E CONTROLE DE MELANOMA,

de acordo com as reivindicações 1 e 2, caracterizado por compreender 1 a 3% de 1,3-Difenil-2-benzil-1,3-propanodiona (DBM2), gel transdérmico, pomada ou creme, 5 a 10% de promotor de absorção (DMSO), 0,5 a 2% agente gelificante, 2 a 5% de propilenoglicol (umectante) e álcool 70%;

4- USO DO COMPOSTO ATIVO definido na reivindicação 2 caracterizado por

ser para a produção de agentes farmacêuticos usados no tratamento e profilaxia de melanoma.

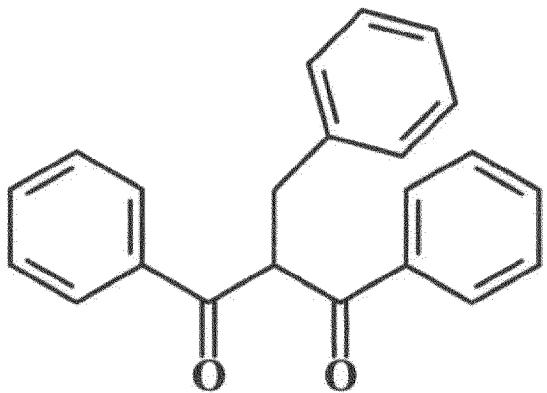


Figura 1

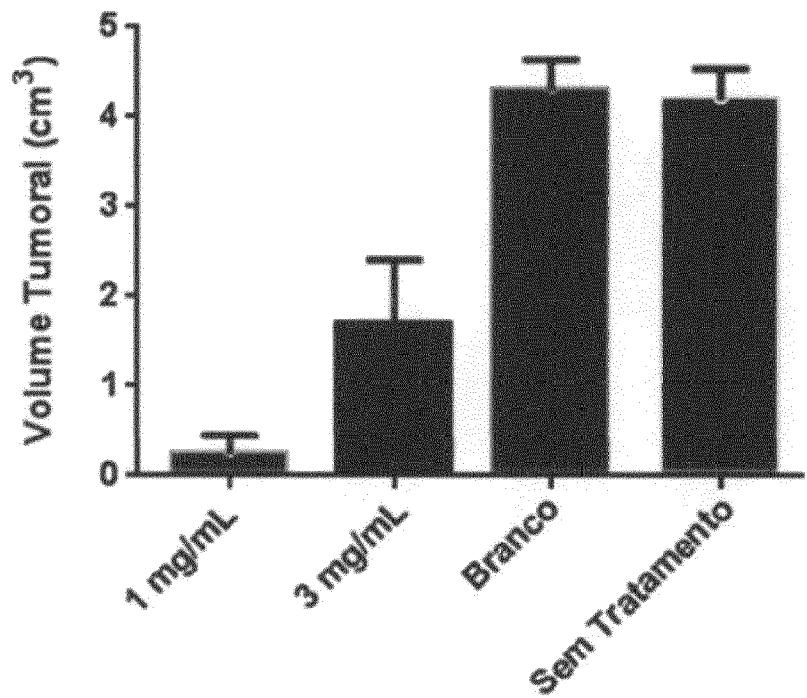


Figura 2

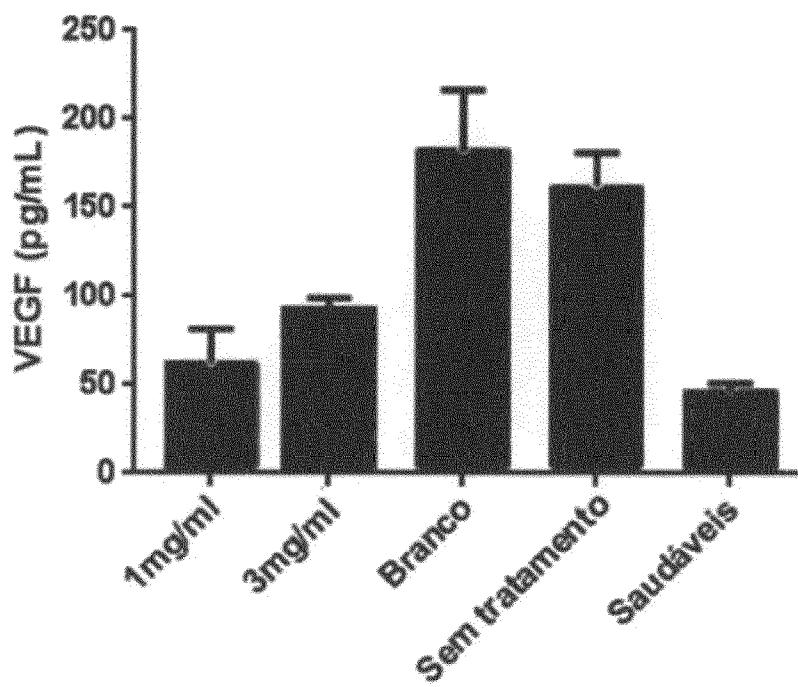


Figura 3

Resumo

COMPOSIÇÃO FARMACÊUTICA CONTENDO DERIVADO DE DIBENZOILMETANO PARA PREVENÇÃO E CONTROLE DE MELANOMA E USO. A presente invenção refere a uma composição farmacêutica contendo 1,3-

5 Difenil-2-benzil-1,3-propanodiona (DBM₂) derivado de dibenzoilmelano. Tal composição é utilizada na prevenção e controle de células de melanoma, sendo de aplicação na indústria farmacêutica como agente antitumoral no tratamento do melanoma.



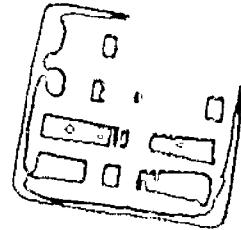
República Federativa do Brasil
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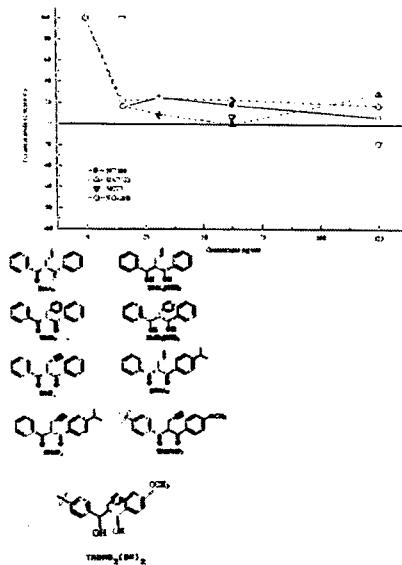
(54) Título: OBTEÇÃO DE NOVOS DERIVADOS DE DIBENZOILMETANO QUE APRESENTAM ATIVIDADE ANTINEOPLÁSICA E DE APLICAÇÃO POTENCIAL COMO PROTETORES SOLARES

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(57) Resumo: "OBTEÇÃO DE NOVOS DERIVADOS DE DIBENZOILMETANO QUE APRESENTAM ATIVIDADE ANTINEOPLÁSICA E DE APLICAÇÃO POTENCIAL COMO PROTETORES SOLARES". Sendo as referidas substâncias caracterizadas pelo fato de apresentar atividade contra as linhagens de células neoplásicas de melanoma, mama, mama resistente a pulmão, ditas substâncias apresentando as seguintes fórmulas gerais abaixo representadas: $TMDMB_2(OH)_2$



"OBTENÇÃO DE NOVOS DERIVADOS
DE DIBENZOILMETANO QUE APRESENTAM ATIVIDADE ANTINEOPLÁSICA
E DE APLICAÇÃO POTENCIAL COMO PROTETORES SOLARES".

Refere-se o presente relatório

5 a uma Patente de Invenção que trata da obtenção de Dibenzoilmetano que apresentam atividade antineoplásica e de aplicação potencial como protetores solares.

O câncer é uma das doenças que mais afligem a humanidade e o desenvolvimento de novas drogas é um fator preponderante para o tratamento quimioterápico e preventivo. Dentre os tipos mais freqüentes podemos citar o câncer de mama, que é uma das neoplasias mais comum entre as mulheres, representando cerca de 32% do total do tipo de câncer que as acometem¹. Muitos são os fatores que 15 podem desencadear este processo, dentre eles se destacam a menarca precoce, parto tardio, menopausa e tendências herdadas geneticamente. Um outro tipo de câncer muito comum e que vem aumentando a cada ano, é o melanoma maligno induzido, o qual pode ser desencadeado por fatores externos, tais 20 como radiações UV.

As radiações ultravioleta dividem-se em UVA (320 a 400 nm), UVB (280 a 320 nm) e UVC (280 a 200 nm), sendo que as radiações UVA e UVB possuem efeitos benéficos ao organismo humano estimulando a formação 25 de vitamina D₃ além, de poderem ser empregadas no tratamento da certas doenças de pele, como eczema, psoriase e herpes bucal².

As radiações UVA penetram pro-

fundamento na pele, chegando até a derme e podem causar malefícios que vão desde reações de fotossensibilidade e envelhecimento precoce da pele, até o aparecimento de câncer de pele. Sua intensidade independe da influência de fatores como altitude, latitude, sazonalidade, hora do dia, alterações da camada de ozônio e concentração de poluentes, mantendo-se praticamente constante³. As radiações UVB atravessam a epiderme, causando eritema, edema, envelhecimento precoce, fotossensibilização, câncer de pele e imunossupressão. São absorvidas parcialmente pela camada de ozônio e atingem a superfície terrestre com diferentes intensidades, estando sujeita a influência da sazonalidade, altitude, latitude, teor de umidade, concentração de poluentes e hora do dia. As radiações UVC podem causar descamação da pele e aparecimento de dois tipos de câncer: melanoma maligno e carcinoma de células escamosas. São quase totalmente absorvidas pela camada de ozônio existente na estratosfera, a qual, nos últimos anos, vem diminuindo progressivamente de espessura⁴.

Os especialistas recomendam o uso de protetores solares (físicos e/ou químicos) para redução dos danos causados pela exposição à luz solar, principalmente em nosso país, que apresenta elevado índice de insolação devido à sua localização geográfica.

Entre os protetores solares que atuam na região do UVA, encontra-se a classe das 1,3-difenilpropano-1,3-dionas, à qual pertencem o [(4-tert-butil)fenil]-(4-metoxifenil)-1,3-propanodiona (Parsol® 1789) e

o [(4-*iso*-propil)fenil]-3-fenil-1,3 propanodiona (Eusolex® 8020), compostos comerciais utilizados em formulações cosméticas. Esta mesma classe de compostos apresentam atividade quimiopreventiva em tumores murino de pele, estômago, 5 cólon e mama⁵.

Portanto é alvo de nosso interesse a obtenção de derivados de 1,3-difenilpropano-1,3-dionas visando agentes quimiopreventivos principalmente para neoplasias como melanoma, mama e mama resistente, 10 fotoquimicamente estáveis, podendo acumular a dupla função de protetor solar e efeito antineoplásico.

A Patente de Invenção em questão será descrita com referência aos desenhos abaixo relacionados, nos quais:

- 15 a figura 1 ilustra um gráfico relativo ao espectro de absorção da solução TMDMB₂(OH)₂ em diferentes tempos de irradiação (min), durante nove horas de irradiação, usando lâmpada UV;
- 20 a figura 2 ilustra um gráfico da curva dose-resposta da atividade antiproliferativa do 5FU sobre linhagens celulares tumorais humanas;
- 25 a figura 3 ilustra um gráfico da curva dose-resposta da atividade antiproliferativa do CPT 11 sobre as linhagens celulares tumorais humanas;
- a figura 4 ilustra um gráfico da curva dose-respos-

ta da atividade antiproliferativa do DOX sobre as linhagens celulares tumorais humanas;

5 a figura 5 ilustra um gráfico da curva dose-resposta da atividade antiproliferativa do DMA₂ sobre linhagens celulares humanas;

10 a figura 6 ilustra um gráfico da curva dose-resposta da atividade antiproliferativa do DMA₂OH₂ sobre linhagens celulares tumorais humanas;

15 a figura 7 ilustra um gráfico da curva dose-resposta da atividade antiproliferativa do DME₂ sobre linhagens celulares tumorais humanas;

a figura 8 ilustra um gráfico da curva dose-resposta da atividade antiproliferativa do DMB₂OH₂ sobre linhagens celulares tumorais humanas;

20 a figura 9 ilustra um gráfico da curva dose-resposta da atividade antiproliferativa do DMP₂ sobre linhagens celulares tumorais humanas;

25 a figura 10 ilustra um gráfico da curva dose-resposta da atividade antiproliferativa do IDMA₂ sobre linhagens celulares tumorais humanas;

a figura 11 ilustra um gráfico da curva dose-respos-

ta da atividade antiproliferativa do IDMB₂ sobre linhagens celulares tumorais humanas;

5 a figura 12 ilustra um gráfico da curva dose-resposta da atividade antiproliferativa do IDMP₂ sobre linhagens celulares tumorais humanas;

10 a figura 13 ilustra um gráfico da curva dose-resposta da atividade antiproliferativa do TMDMA₂ sobre linhagens celulares tumorais humanas;

15 a figura 14 ilustra um gráfico da curva dose-resposta da atividade antiproliferativa do TMDMB₂ sobre linhagens celulares tumorais humanas;

a figura 15 ilustra um gráfico da curva dose-resposta da atividade antiproliferativa do TMDMB₂OH₂ sobre linhagens celulares tumorais humanas; e

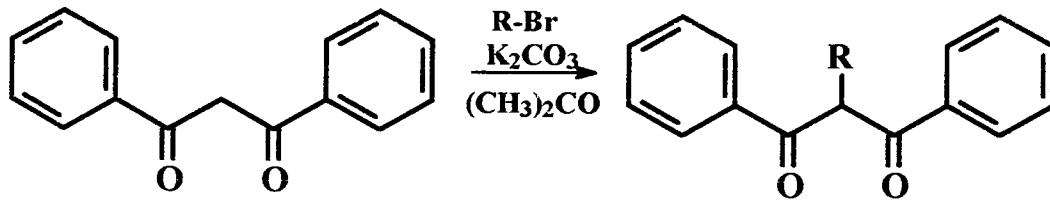
20 a figura 16 ilustra um gráfico da curva dose-resposta da atividade antiproliferativa do TMDMP₂ sobre linhagens celulares tumorais humanas;

Introduziram-se alterações na
25 molécula do dibenzoilmetano (1,3-difenilpropano-1,3-diona) e nas de dois protetores solares: Parsol® 1789 e Eusolex® 8020.

Segue-se abaixo o procedimento

geral de alquilação⁶.

Em um balão de duas bocas de fundo redondo (100 mL), acoplado a um funil de adição contendo a substância a ser alquilada (1,34 mmol) adicionou-se 5 K₂CO₃ (4,02 mmol) e acetona (20 mL) deixou-se sob agitação durante ca. 30 min. Após este tempo, adicionou-se lentamente uma solução de brometo de alquila (1,34 mmol) em acetona (10 mL). A mistura reacional foi agitada vigorosamente por 24 h e, então, filtrada para remoção dos sólidos em suspensão. O filtrado foi concentrado sob pressão reduzida e o resíduo obtido foi purificado por cromatografia em camada preparativa (CCP, hexano/AcOEt 80:20) levando à obtenção do produto alquilado desejado (esquema 1).



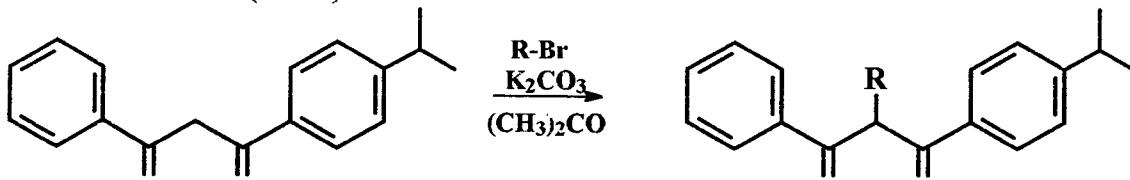
DM

DMA₂ R = CH₂-CH=CH₂; 87%

DMB₂ R = CH₂-; 85%

DMP₂ R = CH₂-C≡CH; 83 %

Eusolex® 8020 (IDM)



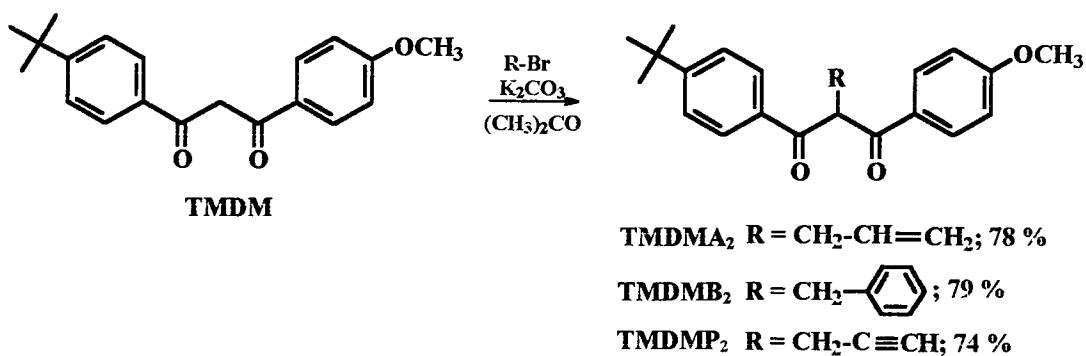
IDM

IDMA₂ R = CH₂-CH=CH₂; 95%

IDMB₂ R = CH₂-; 64%

IDMP₂ R = CH₂-C≡CH; 60 %

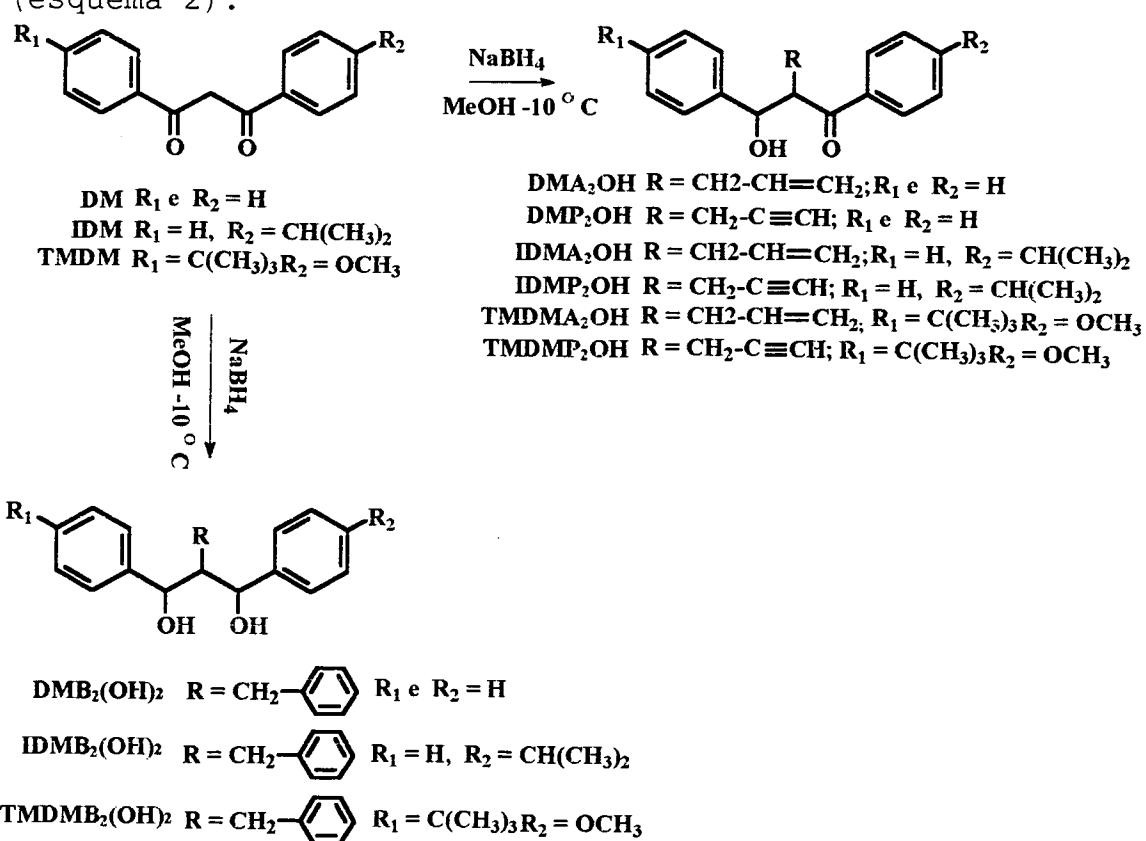
Parsol® 1789 (TMDM)



Segue-se abaixo a redução química prevista no presente processo.

Redução química com NaBH₄.

Em um balão de uma boca de fundo redondo (25 mL) contendo a substância alquilada (1,0 mmol) e MeOH (3 mL), adicionou-se NaBH₄ (0,25 mmol) a -10 °C. A reação foi monitorada por cromatografia em camada delgada (CCD, CH₂Cl₂). A mistura reacional foi purificada por CCP (CH₂Cl₂) levando à obtenção do produto reduzido desejado (esquema 2).



Segue-se abaixo o estudo foto-químico⁷, previsto no presente processo.

As soluções dos derivados alquilados de dibenzoilmetano, Parsol® 1789 e Eusolex® 8020 bem como os compostos comerciais dibenzoilmetano, Parsol® 1789, Eusolex® 8020 e Parsol® MCX (octilmetoxicinamato) foram colocadas em cubetas de quartzo, com 1 cm de caminho óptico. As amostras foram irradiadas com luz proveniente de uma lâmpada de UVA, marca Germetec, modelo Cosmelex UVA-Plus (potência 100 W), cuja emissão abrange, também, a região de UVB de interesse. A lâmpada foi instalada em um suporte apropriado, cujas paredes internas foram enegrecidas (para não refletir luz), no qual as amostras foram colocadas a uma distância pré-determinada (6cm) em relação à lâmpada, de modo que fossem irradiadas sempre com luz à mesma intensidade. A sala foi termostatizada a fim de manter a temperatura constante. Os espectros de absorção foram registrados após os seguintes tempos de irradiação: 0; 5; 15; 20; 30; 40; 50; 60; 70; 80; 90; 100; 110; 120; 140; 160; 180; 200; 220; 240; 260; 300; 360; 420; 480 e 540 minutos.

Os espectros de absorção nas regiões do ultravioleta e visível (UV/VIS) foram obtidos a 25 °C em um espectrofotômetro marca Hewlett-Packard modelo HP 8452A com detector constituído de um arranjo de diodos.

As amostras foram preparadas dissolvendo as substâncias em etanol e as soluções foram diluídas até que as amostras possuissem absorbância de, aproximadamente, uma unidade arbitrária.

Dos vinte compostos analisados fotoquímicamente visando determinar a estabilidade frente as radiações UVB e UVC, o composto TMDME₂(OH)₂ foi o que apresentou melhor estabilidade fotoquímica na região do 5 UVB.

Seguem-se abaixo considerações sobre a Citotoxicidade em linhagens de células neoplásicas de humanos ⁸.

A avaliação da atividade anti-proliferativa foi efetuada em cultura de células tumorais humanas fornecidas pelo "National Cancer Institute" (NCI-USA). Os diversos produtos foram avaliados em cultura de células tumorais de mama (MCF 7), mama resistente (NCI ADR), pulmão (NCI 460) e melanoma (UACC 62) em concentrações crescentes (15,6; 31,2; 62,5 e 125 µg/mL). Após um período de incubação de 48 horas, as células foram fixadas através da adição de ácido tricloroacético (50%). Após 60 minutos, o ácido tricloroacético foi removido por aspiração e a seguir as placas foram lavadas com água corrente para, 15 após secagem, serem coradas com a sulforrodamina B (SRB). O excesso de SRB foi removido das placas após 10 minutos através de lavagem com ácido acético a 1%. Finalmente, o corante foi solubilizado por adição de tampão tris base. A leitura óptica foi realizada por leitor ELISA em 515 nm.

20 O índice de citotoxicidade (IC) foi calculado de acordo com a seguinte fórmula:

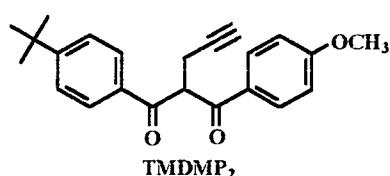
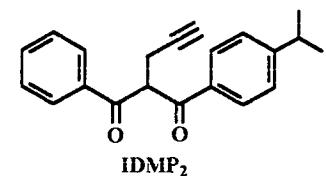
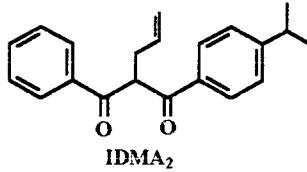
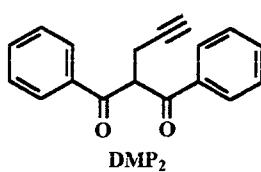
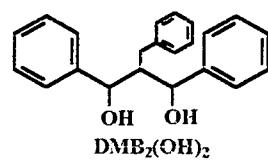
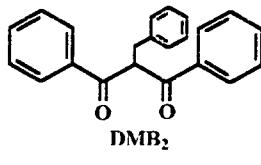
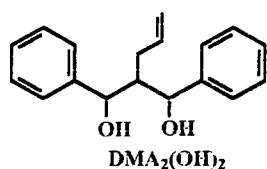
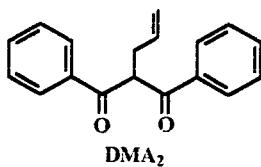
$$100 \% \times \frac{(1-\text{valor de DO experimental})}{(\text{valor de DO controle})}$$

∴ DO é a densidade ótica.

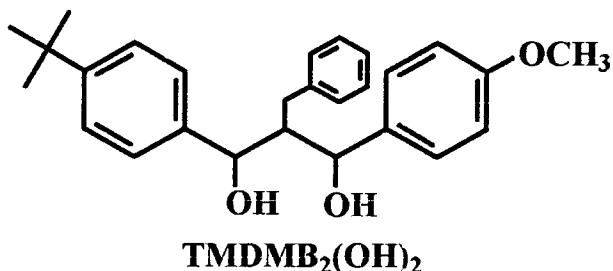
Segue-se as informações referentes as curvas dose-resposta das drogas padrão.

Foram avaliados os perfis de quimiossensibilidade das linhagens celulares aos quimioterápicos: 5 fluorouracil (5 FU), camptotecina (CPT11) e doxorubicina (DOX) com o objetivo de padronizar a resposta biológica das linhagens celulares a estas drogas. Esta determinação é utilizada como controle de qualidade das culturas. Os gráficos 1, 2 e 3 representam as curvas dose resposta das células em presença de diferentes concentrações de quimioterápico as quais relacionam a porcentagem de crescimento das células e a concentração de droga utilizada.

Das doze substâncias avaliadas para atividade antiproliferativa em cultura de células tumorais humanas as mais ativas são as representadas nos esquemas 4 e 5.



Esquema 4 - Substâncias mais ativas contra as linhagens de células neoplásicas de melanoma, mama, mama resistente e pulmão.



Esquema 5 - Substância ativa
5 contra as linhagens de células neoplásicas de melanoma, mama, mama resistente e pulmão e que atua como protetor solar contra radiações UVC e UVB.

Assim sendo, o presente invento compreende :

- 10 a) o uso das referidas substâncias como protetores solares UVB e UVC em formulações cosméticas;
- b) o uso das referidas substâncias como agentes antineoplásicos em formulações medicamentosas de uso interno;
- c) o uso das referidas substâncias como protetor solar UVB e UVC e como agentes antineoplásicos em formulações cosméticas.

As substâncias DMA₂, DMA₂(OH)₂, DMB₂, DMB₂(OH)₂, DMP₂, IDMA₂, IDMP₂, TMDMB₂(OH)₂ e TMDMP₂ apresentam eficiência como agentes antineoplásicos contra células neoplásicas de mama (MFC 7), mama resistente (NCI ADR), melanoma (UACC62) e pulmão (NCI460) *in vitro*.

As substâncias DMP₂, DMB₂(OH)₂ e TMDMB₂(OH)₂ apresentam atividade contra linhagens de células neoplásicas de melanoma (UACC 62) *in vitro*.

A substância TMDMB₂(OH)₂ se destaca, pois apresenta atividade contra linhagens de células neoplásicas de melanoma (UACC 62) *in vitro*, além de atuar como protetor solar contra radiações UVC e UVB.

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15 3 Van Der Leun, J. C. *et al.* *J. Photochem. Photobiol. B: Biol.*, 35 (237): 1996 apud Biloti, D. N. Dissertação (Mestre em Ciências). Instituto de Química UNICAMP, 61p, 1998.

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25 5 Singletary, K., MacDonald, C., Iovinelli, M., Fisher, C., Walling, M. *Carcinogenesis* 19 (6): 1034-1043, 1998.

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7 Biloti, D. N. Estudo Sobre o

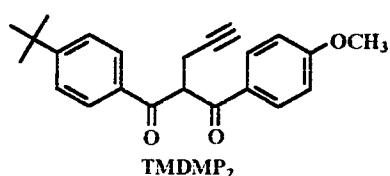
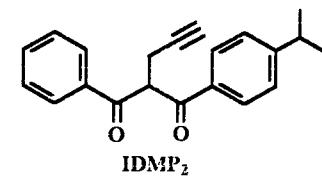
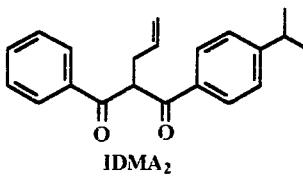
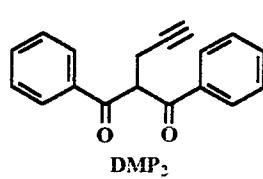
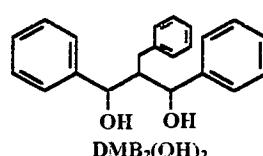
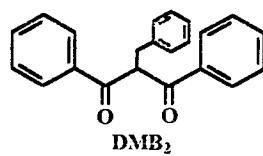
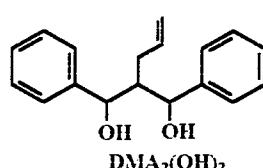
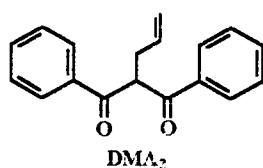
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⁸Monks, a., Scudiero, D., Skehan, P., Shoemaker, R., Paull, K., Vistica, D., Hose, C., Langley, J., Cronise, P., Vaigo-Wolff, A., Gray-Goodrich, Mlk Campbell, H., Mayo, J., Boyd, M. Journal of the National Institute, 83, 758 (1991).

REIVINDICAÇÕES

1. "OBTENÇÃO DE NOVOS DERIVADOS DE DIBENZOILMETANO QUE APRESENTAM ATIVIDADE ANTINEOPLÁSICA E DE APLICAÇÃO POTENCIAL COMO PROTETORES SOLARES",
 5 sendo as referidas substâncias caracterizadas pelo fato de apresentar atividade contra as linhagens de células neoplásicas de melanoma, mama, mama resistente e pulmão, ditas substâncias apresentando as seguintes fórmulas gerais abaixo representadas:

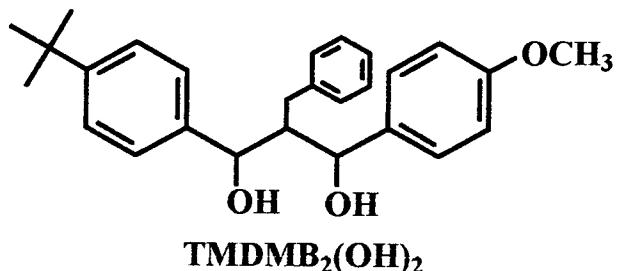


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2. "OBTENÇÃO DE NOVOS DERIVADOS DE DIBENZOILMETANO QUE APRESENTAM ATIVIDADE ANTINEOPLÁSICA E DE APLICAÇÃO POTENCIAL COMO PROTETORES SOLARES",

compreendendo uma substância que é caracterizada pelo fato de apresentar atividade contra as linhagens de células neoplásticas de melanoma, mama, mama resistente e pulmão, dita
 15

substância apresentando a fórmula geral abaixo representada:



3. "OBTENÇÃO DE NOVOS DERIVADOS DE DIBENZOILMETANO QUE APRESENTAM ATIVIDADE ANTINEOPLÁSICA E DE APLICAÇÃO POTENCIAL COMO PROTETORES SOLARES", segundo o reivindicado em 1, sendo a referida substância caracterizada ainda pelo fato de apresentar atividade como protetor solar contra radiações UVC e UVB.

ESTUDOS DE
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FIG. - I

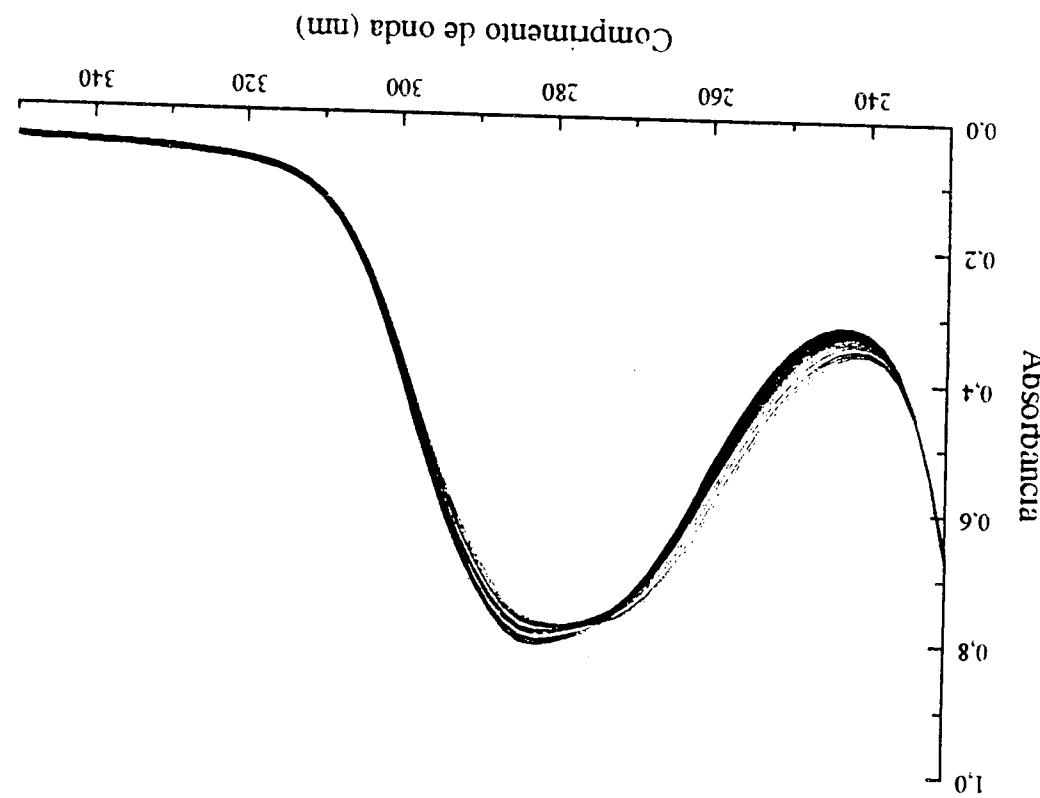
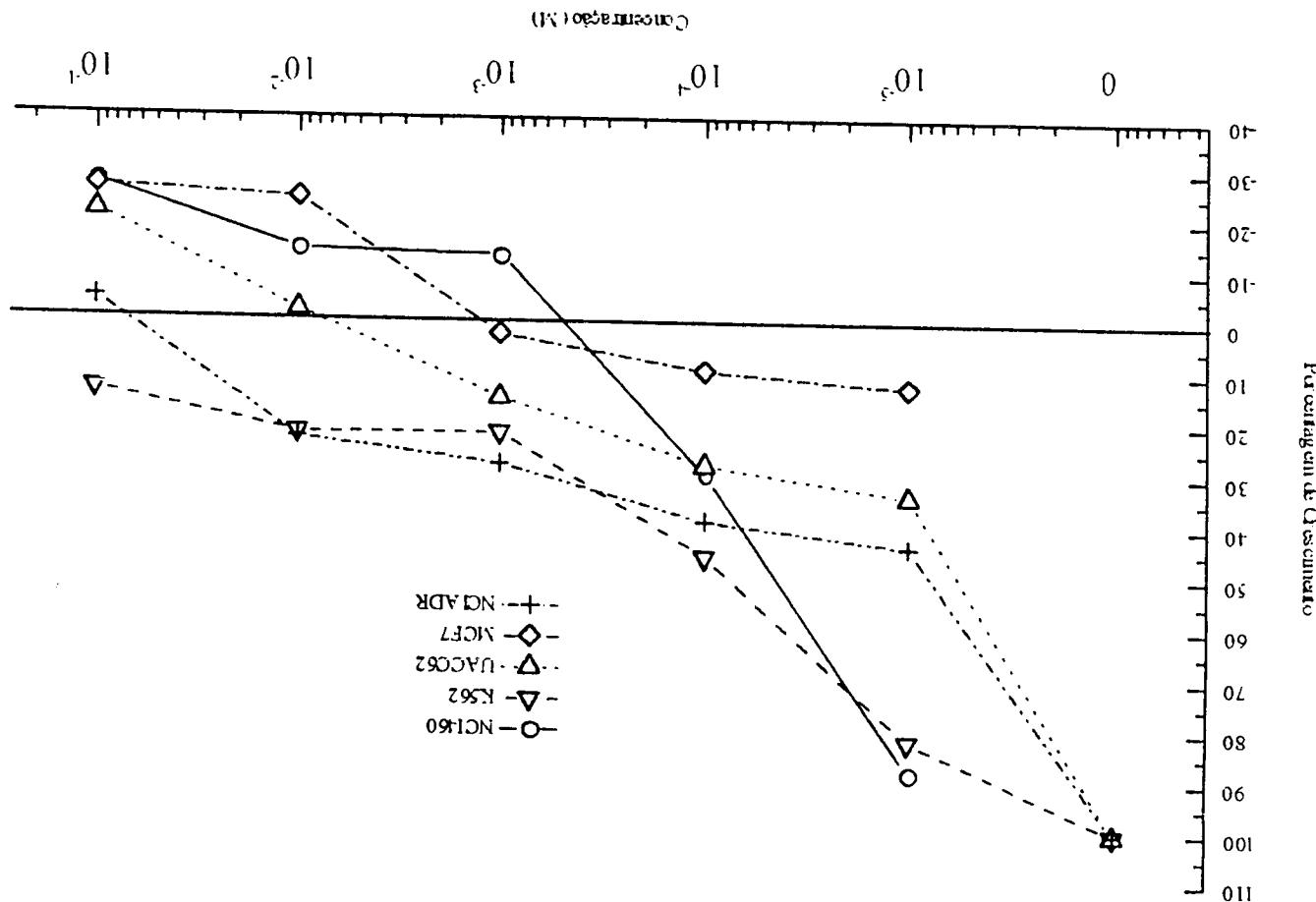


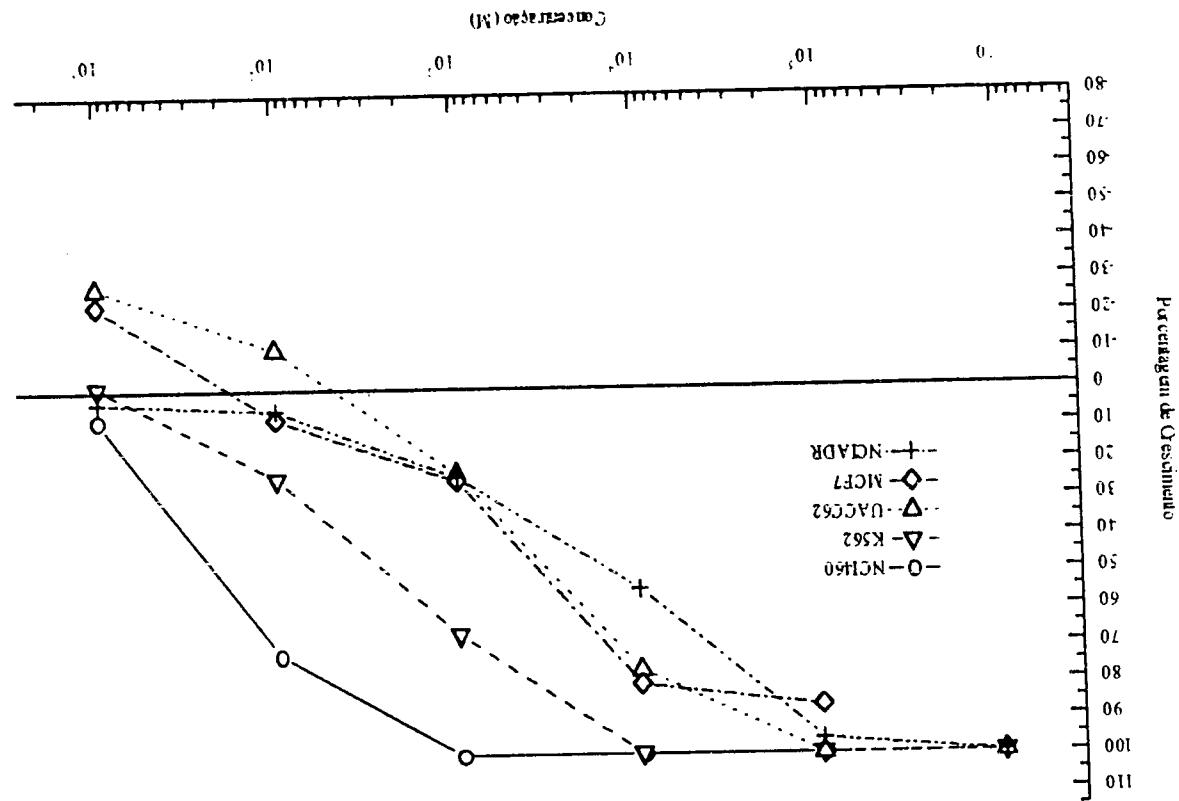
FIG -Z



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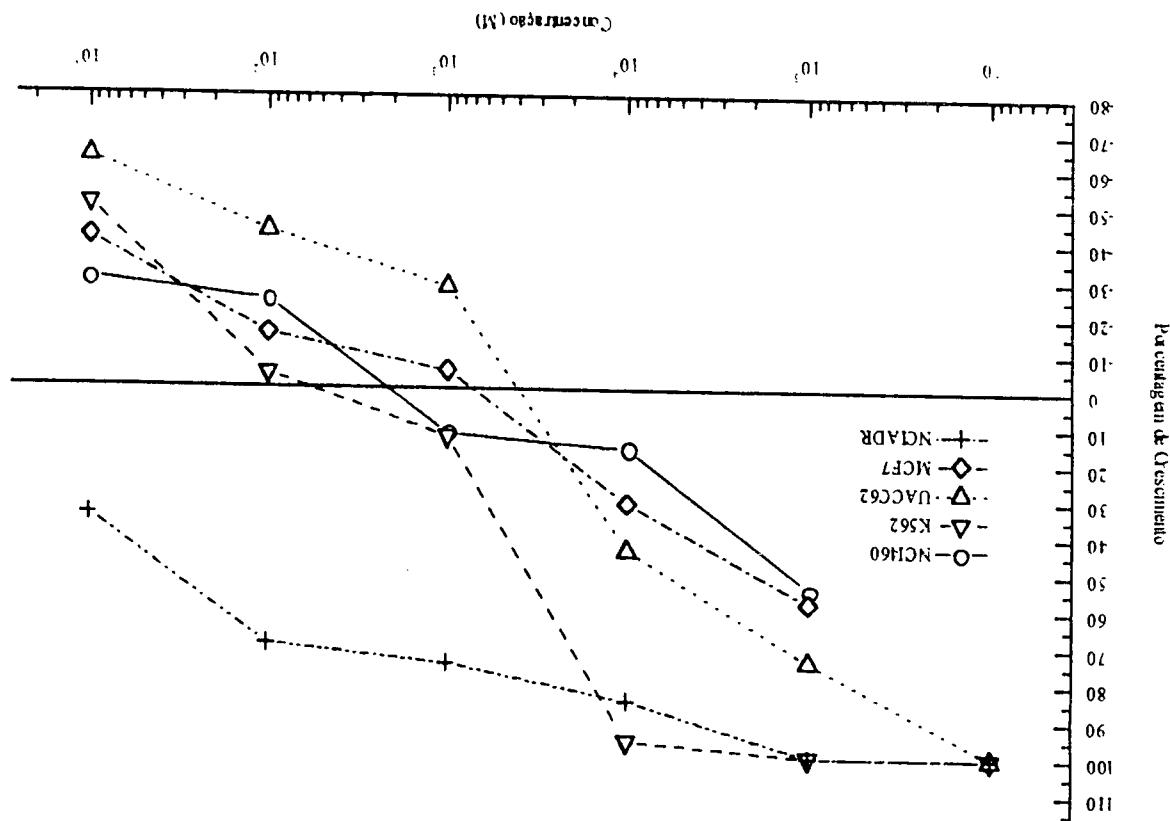
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bioassay

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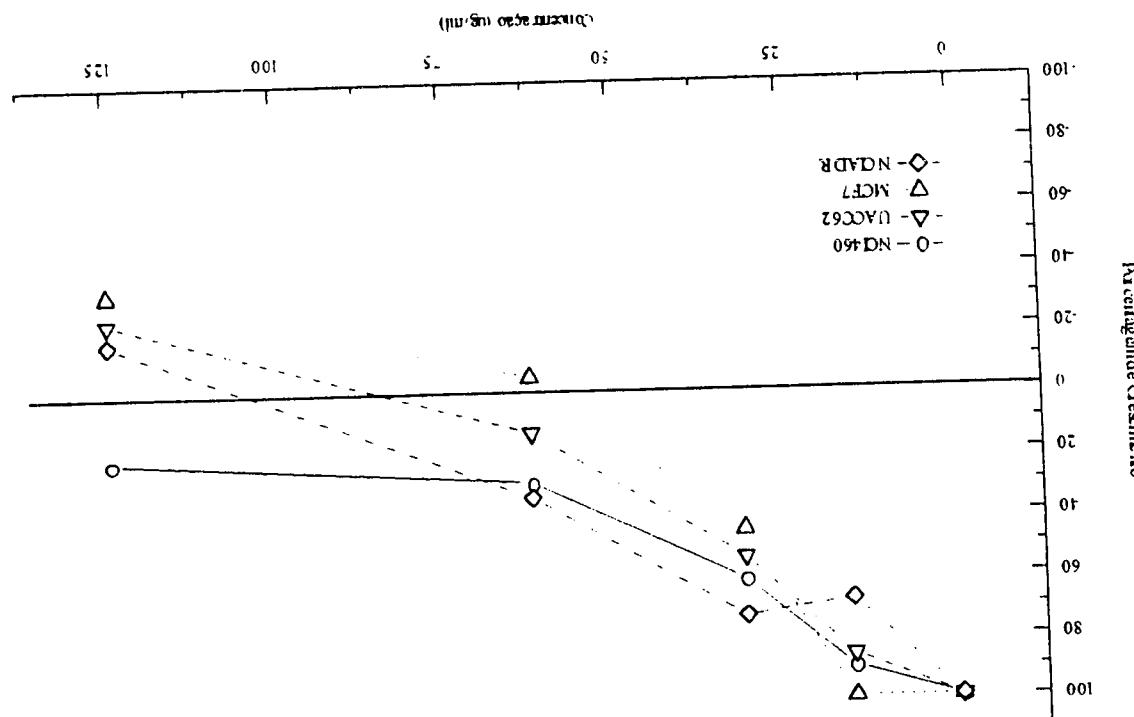
FIG - 4



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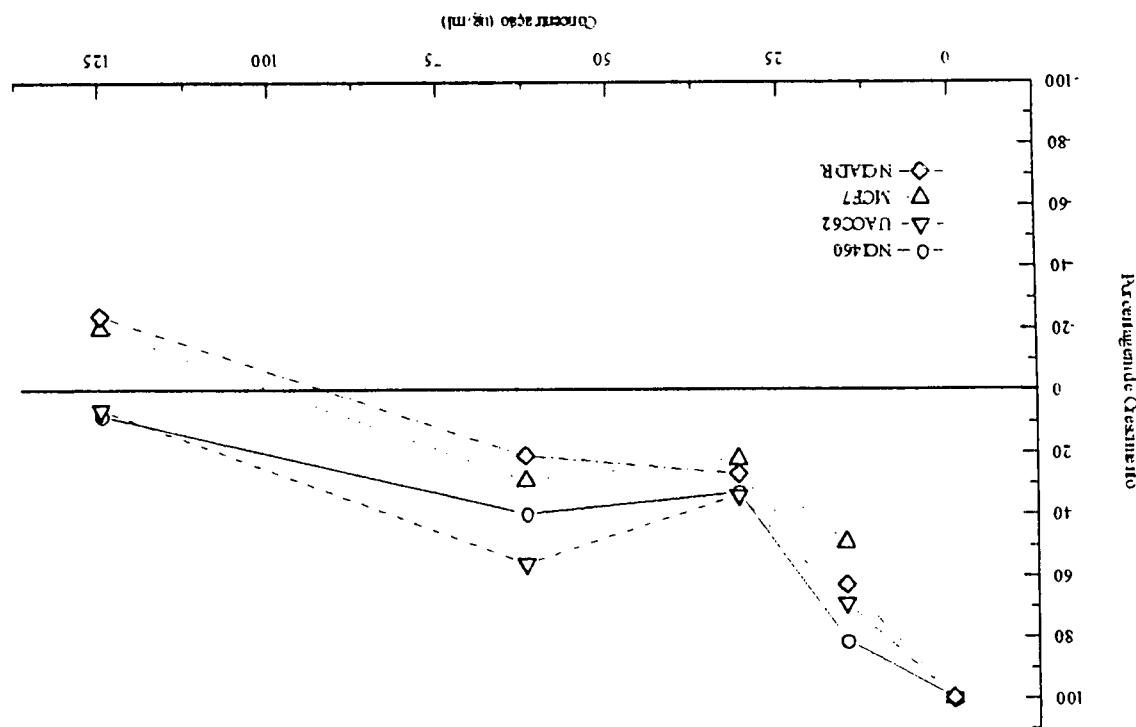
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FIG - 5



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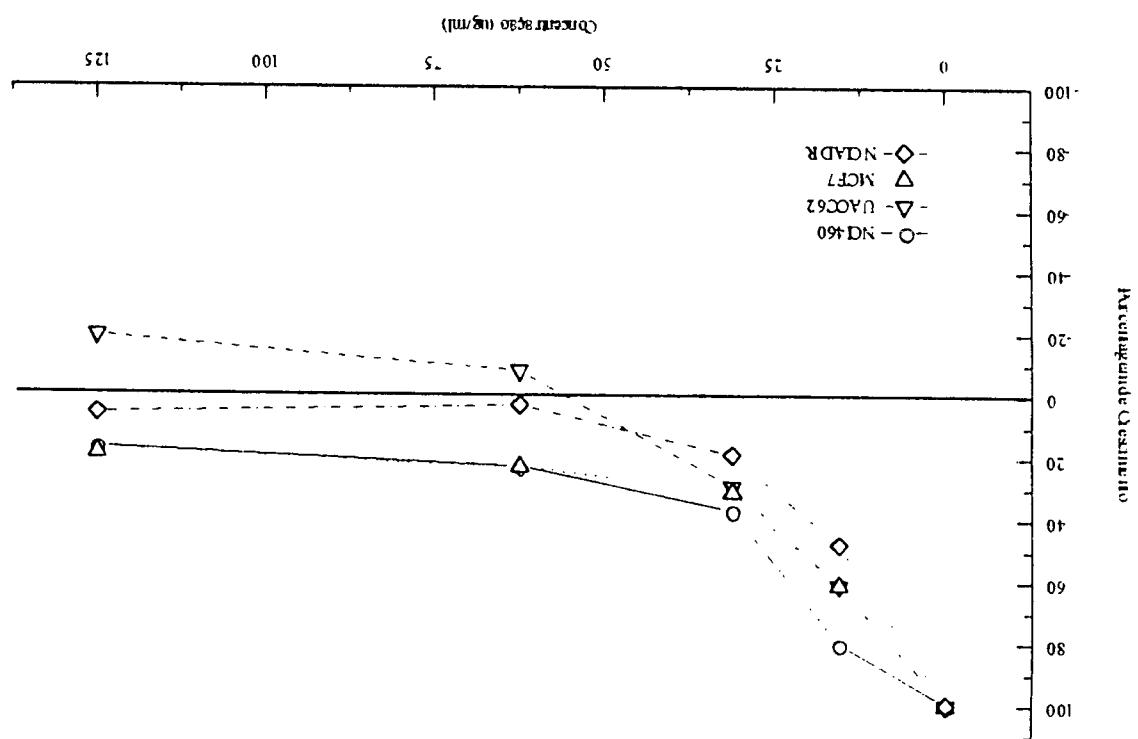
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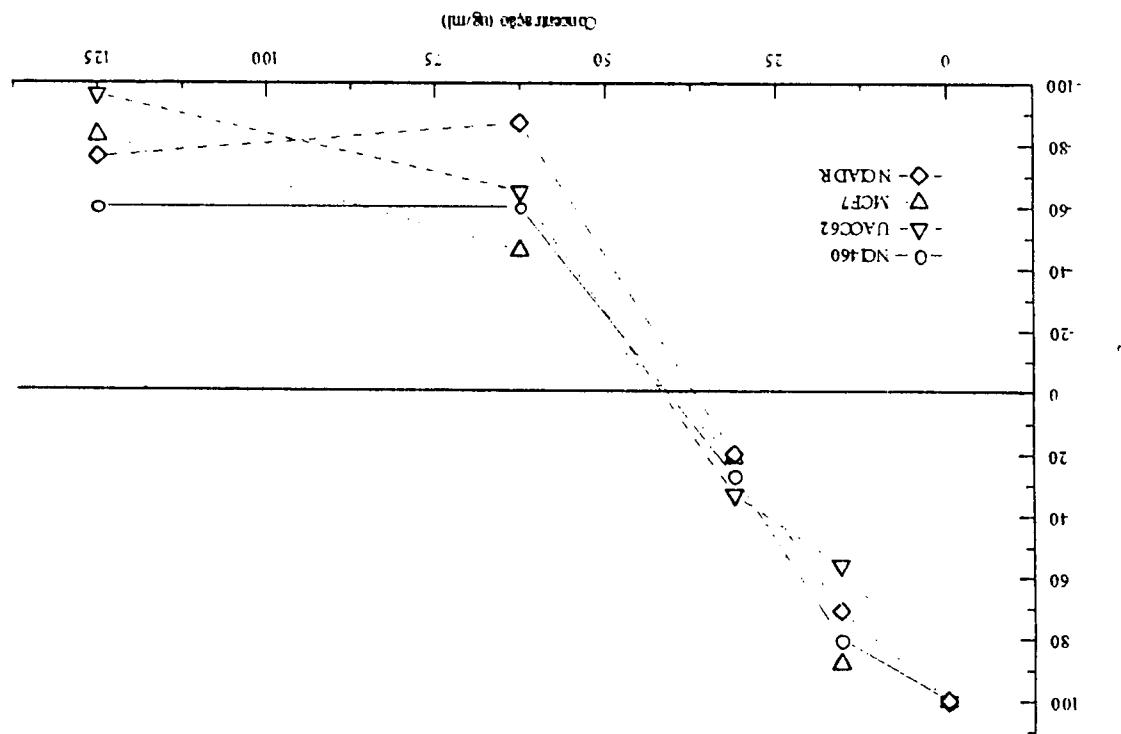
L- E-7



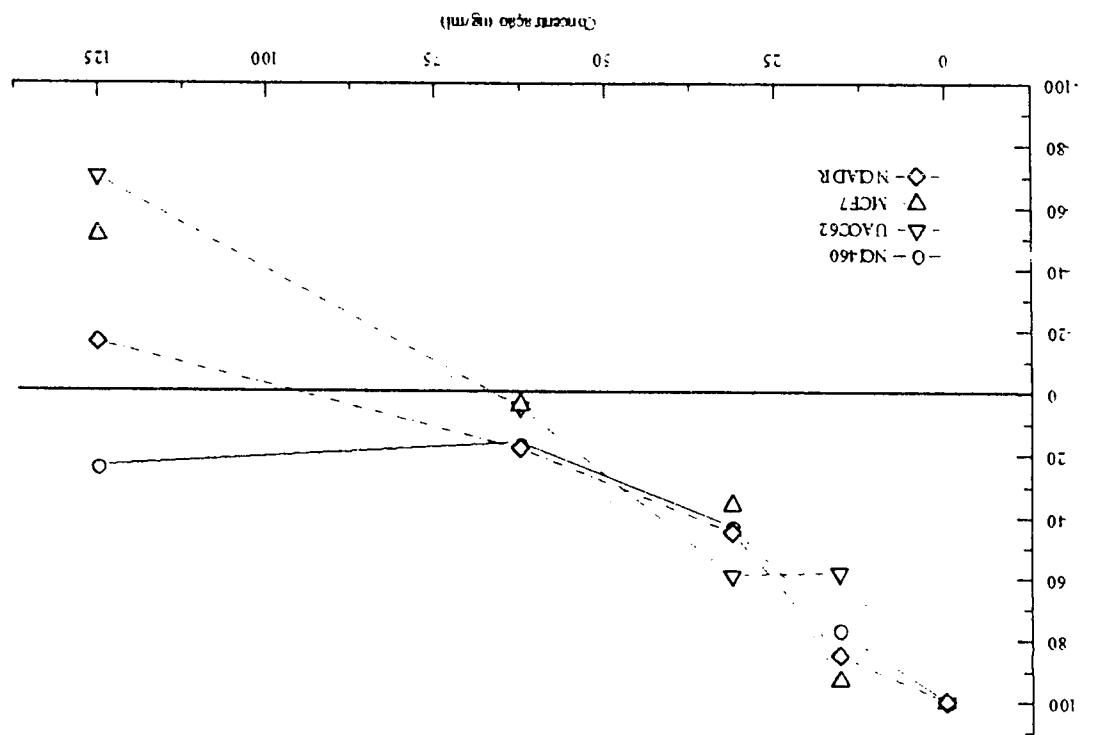
STANDARD

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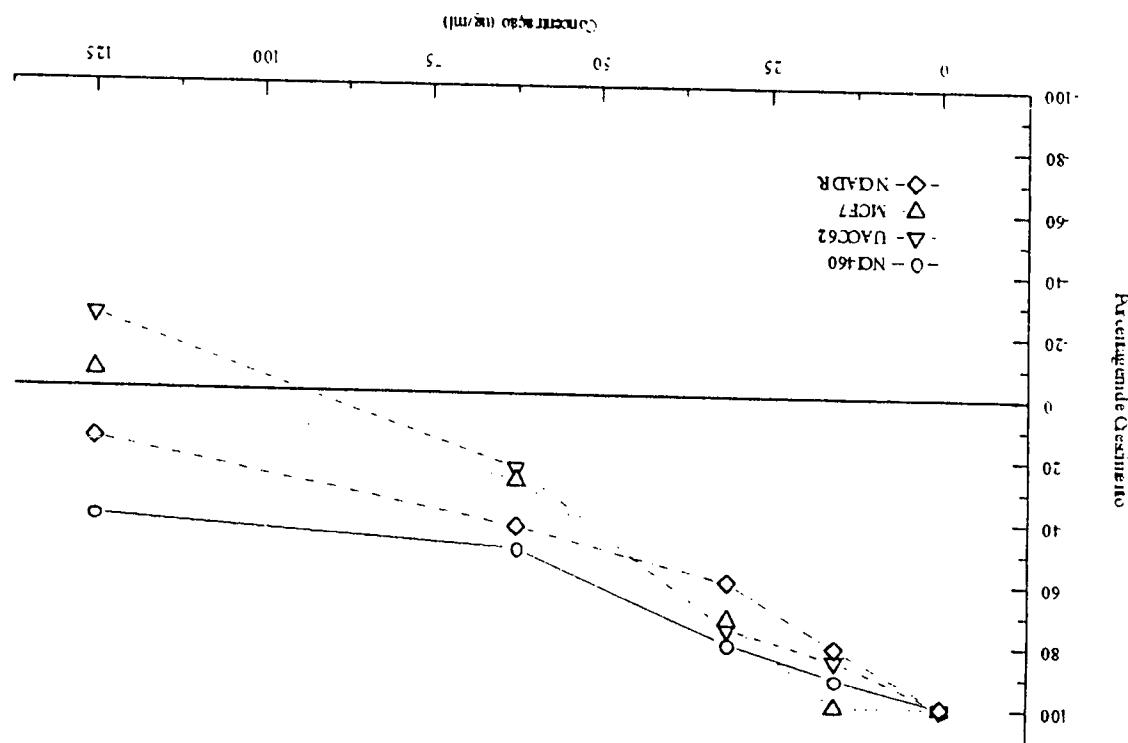


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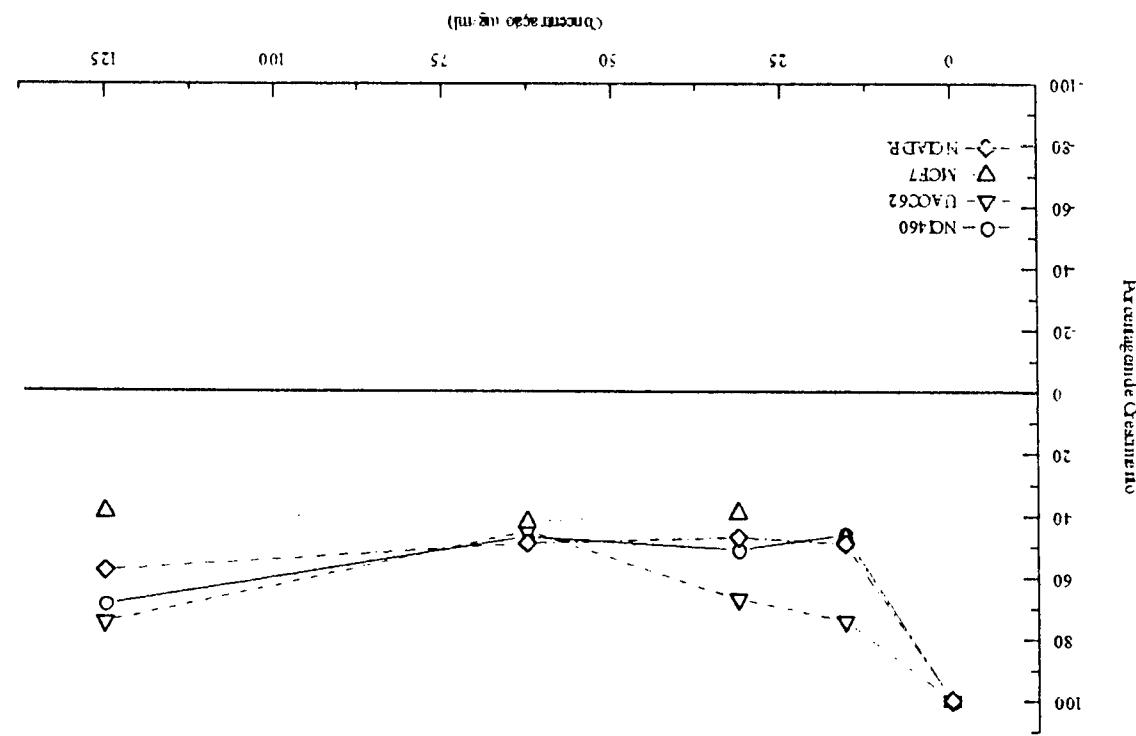


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E16-10



EE - II



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F/G - 12

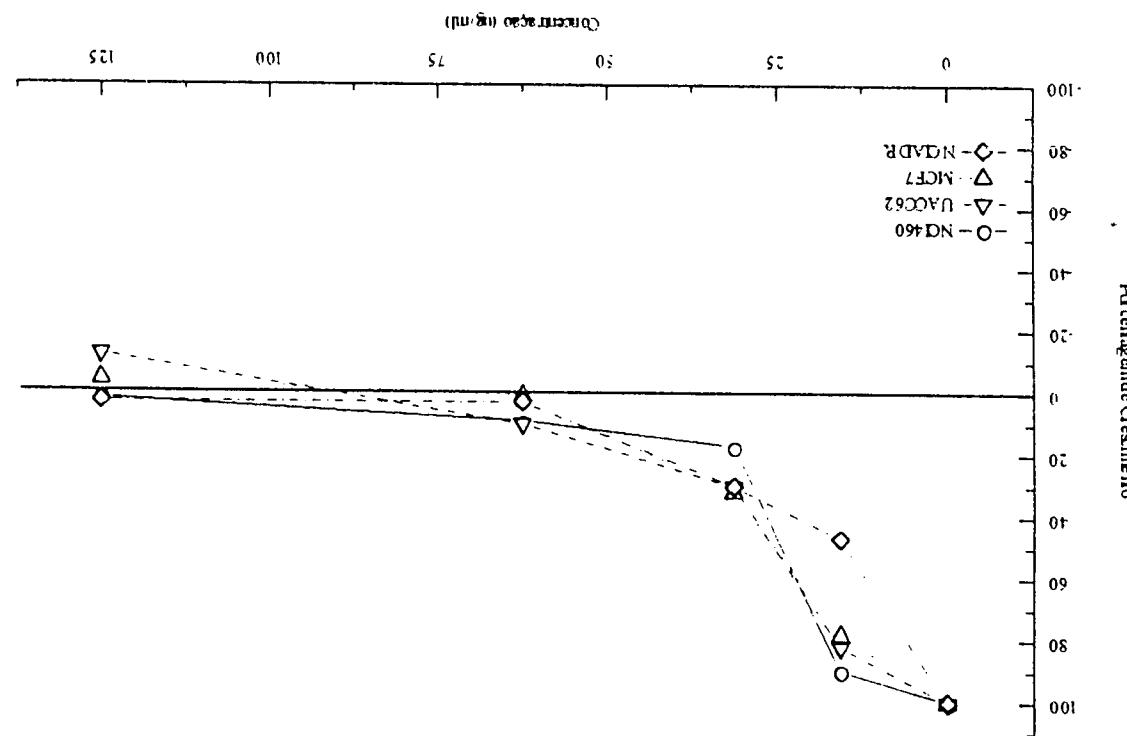
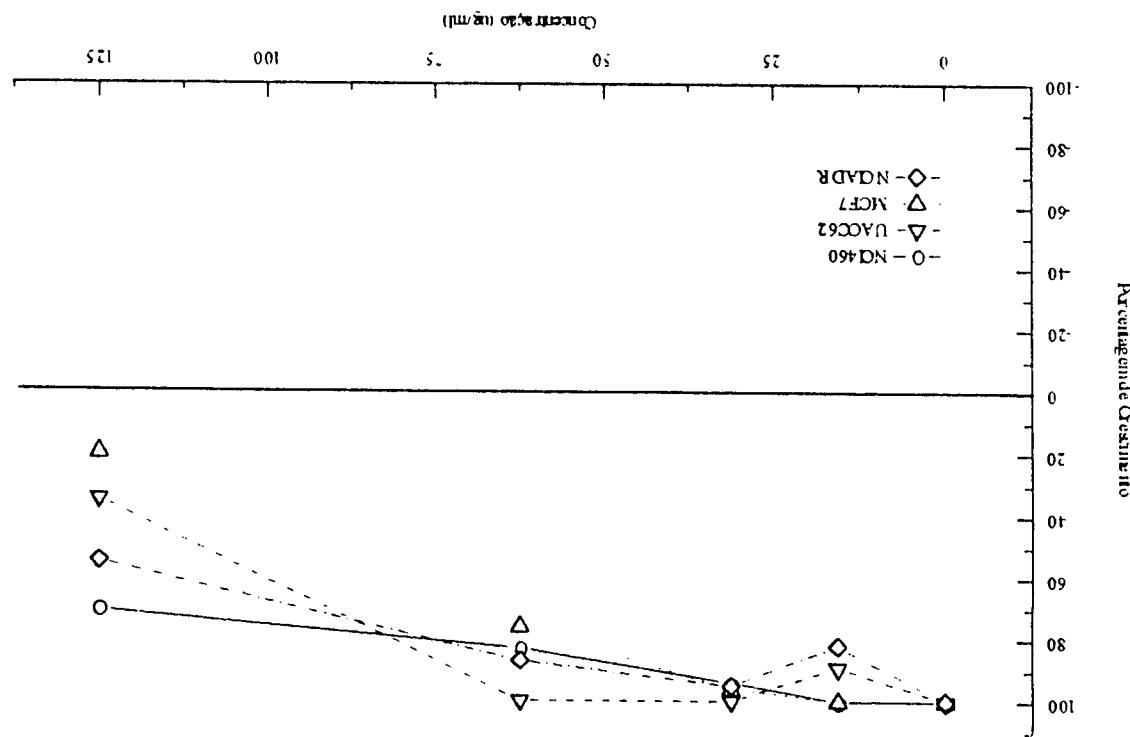


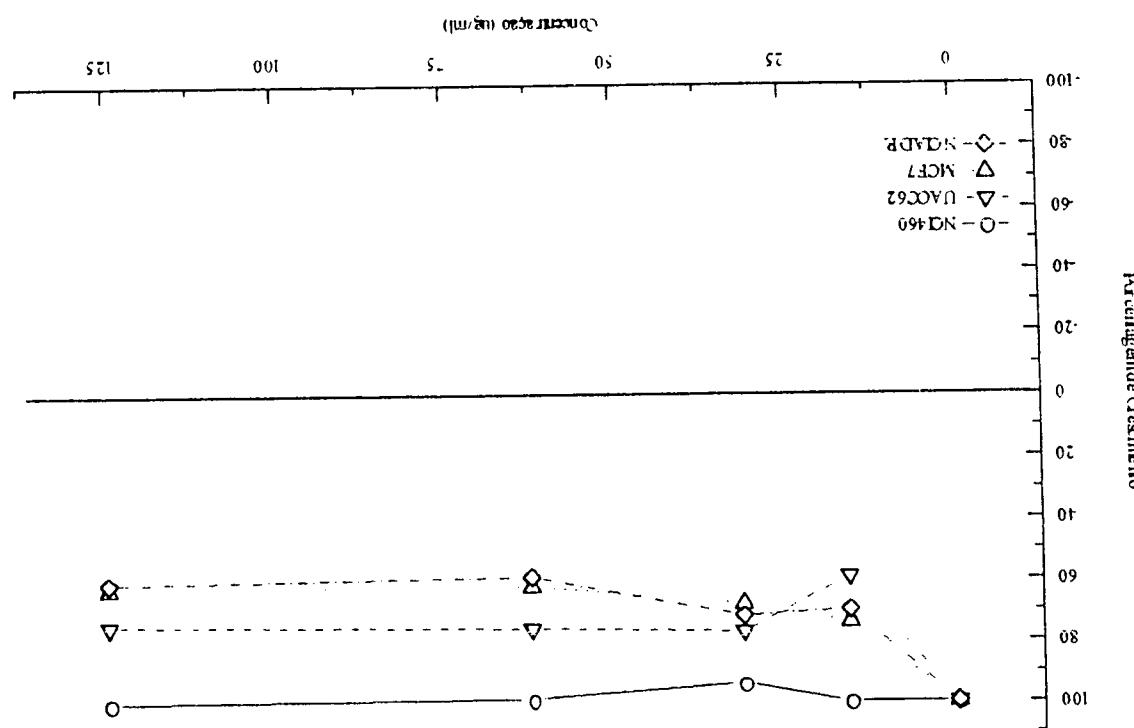
FIG. - 13



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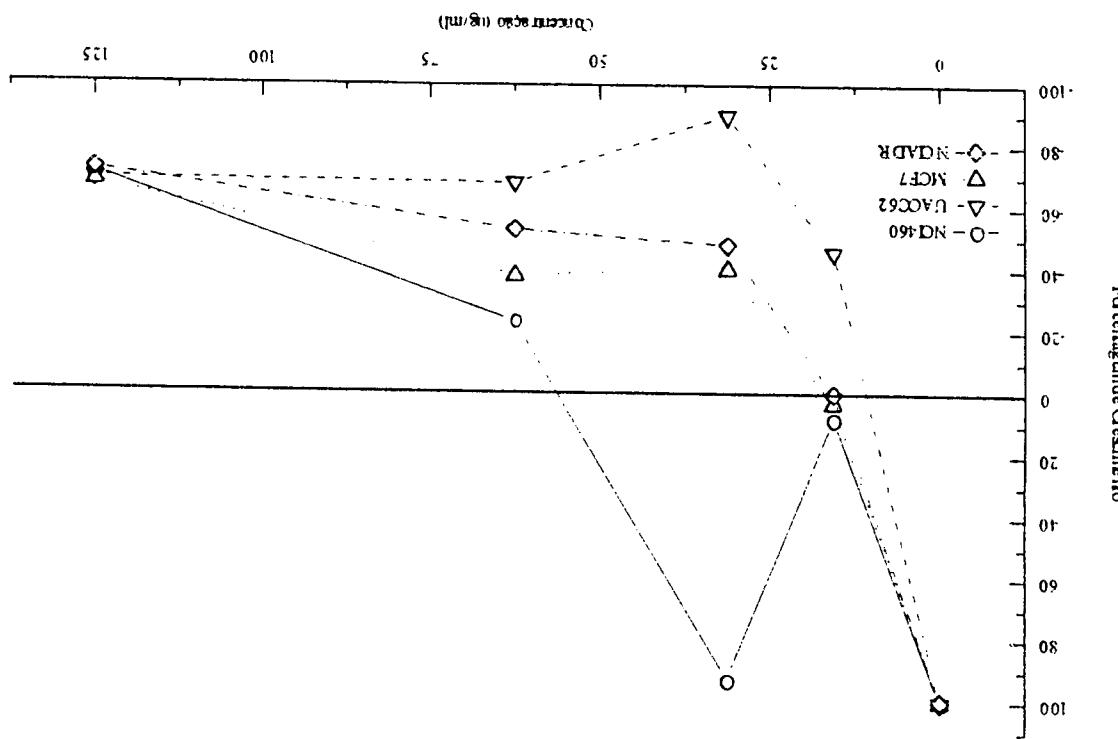
E/G-14



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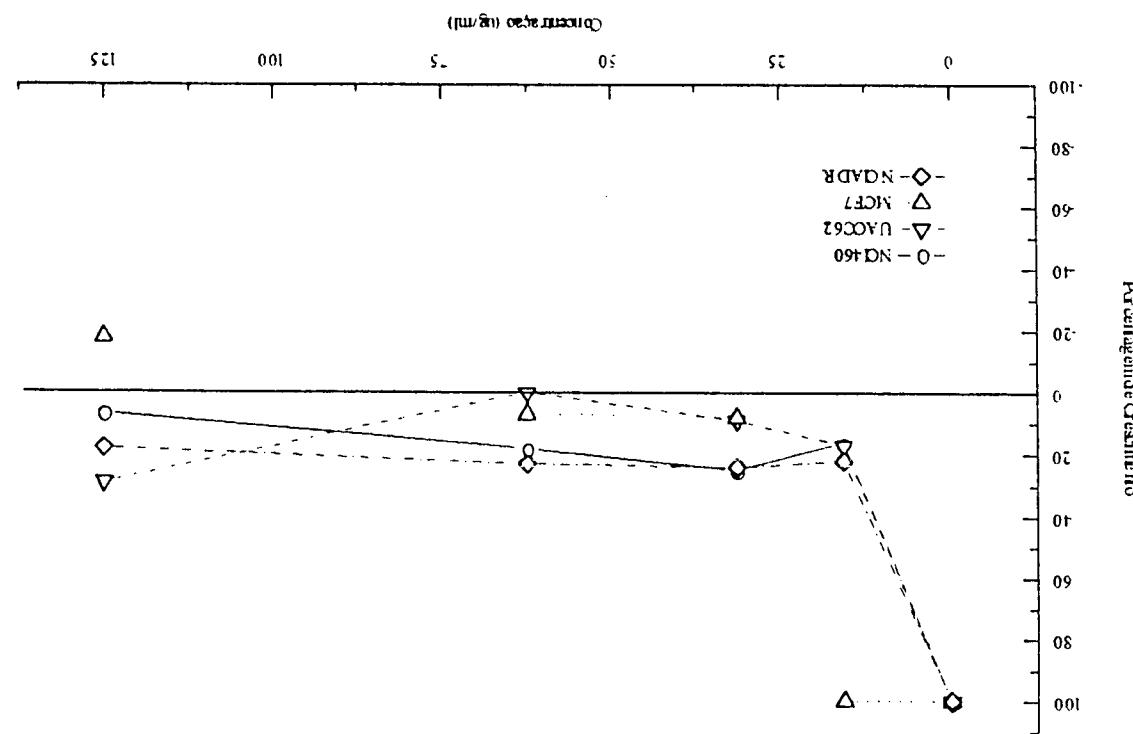
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FIG - 15



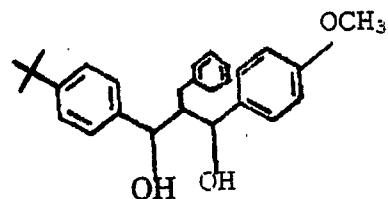
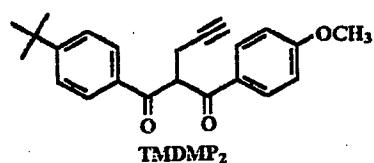
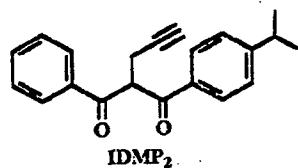
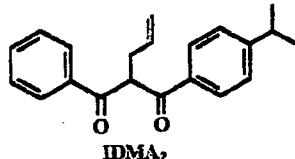
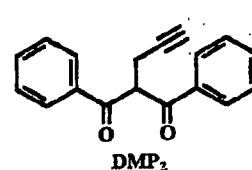
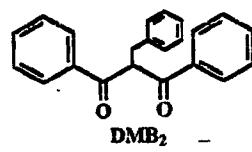
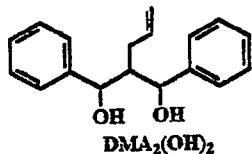
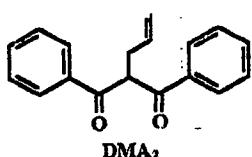
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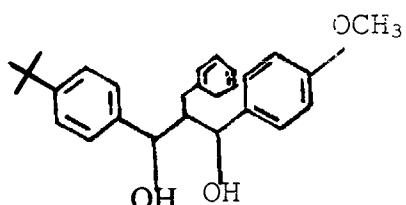
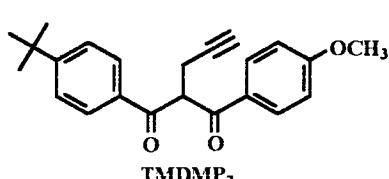
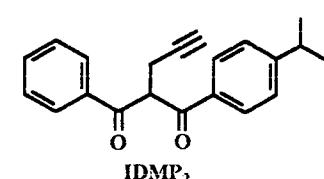
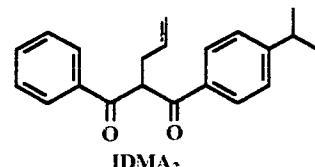
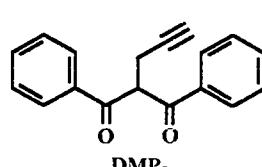
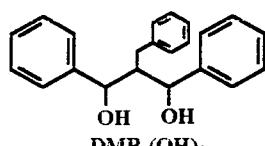
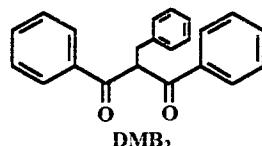
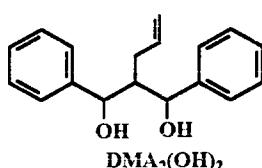
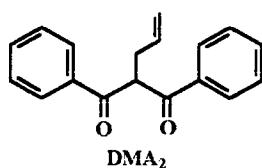
RESUMO

"OBTENÇÃO DE NOVOS DERIVADOS DE DIBENZOILMETANO QUE APRESENTAM ATIVIDADE ANTINEOPLÁSICA E DE APLICAÇÃO POTENCIAL COMO PROTETORES SOLARES", sendo 5 as referidas substâncias caracterizadas pelo fato de apresentar atividade contra as linhagens de células neoplásicas de melanoma, mama, mama resistente e pulmão, ditas substâncias apresentando as seguintes fórmulas gerais abaixo representadas:

TMDDMB₂(OH)₂

RESUMO

"OBTENÇÃO DE NOVOS DERIVADOS
DE DIBENZOILMETANO QUE APRESENTAM ATIVIDADE ANTINEOPLÁSICA
E DE APLICAÇÃO POTENCIAL COMO PROTETORES SOLARES", sendo
5 as referidas substâncias caracterizadas pelo fato de apresentar atividade contra as linhagens de células neoplásicas de melanoma, mama, mama resistente e pulmão, ditas substâncias apresentando as seguintes fórmulas gerais abaixo representadas:



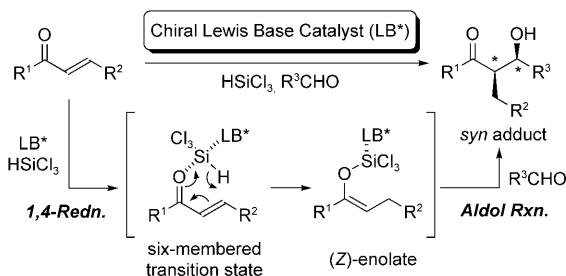
TMDDMB₂(OH)₂

Diastereo- and Enantioselective Reductive Aldol Reaction with Trichlorosilane Using Chiral Lewis Bases as Organocatalysts

Masaharu Sugiura,^{*[a]} Norimasa Sato,^[a] Yuko Sonoda,^[a] Shunsuke Kotani,^[b] and Makoto Nakajima^{*[a]}

Dedicated to the 150th anniversary of Japan–UK diplomatic relations

The catalytic enantioselective tandem reaction is an efficient synthetic methodology in which optically active compounds are assembled from simple prochiral substrates via two (or more) distinct catalytic processes taking place under the same conditions.^[1] The synthetic efficiency is enhanced by avoiding the time-intensive and yield-reducing isolation and purification of synthetic intermediates and by decreasing the amounts of chemicals and solvents used. The asymmetric catalytic reductive aldol reaction is an efficient tandem transformation involving conjugate reduction of α,β -unsaturated carbonyl compounds followed by aldol reaction of the enolate intermediate with aldehydes or ketones. Chiral transition-metal catalysts have been used to control the stereochemistry of these transformations.^[2,3] We recently reported that achiral phosphorus oxides function as Lewis base organocatalysts^[4] to promote both the conjugate reduction of enones with trichlorosilane and the reductive aldol reaction of enones with aldehydes.^[5] Herein we report that enantioselective catalysis of this tandem reaction by chiral Lewis bases provides good to high diastereo- and enantioselectivities.



Scheme 1. The enantioselective reductive aldol reaction with trichlorosilane catalyzed by a chiral Lewis base catalyst.

Scheme 1 outlines the current catalytic method. Our previous study had shown that the Lewis base catalyzed conjugate reduction with trichlorosilane proceeds via a six-membered transition state with an enone in the *s-cis* conformation to give the (*Z*)-trichlorosilyl enolate exclusively.^[5] Therefore, high *syn* selectivity is expected for the subsequent aldol process, assuming that the reaction proceeds through a chair-like cyclic transition state. Moreover, high enantioselectivity could also be achieved by judicious selection of chiral Lewis base catalysts (LB*).^[6,7]

We first examined various chiral Lewis base catalysts (Figure 1) for the reductive aldol reaction of chalcone (**1a**) and benzaldehyde (**2a**) with trichlorosilane at -78°C (Table 1). With (*S*)-BINAP, the reaction in dichloromethane gave aldol adduct **3a** with respectable stereoselectivities (Table 1, entry 1). By simply changing the solvent from dichloromethane to propionitrile, both the stereoselectivities and chemical yield dramatically improved (Table 1, entry 2). Other Lewis base catalysts were then examined using this solvent (Table 1, entries 3–6). (*R,R*)-DIOPO showed a comparable activity to BINAP to afford similar enantioselectivity with a slight loss of diastereoselectivity (Table 1, entry 3). Although structurally similar to BINAP, (*S*)-

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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/asia.200900450>.

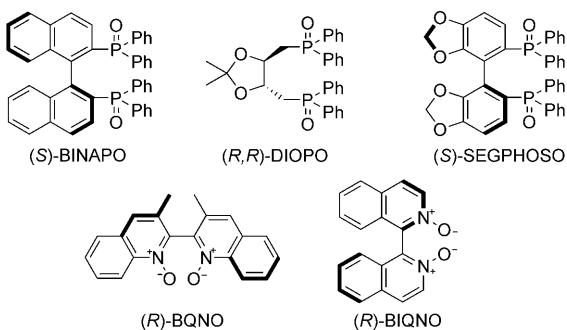
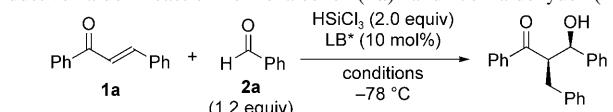


Figure 1. Chiral Lewis base catalysts used in this study.

Table 1. Optimization of reaction conditions for the enantioselective reductive aldol reaction of chalcone (**1a**) and benzaldehyde (**2a**).^[a]

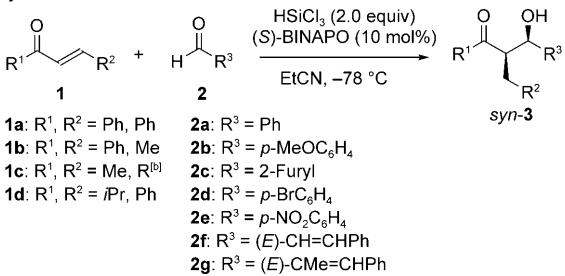
Entry	LB*	Conditions	Yield [%]	syn/ anti	ee [%] (syn) ^[b]
1	(S)-BINAPo	CH ₂ Cl ₂ , 30 h	68	85:15	84
2	(S)-BINAPo	EtCN, 24 h	87	96:4	92
3	(R,R)-DIOPO	EtCN, 5 h	80	92:8	92
4	(S)-SEPHOSO	EtCN, 24 h	17	72:28	61
5	(R)-BQNO	EtCN, 24 h	68	94:6	80 ^[c]
6	(R)-BIQNO	EtCN, 24 h	75	95:5	4

[a] All reactions were carried out by addition of trichlorosilane (1.0 mmol, ca. 3 M solution in CH₂Cl₂) to a solution of chalcone (0.5 mmol), benzaldehyde (0.6 mmol), and a Lewis base catalyst (10 mol %) in a solvent (2 mL) at -78°C. [b] 2*R*,3*R* configuration. [c] 2*S*,3*S* configuration.

SEPHOSO was found to significantly lower the reactivity and selectivities (Table 1, entry 4). On the other hand, (R)-BQNO, a bisquinoline *N,N'*-dioxide developed in our laboratory^[8] exhibited good activity and selectivity, while (R)-BIQNO, a bisisoquinoline *N,N'*-dioxide,^[9] afforded low enantioselectivity (Table 1, entries 5 and 6).^[10,11]

Having discovered several effective catalysts, we next investigated the reductive aldol reaction of a variety of substrates (Table 2). The reactions of several β -monosubstituted enones (**1b-d**) with benzaldehyde (**2a**) were smoothly catalyzed by (S)-BINAPo to afford the corresponding adducts in good yields with high *syn* diastereoselectivity and enantioselectivities (Table 2, entries 1–4).^[11] Dichloromethane was found to provide a higher yield and enantioselectivity than did propionitrile in the reaction of β -ionone, although diastereoselectivities were comparable in the two solvents (Table 2, entries 2 vs. 3). The rapid transformation of enone **1d**, which bears a bulky isopropyl group, presumably results from the substrate's preference for the *s-cis* conformation, which is favorable for the conjugate reduction (Table 2, entry 4).^[12,13]

Using chalcone (**1a**) as the enone component, (S)-BINAPo-catalyzed reactions with other aldehydes were in-

Table 2. Enantioselective reductive aldol reaction of various enones and aldehydes.^[a]

Entry	Enone	Aldehyde	t [h]	Product	Yield [%]	syn/ anti	ee [%] (syn)
1	1b	2a	24	3b	70	94:6	91
2	1c	2a	24	3c	37	99:1	91
3 ^[c]	1c	2a	21	3c	67	99:1	96
4	1d	2a	1.5	3d	74	99:1	97
5	1a	2b	8	3e	72	95.5	85
6	1a	2c	6	3f	84	99:1	90
7	1a	2d	24	3g	78	97:3	94
8	1a	2e	24	3h	58	95:5	96
9	1a	2f	24	3i	91	95:5	51
10	1a	2g	8	3j	71	98:2	50
11 ^[d]	1a	2f	4.5	3i	71	95:5	85
12 ^[d]	1a	2g	24	3j	92	99:1	98

[a] Unless otherwise noted, reactions were carried out by addition of trichlorosilane (1.0 mmol, ca. 3 M solution in CH₂Cl₂) to a solution of an enone (0.5 mmol), an aldehyde (0.6 mmol), and (S)-BINAPo (10 mol %) in EtCN (2 mL) at -78°C. [b] R = 2,6,6-trimethyl-1-cyclohexenyl (β -ionone). [c] With benzaldehyde (2 equiv) in CH₂Cl₂ instead of EtCN. [d] With (R,R)-DIOPO (10 mol %) instead of (S)-BINAPo.

vestigated (Table 2, entries 5–10).^[10,11] *p*-Anisaldehyde (**2b**) and 2-furaldehyde (**2c**) having electron-rich aromatic rings showed higher reactivity than benzaldehyde (**2a**; see Table 1, entry 2), but the enantioselectivity was slightly decreased (Table 2, entries 5 and 6). On the other hand, an opposite tendency was observed for *p*-bromobenzaldehyde (**2d**) and *p*-nitrobenzaldehyde (**2e**) having electron-withdrawing substituents, which resulted in higher enantioselectivity (Table 2, entries 7 and 8). In all cases, high *syn* diastereoselectivities were observed. The reaction tolerated α,β -unsaturated aldehydes to give the corresponding adducts in good yields with high *syn* diastereoselectivity and moderate enantioselectivity (Table 2, entries 9 and 10). For the reaction of these enals, significantly improved enantioselectivity was obtained by using (R,R)-DIOPO instead of (S)-BINAPo (Table 2, entries 11 and 12). It is noteworthy that the enone was chemoselectively reduced with trichlorosilane in the presence of enals. The low reactivity of α,β -unsaturated aldehydes in the conjugate reduction might be attributed to unfavorable conformations of enals in the reaction (see Figure 2).^[13] As shown in Figure 2a, the *s-trans* conformer predominates for enals. Furthermore, the trichlorosilane–Lewis base complex predominantly coordinates to the sterically less hindered lone pair of the carbonyl oxygen leading to *anti* complex **B**, even in the *s-cis* conformation (Figure 2b). Both the *s-trans* conformation and *anti* complex **B**

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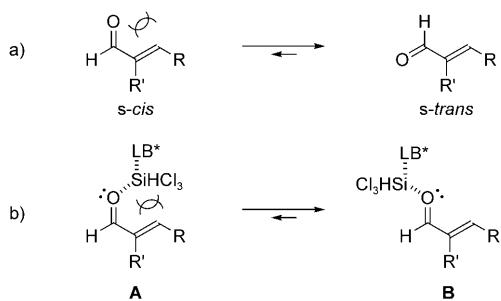
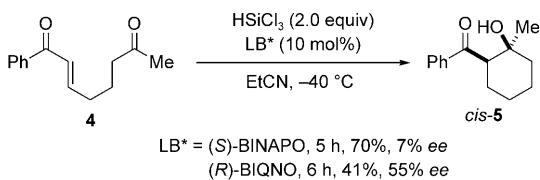


Figure 2. Conformational preference of α,β -unsaturated aldehydes and their trichlorosilane complexes.



Scheme 2. Intramolecular enantioselective reductive aldol reaction.

are unfavorable for the six-membered transition state required for the conjugate reduction.

Preliminary investigation has indicated that the current method can be applied to an intramolecular process (Scheme 2).^[14] The (S)-BINAPo-catalyzed reaction of keto-enone **4**^[14c] with trichlorosilane proceeded smoothly at -40 °C to give the expected cyclized product *cis*-**5** in a good yield, but with low enantioselectivity. The enantioselectivity was improved when (R)-BIQNO was used instead of BINAPo, although the yield was moderate.^[15] Further improvement of the intramolecular transformation is under investigation.

In summary, we have demonstrated that the reductive aldol reaction of enones and aldehydes with trichlorosilane is catalyzed by chiral Lewis base organocatalysts to afford optically active β -hydroxy ketones with good to high diastereoeo- and enantioselectivities. Further investigations including extension of the scope of the reaction and application to natural product synthesis are currently underway.

Experimental Section

General procedure for enantioselective reductive aldol reaction with trichlorosilane: To a solution of a chiral Lewis base (10 mol %), an enone (0.5 mmol), and an aldehyde (0.6 mmol, 1.2 equiv) in dry propionitrile (2 mL) was added dropwise trichlorosilane (ca. 3 M CH₂Cl₂ solution, 2 equiv) at -78 °C. The reaction was monitored by TLC analysis. After the enone was consumed or no significant change was observed, the reaction was quenched with sat. aqueous NaHCO₃ (3 mL). After addition of ethyl acetate (10 mL), the mixture was stirred for 1 h, filtered through a celite pad and extracted with ethyl acetate (3 \times). The combined organic layers were washed with brine (1 \times), dried over anhydrous MgSO₄, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=20:1–3:1) to give the corresponding aldol product.

Acknowledgements

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Keywords: aldol reaction • Lewis bases • organocatalysis • reduction • silanes

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Organotin Iodide Hydride: Chemoselective 1,4-Hydrostannations of Conjugated Enones in the Presence of Aldehydes and Subsequent Intermolecular Aldol Reactions

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The 1,2- and 1,4- regiochemistry of the reduction of conjugated enones has been intensively investigated with a variety of reductants.¹ Recently, efforts have been directed toward chemoselective reductions of conjugated enones with tolerance by susceptible functional groups. As exhibited in the reductions with NaBH₄, a general order of reactivity among carbonyl groups is conjugated enones < ketones < conjugated enals < aldehydes.^{2,3} Not in keeping with this general reactivity order of aldehydes and conjugated enones, it is notable that the Luche reagent (NaBH₄/LnCl₃)⁴ even in the presence of aldehydes, can reduce conjugated enones to furnish allylic alcohols in 1,2-fashion.⁵ No selective 1,4-reduction of conjugated enones in the presence of aldehydes has been demonstrated, to our knowledge, although reductions by copper hydride tolerate the presence of ketone moieties in the same substrate.⁶ If the 1,4-hydrometalation of

(1) The selective 1,2-reduction of conjugated enones has been carried out by aluminum hydrides such as LiAlH₄^{a,b} and DIBAL-H,^{c–f} and boron hydrides such as 9-BBN-H^{g,h} and NaBH₄^{i,j}. On the other hand, the selective 1,4-reductions have been accomplished by silicon hydrides,^{k–n} copper hydrides,^{o–r} iron hydrides,^{s–v} and organoborohydrides such as L- and K-Selectride.^{w,x} (a) Hudlicky, M. *Reductions in Organic Chemistry*; John Wiley & Sons, Inc.: New York, 1984; pp 119–121. (b) Balachander, N.; Wang, S. S.; Sukenik, N. *Tetrahedron Lett.* **1986**, *27*, 4849–4852. (c) Wilson, K. E.; Seidner, R. T.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1970**, 213–214. (d) Ashby, E. C.; Lin, J. J. *Tetrahedron Lett.* **1976**, 3865–3868. (e) Antus, S.; Gottslegen, A.; Nogradi, M. *Synthesis* **1981**, 574–576. (f) Zoretic, P.; Golen, J. A. *J. Org. Chem.* **1981**, *46*, 3555–3558. (g) Krishnamurthy, S.; Brown, H. *C. J. Org. Chem.* **1975**, *40*, 1864–1865. (h) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 1197–1201. (i) Johnson, M. R.; Rickborn, B. *J. Org. Chem.* **1970**, *35*, 1041–1045. (j) Komiya, S.; Tsutsumi, O. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3423–3424. (k) Ojima, I.; Nihonyanagi, M.; Kogure, T.; Kumagai, M.; Horuichi, S.; Nakatsugawa, K. *J. Organomet. Chem.* **1975**, *94*, 449–461. (l) Keinan, E.; Greenspoon, N. *Tetrahedron Lett.* **1985**, *26*, 1353–1356. (m) Keinan, E.; Greenspoon, N. *J. Am. Chem. Soc.* **1986**, *108*, 7314–7325. (n) Schmidt, T. *Tetrahedron Lett.* **1994**, *35*, 3513–3516. (o) Boeckman, J. R. K.; Michalak, R. *J. Am. Chem. Soc.* **1974**, *96*, 1623–1625. (p) Semmelhack, M. F.; Stauffer, R. D. *J. Org. Chem.* **1975**, *40*, 3619–3621. (q) Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. *J. Org. Chem.* **1977**, *42*, 3180–3188. (r) Tsuda, T.; Fujii, T.; Kawasaki, K.; Saegusa, T. *J. Chem. Soc., Chem. Commun.* **1980**, 1013–1014. (s) Noyori, R.; Umeda, I.; Ishigami, T. *J. Org. Chem.* **1972**, *37*, 1542–1545. (t) Collman, J. P.; Finke, R. G.; Matlock, P. L.; Wahren, R.; Brauman, J. I. *J. Am. Chem. Soc.* **1970**, *98*, 4685–4687. (u) Collman, J. P.; Finke, R. G.; Matlock, P. L.; Wahren, R.; Komoto, R. G.; Brauman, J. I. *J. Am. Chem. Soc.* **1978**, *100*, 1119–1140. (v) Boldrini, G. P.; Umani-Ronchi, A. *J. Organomet. Chem.* **1979**, *171*, 85–88. (w) Ganem, B. *J. Org. Chem.* **1975**, *40*, 146–147. (x) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194–2200. (2) (a) Adams, C. *Synth. Commun.* **1984**, *14*, 1349–1353. (b) Ward, D. E.; Rhee, C. K. *Can. J. Chem.* **1989**, *67*, 1206–1211.

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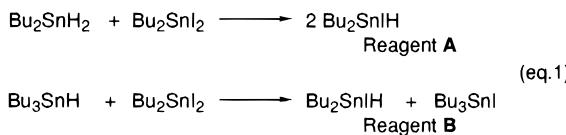
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conjugated enones could be accomplished in preference to the reduction of aldehydes, the subsequent aldol reaction of the resulting metal enolates could be expected. Organotin hydrides appear to be good candidates for this. They appear to act as soft Lewis acids leading to 1,4-addition,^{7,8} and the resulting tin enolates can be expected to show pronounced reactivity toward aldehydes.⁹ Quite recently, Enholm and co-workers have reported the selective 1,4-hydrostannation of cyclic enones by Bu₃SnH under free radical conditions and a subsequent intramolecular aldol reaction.¹⁰ In this paper, we demonstrate that Bu₂SnIH reagents accomplish the selective 1,4-reduction of conjugated enones **1**, irrespective of coexistent aldehydes, and a subsequent diastereoselective intermolecular aldol reaction.

Tin iodide hydride reagents can be prepared by the two methods shown in eq 1, to obtain pure Bu₂SnIH (reagent A)¹¹ or an equimolar mixture of Bu₂SnIH and Bu₃SnI (reagent B).¹² The former (1 mmol) was synthesized by mixing Bu₂SnH₂ (0.5 mmol) and Bu₂SnI₂ (0.5 mmol) at room temperature in THF (1 mL). The latter (1 mmol) was prepared by mixing Bu₃SnH (1 mmol) and Bu₂SnI₂ (1 mmol) at room temperature in THF (1 mL). The complete formation of the Bu₂SnIH species was spectroscopically confirmed by ¹H, ¹³C, and ¹¹⁹Sn NMR.



The selective 1,4-reduction of conjugated enone **1a** took place with either of these reagents (entries 1 and 2 in Table 1). Moreover, good enhancement of yield was achieved with reagent B, possibly because of the assistance of a soft Lewis acid, Bu₃SnI.¹³ As shown in Table 1, these results are in sharp contrast with the original tin hydrides, Bu₂SnH₂ and Bu₃SnH. The former showed a lack of regioselectivity (entry 4), and the latter had poor reducing ability toward **1a** (entry 5). Other dibutyltin halide hydrides prepared in a manner similar to reagent B also effected the selective 1,4-reduction (entries 6 and 7), although the corresponding fluoride reagent predominantly promoted 1,2-reduction to furnish the allylic alcohol **3a** in 36% yield (entry 8). When 1,4-dinitrobenzene (DNB) was added as a radical scavenger, little effect on the 1,4-reduction of **1a** was observed (entry 3). This suggests that 1,4-hydrostannation by organotin iodide hydride proceeds by an ionic reaction path.

Table 2 lists the reductions of conjugated enones **1b–e** with reagent B in THF at ambient temperature. All runs demonstrated complete 1,4-selectivity to provide the

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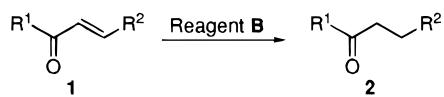
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(13) In the reaction with Bu₃SnH/Pd(PPh₃)₄, the yield increased using ZnCl₂ as the coactivating Lewis acid catalyst.^{1b}

Table 1. Reductions of Chalcone **1a by Various Tin Hydrides**

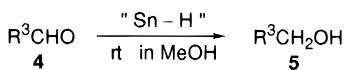
entry	"Sn-H"	yield, %	
		2a	3a
1	Reagent A ^a	69	0
2	Reagent B ^b	91	0
3	Reagent B-DNB ^{b,c}	77	0
4	Bu ₂ SnH ₂	18	45
5	Bu ₃ SnH	19	0
6	Bu ₂ SnBrH-Bu ₃ SnBr ^b	53	0
7	Bu ₂ SnClH-Bu ₃ SnCl ^b	86	0
8	Bu ₂ SnFH-Bu ₃ SnF ^b	5	36

^a Chalcone **1a** 1 mmol, Bu₂SnH₂ 0.5 mmol, Bu₂SnI₂ 0.5 mmol, THF 1 mL. ^b Chalcone **1a** 1 mmol, Bu₃SnH 1 mmol, Bu₂SnX₂ 1 mmol, THF 1 mL. ^c DNB 0.1 mmol.

Table 2. Reductions of Various Conjugated Enones by Reagent B^a

entry	R ¹	R ²	1	conditions	yield %
1	Ph	Me	1b	rt, 2 h	2b , 72
2	Me	Ph	1c	rt, 2.5 h	2c , 67
3	Ph	H	1d	rt, 1 h	2d , 63
4	cis-cyclohexenone		1e	rt, 2 h	2e , 42 (4) ^b

^a Enone **1** 1 mmol, Bu₃SnH 1 mmol, Bu₂SnI₂ 1 mmol, THF 1 mL. ^b Cyclohexanol.

Table 3. Reductions of Aldehydes **4 by Various Tin Hydrides^a**

entry	aldehyde 4	"Sn-H"	yield of 5 , %
1	R ³ = Ph (4a)	Reagent A	5a , 5
2	R ³ = Ph (4a)	Reagent B	5a , 6
3	R ³ = Ph (4a)	Bu ₃ SnH	5a , 93
4	R ³ = Ph (4a)	Bu ₂ SnH ₂	5a , 100
5	R ³ = c-hex (4b)	Reagent B	5b , 31
6	R ³ = i-Pr (4c)	Reagent B	5c , 17

^a Aldehyde **4** 1 mmol, SnH reagent 1 mmol, MeOH 1 mL.

corresponding ketones **2b-e**; no allylic alcohols arising from 1,2-reduction were detected. In the case of cyclohexenone **1e** (entry 4), 4% of cyclohexanol was formed, plausibly generated by further reduction of the 1,4-reduction product.

Next we examined the reduction of aldehydes by these tin reagents. As shown in Table 3, the reagents A and B showed quite low reducing ability (entries 1 and 2), while either Bu₃SnH or Bu₂SnH₂ readily reduced benzaldehyde **4a** to benzyl alcohol **5a** (entries 3 and 4). Reagent B also exhibited poor reactivity toward cyclohexanecarboxaldehyde **4b** and isobutyraldehyde **4c** (entries 5 and 6).

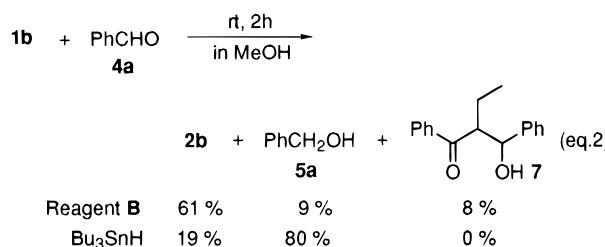
This interesting outcome prompted us to try a competitive reduction of a conjugated enone and an aldehyde. When an equimolar mixture of **1b** (1 mmol) and benzaldehyde **4a** (1 mmol) was treated with reagent B in MeOH (1 mL) at ambient temperature, the selective 1,4-reduction of **1b** produced ketone **2b** in 61% yield without any 1,2-reduction, while benzyl alcohol **5a** was furnished in only 9% yield (eq 2). Surprisingly, the aldol product **7** was also obtained in spite of the MeOH solvent—the tin

Table 4. Intermolecular Aldol Reactions of Conjugated Enones **1 with Aldehydes **4** by Using Reagent B^a**

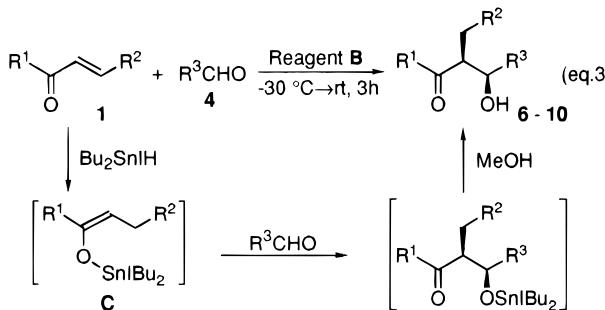
entry	enone 1	aldehyde 4	conditions	yield, %	syn:anti ^b
1	1a	4a	rt, 2 h	6 , 68	38:62
2	1a	4a	-30 °C → rt, 3 h	6 , 47	80:20
3	1b	4a	-30 °C → rt, 3 h	7 , 53	91:9
4	1d	4a	-30 °C → rt, 3 h	8 , 74	89:11
5 ^c	1d	4a	-30 °C → rt, 3 h	8 , 55	90:10
6	1d	4b	-30 °C → rt, 3 h	9 , 74	>99:1
7	1d	4c	-30 °C → rt, 3 h	10 , 67	92:8

^a Enone **1** 1 mmol, aldehyde **4** 1 mmol, Bu₃SnH 1 mmol, Bu₂SnI₂ 1 mmol, THF 1 mL. ^b Determined by 400 MHz ¹H NMR. ^c **1d** 1 mmol, **4a** 1 mmol, Bu₂SnH₂ 0.5 mmol, Bu₂SnI₂ 0.5 mmol, THF 1 mL.

enolate had been expected to be quenched. In contrast, Bu₃SnH reduced aldehyde **4a** to **5a** in 80% yield (eq 2).



These results suggested that reagent B would be a good candidate for an intermolecular aldol reaction by the tin enolate (C), as illustrated in eq 3. As expected, when a mixture of **1a** and **4a** was treated with Bu₂SnI₂ and Bu₃SnH in THF at ambient temperature, aldol product **6** was obtained in 68% yield (entry 1 in Table 4). However, the



diastereoselectivity obtained at ambient temperature was not satisfactory (syn:anti = 38:62). The striking dependency of the diastereoselectivity on reaction temperature is indicated in entries 1 and 2 (Table 4). Excellent syn-selectivity was observed at -30 °C → rt (entry 2). This diastereoselectivity is not due to the Lewis acid, Bu₃SnI in reagent B, because the alternative use of reagent A also gave **8** with high syn-selectivity (entry 5).¹⁴ It can be presumed that a (Z)-enolate is generated by the 1,4-hydrostannation of **1d** when in an s-cis conformation¹⁵ and that the resulting (Z)-enolate gives the syn aldol

(14) It has been reported that the reaction of tributylstannyl enolate, analogous to the tin enolate C arising from 1,4-hydrostannation of **1c**, with **4a** gave moderate anti-selectivity at low temperature.⁹

(15) (a) Boldrini, G. P.; Mancini, F.; Tagliavini, E.; Trombini, C.; Ronchi, A. U. *J. Chem. Soc., Chem. Commun.* **1990**, 1680–1681. (b) Boldrini, G. P.; Bortolotti, M.; Mancini, F.; Tagliavini, E.; Trombini, C.; Ronchi, A. U. *J. Org. Chem.* **1991**, 56, 5820–5826.

product under conditions of kinetic control.¹⁶ The enones **1b** and **1d** also provided the aldol products **7** and **8**, respectively, with high *syn*-selectivities (entries 3 and 4). Moreover, cyclohexanecarboxaldehyde **4b** and isobutyraldehyde **4c** behaved similarly (entries 6 and 7).

In conclusion, Bu_2SnIH reagents selectively reduce conjugated enones **1** in the presence of aldehydes at ambient temperature. In addition, a subsequent aldol reaction proceeds with *syn*-selectivity at -30°C . Further work on related systems including the characterization of the tin enolates C is underway.

Experimental Section

Analysis. ^1H , ^{13}C , and ^{119}Sn NMR spectra were recorded at 400, 100, and 149 MHz, respectively. Samples for ^1H and ^{13}C NMR spectra of produced ketones and aldols were examined in deuteriochloroform (CDCl_3) containing 0.03% (w/v) of tetramethylsilane. Samples for ^1H , ^{13}C , and ^{119}Sn NMR spectra of tin hydrides were examined in tetrahydrofuran- d_8 containing tetramethyltin. GLC analyses were performed using FFAP and OV-1 (2-m x 3-mm) columns. Column chromatography was performed by using Wakogel C-200 mesh silica gel. Preparative TLC was carried out on Wakogel B-5F silica gel. Yields were determined by ^1H NMR or GLC using internal standards.

Materials. Tributyltin hydride (Bu_3SnH) and dibutyltin dihydride (Bu_2SnH_2) were, respectively, prepared by the reduction of tributyltin chloride (Bu_3SnCl) and dibutyltin dichloride (Bu_2SnCl_2) with LiAlH_4 .¹⁷ THF and toluene were freshly distilled over sodium benzophenone ketyl. All reactions were carried out under dry nitrogen.

Preparation of Organotin Iodide Hydrides. Reagent A (1 mmol) was synthesized by mixing Bu_2SnH_2 (0.5 mmol) and Bu_2SnI_2 (0.5 mmol) in THF. Reagent B (1 mmol) was prepared by mixing Bu_3SnH (1 mmol) and Bu_2SnI_2 (1 mmol) in THF. We spectroscopically confirmed that these reagents were immediately formed even at -50°C .

Reagent A (8.00 M in $\text{THF}-d_8$): ^1H NMR (rt) δ 6.41 (Sn-H, $^1J(\text{Sn}-^1\text{H}) = 2060$ Hz, $^1J(\text{Sn}-^1\text{H}) = 1968$ Hz); ^{13}C NMR (rt) δ 14.1, 17.3 ($^1J(\text{Sn}-^{13}\text{C}_\alpha) = 408$ Hz, $^1J(\text{Sn}-^{13}\text{C}_\alpha) = 390$ Hz, 26.7 ($^3J(\text{Sn}-^{13}\text{C}_\gamma) = 74$ Hz), 29.7 ($^2J(\text{Sn}-^{13}\text{C}_\beta) = 29$ Hz); ^{119}Sn NMR (rt) δ -76.3 (d).

Reagent B (8.00 M in $\text{THF}-d_8$): ^1H NMR (rt) Bu_2SnIH δ 6.37 (Sn-H, $^1J(\text{Sn}-^1\text{H}) = 2046$ Hz, $^1J(\text{Sn}-^1\text{H}) = 1955$ Hz); ^{13}C NMR (rt) Bu_2SnIH δ 14.2, 17.2 ($^1J(\text{Sn}-^{13}\text{C}_\alpha) = 404$ Hz, $^1J(\text{Sn}-^{13}\text{C}_\alpha) = 387$ Hz), 26.8 ($^3J(\text{Sn}-^{13}\text{C}_\gamma) = 74$ Hz, $^3J(\text{Sn}-^{13}\text{C}_\gamma) = 70$ Hz), 29.8 ($^2J(\text{Sn}-^{13}\text{C}_\beta) = 29$ Hz); Bu_3SnI δ 14.2, 17.4 ($^1J(\text{Sn}-^{13}\text{C}_\alpha) = 325$ Hz, $^1J(\text{Sn}-^{13}\text{C}_\alpha) = 311$ Hz), 27.2 ($^3J(\text{Sn}-^{13}\text{C}_\gamma) = 66$ Hz, $^3J(\text{Sn}-^{13}\text{C}_\gamma) = 63$ Hz), 29.8 ($^2J(\text{Sn}-^{13}\text{C}_\beta) = 24$ Hz); ^{119}Sn NMR (rt) Bu_2SnIH δ -76.3 (d); Bu_3SnI δ 80.5 (s).

Representative Procedure for the 1,4-Selective Reduction of Enones. To the solution of Bu_2SnI_2 (1 mmol) in 1 mL of THF was added Bu_3SnH (1 mmol). The mixture was stirred at rt for 10 min. Conjugated enone **1a** (1 mmol) was added, and the solution was stirred until the Sn-H absorption disappeared in the IR spectra. After quenching the reaction with MeOH (5 mL), volatiles were removed under reduced pressure. The residue was subjected to column chromatography eluting with hexane-EtOAc (9:1) to give the product **2a**. Further purification was performed by TLC eluting with hexane-EtOAc (10:1).

1,3-Diphenylpropanone (2a): white solid; mp 68.7–70.3 °C; IR (KBr) 1665 cm^{-1} ; ^1H NMR (CDCl_3) δ 3.07 (t, 2H, $J = 7.32$ Hz), 3.30 (t, 2H, $J = 7.32$ Hz), 7.18–7.97 (m, 10H); ^{13}C NMR (CDCl_3) δ 30.1, 40.4, 126.1, 128.0, 128.4, 128.5, 128.6, 133.0, 136.8, 141.3, 199.2; HRMS calcd for $\text{C}_{15}\text{H}_{14}\text{O}$ 210.1045, found 210.1024.

1,3-Diphenyl-2-propenol (3a): colorless liquid, purified by TLC eluting with hexane-EtOAc (4:1); IR (neat) 3200 cm^{-1} ; ^1H NMR (CDCl_3) δ 2.12 (br, 1H), 5.37 (dd, 1H, $J = 6.35$ and 2.44

Hz), 6.38 (dd, 1H, $J = 16.11$ and 6.35 Hz), 6.68 (d, 1H, $J = 16.11$ Hz), 7.20–7.44 (m, 10H); ^{13}C NMR (CDCl_3) δ 75.1, 126.3, 126.6, 127.8, 127.8, 128.5, 128.6, 130.5, 131.5, 136.5, 142.8; HRMS calcd for $\text{C}_{15}\text{H}_{14}\text{O}$ 210.1045, found 210.1038.

Butyrophenone (**2b**) [495-40-9], 4-phenyl-2-butanone (**2c**) [2550-26-7], propiophenone (**2d**) [93-55-0], cyclohexanone (**2e**) [108-94-1], cyclohexanol [108-93-0] were identified in comparison with commercially available samples.¹⁸

Procedure for the Competitive Reaction between Enones and Aldehydes. To the solution of Bu_2SnI_2 (1 mmol) in 1 mL of MeOH were added **1b** (1 mmol) and **4a** (1 mmol). Bu_3SnH (1 mmol) was added, and the solution was stirred for 2 h. After quenching with MeOH (5 mL), volatiles were removed under reduced pressure. The residue was subjected to column chromatography, eluting with hexane-EtOAc (9:1) to give mainly ketone **2b** (61%); benzyl alcohol **5a** (9%) and aldol product **7** (8%) were also detected.

Representative Procedure for the Aldol-Type Reaction. To the solution of Bu_2SnI_2 (1 mmol) in 1 mL of THF were added conjugated enone **1** (1 mmol) and aldehyde **4** (1 mmol). Bu_3SnH (1 mmol) was added at -30°C , and the solution was stirred for 3 h with warming to room temperature. After quenching with MeOH (5 mL), volatiles were removed under reduced pressure. The residue was subjected to column chromatography eluting with hexane-EtOAc (1:2) to give the corresponding products **6–10**. Further purification was performed by TLC eluting with hexane-EtOAc (1:1).

syn- and anti-2-Benzyl-1,3-diphenyl-3-hydroxypropan-1-one (6): colorless liquid, purified by TLC with hexane-EtOAc (1:1); IR (neat) 3400 and 1658 cm^{-1} ; ^1H NMR (CDCl_3) **syn** δ 3.07 (dd, 1H, $J = 3.90$ and 13.67 Hz), 3.18 (dd, 1H, $J = 10.74$ and 13.67 Hz), 3.35 (d, 1H, $J = 1.47$ Hz), 4.00–4.07 (m, 1H), 5.08 (d, 1H, $J = 4.39$ Hz), 6.93–7.95 (m, 15H); ^{13}C NMR (CDCl_3) **syn** δ 33.5, 55.6, 74.0, 126.0, 126.2, 127.6, 128.1, 128.2, 128.3, 128.9, 133.0, 137.3, 139.3, 141.6, 205.5; ^1H NMR (CDCl_3) **anti** δ 2.87 (dd, 1H, $J = 6.35$ and 13.68 Hz), 3.03 (dd, 1H, $J = 8.79$ and 13.68 Hz), 3.52 (d, 1H, $J = 6.84$ Hz), 4.07–4.12 (m, 1H), 4.95 (dd, 1H, $J = 5.86$ and 6.84 Hz), 6.94–7.94 (m, 15H); ^{13}C NMR (CDCl_3) **anti** δ 36.6, 54.7, 75.4, 126.1, 126.3, 127.7, 128.1, 128.3, 128.4, 128.9, 133.0, 138.0, 138.5, 142.6, 204.7.

^1H and ^{13}C NMR data of **syn-6** were consistent with the ones reported previously: Boldrini, G. P.; Bortolotti, M.; Mancini, G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1991**, *56*, 5820–5826. Registry No. **syn-6**, 132455-70-0; **anti-6**, 135414-46-9.¹⁸

syn- and anti-1,3-Diphenyl-2-ethyl-3-hydroxypropan-1-one (7): colorless liquid, purified by TLC with hexane-EtOAc (1:1); IR (neat) 3250 and 1640 cm^{-1} ; HRMS calcd for $\text{C}_{17}\text{H}_{18}\text{O}_2$ 254.1307, found 254.1304; ^1H NMR (CDCl_3) **syn** δ 0.77 (t, 3H, $J = 7.57$ Hz), 1.72–1.99 (m, 2H), 3.39 (br, 1H), 3.74 (m, 1H), 5.37 (d, 1H, $J = 4.88$ Hz), 7.16–7.86 (m, 10H); ^{13}C NMR (CDCl_3) **syn** δ 12.0, 20.6, 54.2, 73.8, 126.1, 127.3, 127.7, 128.1, 128.2, 128.5, 137.4, 142.1, 205.0; ^1H NMR (CDCl_3) **anti** δ 0.78 (t, 3H, $J = 7.33$ Hz), 1.46–1.75 (m, 2H), 3.29 (br, 1H), 3.76 (m, 1H), 4.99 (d, 1H, $J = 7.33$ Hz), 7.16–7.92 (m, 10H); ^{13}C NMR (CDCl_3) **anti** δ 11.5, 23.6, 54.3, 75.6, 126.3, 127.7, 128.2, 128.3, 128.5, 133.1, 138.2, 142.7, 205.6.

syn- and anti-1,3-Diphenyl-3-hydroxy-2-methylpropan-1-one (8): colorless liquid, purified by TLC with hexane-EtOAc (1:1); IR (neat) 3000 and 1705 cm^{-1} ; HRMS calcd for $\text{C}_{16}\text{H}_{16}\text{O}_2$ 240.1151, found 240.1148; ^1H NMR (CDCl_3) **syn** δ 1.12 (d, 3H, $J = 7.33$ Hz), 3.63 (qd, 1H, $J = 7.33$ and 2.93 Hz), 5.17 (d, 1H, $J = 2.93$ Hz), 7.25–7.95 (m, 10H); ^{13}C NMR (CDCl_3) **syn** δ 11.1, 47.0, 73.1, 126.0, 127.3, 128.2, 128.5, 128.8, 133.6, 135.6, 141.8, 205.8; ^1H NMR (CDCl_3) **anti** δ 1.00 (d, 3H, $J = 7.32$ Hz), 3.88–4.07 (m, 1H), 4.93 (d, 1H, $J = 7.81$ Hz), 7.25–7.99 (m, 10H).

^1H NMR data of **syn-** and **anti-8** were consistent with the ones reported previously; Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598–1608. Registry No. **syn-8**, 71908-03-7; **anti-8**, 71908-02-6.¹⁸

syn-3-Cyclohexyl-3-hydroxy-2-methyl-1-phenylpropan-1-one (9): colorless liquid, purified by TLC with hexane-EtOAc (1:1); IR (neat) 3200 and 1630 cm^{-1} ; HRMS calcd for $\text{C}_{16}\text{H}_{22}\text{O}_2$ 246.1621, found 246.1623; ^1H NMR (CDCl_3) **syn** δ 0.88–1.79 (m, 10H), 1.24 (d, 3H, $J = 6.84$ Hz), 2.06–2.15 (m, 1H), 3.10 (br,

(16) For example: Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120–6123.

(17) (a) Finholt, A. E.; Bond, A. C., Jr.; Wilzbach, K. E.; Schlesinger, H. I. *J. Am. Chem. Soc.* **1947**, *69*, 2692–2696. (b) Kerk, G. J. M.; Noltes, J. G.; Luijten, J. G. A. *J. Appl. Chem.* **1957**, *7*, 366–369.

(18) Registry numbers are provide by the author.

1H), 3.64–3.71 (m, 2H), 7.26–7.97 (m, 5H); ^{13}C NMR (CDCl₃) *syn* δ 10.5, 25.8, 26.1, 26.3, 29.2, 29.4, 40.2, 41.3, 75.4, 128.4, 128.8, 133.4, 135.9, 205.9.

***syn*- and *anti*-3-Isopropyl-3-hydroxy-2-methyl-1-phenylpropan-1-one (10):** colorless liquid, purified by TLC with hexane-EtOAc (1:1); IR (neat) 3350 and 1640 cm⁻¹; HRMS calcd for C₁₃H₁₈O₂ 206.1307, found 206.1301; ^1H NMR (CDCl₃) *syn* δ 0.96 (d, 3H, *J* = 6.35 Hz), 1.03 (d, 3H, *J* = 6.35 Hz), 1.25 (d, 3H, *J* = 6.83 Hz), 1.74–1.83 (m, 1H), 3.15 (d, 1H, *J* = 2.44 Hz), 3.62–3.71 (m, 2H), 7.45–7.98 (m, 5H); ^{13}C NMR (CDCl₃) *syn* δ 10.8, 18.9, 19.1, 30.7, 41.9, 76.6, 128.4, 128.7, 133.3, 135.9, 205.7; ^1H NMR (CDCl₃) *anti* δ 0.94 (d, 3H, *J* = 6.84 Hz), 1.00 (d, 3H, *J* = 6.84 Hz), 1.27 (d, 3H, *J* = 6.84 Hz), 1.74–1.85 (m, 1H), 1.89 (br, 1H), 2.97–3.00 (m, 1H), 3.56–3.62 (m, 1H), 7.45–7.98 (m, 5H); ^{13}C NMR (CDCl₃) *anti* δ 15.9, 16.9, 19.9, 31.2, 42.4, 79.1, 128.5, 128.7, 132.8, 136.7, 206.2.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR and HRMS spectral data for the products **2a**, **3a**, **6–10** (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Aqueous Asymmetric Mukaiyama Aldol Reaction Catalyzed by Chiral Gallium Lewis Acid with Trost-Type Semi-Crown Ligands

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Abstract: The combination of Ga(OTf)₃ with chiral semi-crown ligands (**1a–e**) generates highly effective chiral gallium Lewis acid catalysts for aqueous asymmetric aldol reactions of aromatic silyl enol ethers with aldehydes. A ligand-acceleration effect was observed. Water is essential for obtaining high diastereoselectivity and enantioselectivity. The *p*-phenyl substituent in aromatic silyl enol ether (**2 h**) plays an important role and increases the enantioselectivity up to 95% ee. Although aliphatic silyl enol ethers provided low enantioselectivities and silylketene acetal is easily

hydrolyzed in aqueous alcohol, the aldol reactions of silylketene thioacetal (**12**) with aldehydes in the presence of gallium-Lewis acid catalysts give the β -hydroxy thioester with reasonable yields and high diastereo- (up to 99:1) and enantioselectivities (up to 96% ee).

Keywords: aqueous asymmetric C–C bond-forming reaction; chiral semi-crown ligand; gallium-Lewis acid catalyst, Mukaiyama aldol reaction

Introduction

Among the Lewis acid-catalyzed carbon–carbon bond forming reactions, the aldol-type reaction of silyl enol ethers with carbonyl compounds (the Mukaiyama reaction)^[1] has been recognized as one of the most important. In 1990 Mukaiyama^[2] reported the first asymmetric aldol reaction of silyl enol ethers catalyzed by chiral diamine/Sn(OTf)₂. Since then, several successful examples of the catalytic asymmetric Mukaiyama aldol reaction have been developed, including the use of *p*-Tol-BINAP with AgF^[3] or CuF^[4] BINOL with Zr(O-*t*-Bu)₄^[5] or Ti(O-*i*-Pr)₄,^[6] and chiral bis(oxazoline) with Cu(II)^[7] or Sc(III)^[8] as chiral catalysts. However, most of these reactions must be conducted at low reaction temperatures in aprotic anhydrous solvents. Recently, the performance of organic reactions in water^[9] has attracted considerable attention, which was followed by a growing interest in the development of asymmetric Mukaiyama-type reaction in aqueous media.^[10] Kobayashi and co-workers^[11] have reported excellent results using the combination of Cu(OTf)₂ with a chiral bis(oxazoline) ligand,^[12] Pb(OTf)₂ with a chiral crown ether^[13] and Ln(OTf)₃ [e.g., Nb(OTf)₃, Ce(OTf)₃ and Pr(OTf)₃] with chiral

bis-pyridino-18-crown-6^[14] for asymmetric Mukaiyama aldol reactions in aqueous ethanol (ethanol-water = 9:1). However, when the amount of water in the mixture was increased, yields and selectivities of the reaction decreased remarkably and, in water alone, both low yield (4%) and selectivity (ee 15%) were observed.^[14] Furthermore, compared to “heavier” metals, the use of ‘light’, main-group metal catalysts has environmental benefits and is more attractive. More recently, Kobayashi reported the catalytic asymmetric hydroxymethylation of silicon enolates with formaldehyde in aqueous solution with up to 90% ee by using a chiral scandium complex as catalyst^[15] and Jankowska reported an asymmetric Mukaiyama aldol reaction in aqueous media with up to 75% ee by using Zn-based chiral Lewis acid.^[16]

On the other hand, there are still various challenging problems to face in developing catalytic asymmetric reaction in aqueous media. Will water promote or prevent the reaction? How do we address the hydrolysis and solubility of the substrate in water? How do we balance the binding affinity of the metal with the ligand for asymmetric induction and reactivity of the chiral catalyst in water (i.e., how to complete the catalytic cycle in water)? Recently, Trost developed a chiral semi-crown ligand/di-

nuclear zinc catalyst system, which has been successfully applied in catalytic enantioselective direct aldol reactions,^[17] nitroaldol (Henry) reactions,^[18] Mannich-type reactions^[19] and diol-desymmetrizations.^[20] As shown by Trost, the semi-crown ligand (bearing more hydroxy groups) has more binding sites towards metals, which can meet both requirements of good affinity to metals and higher catalytic activity. It appears that these compounds are highly promising chiral ligands in asymmetric reactions in aqueous media. Herein, we report on the use of chiral gallium catalysts with chiral semi-crown ligands for a catalytic asymmetric Mukaiyama reaction in aqueous media.^[21]

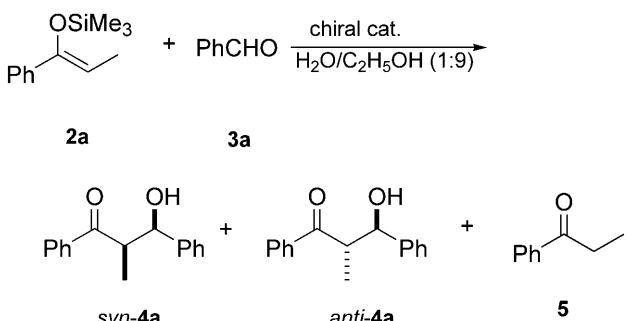
Results and Discussion

According to the literature methods^[16], the chiral semi-crown type ligands **1a–g** used in our study were synthesized (Figure 1) by two synthetic routes. The mono-arm ligand **1h** was prepared similarly starting from 2-methanol-4-*t*-butylphenol. Treatment of various ketones with NaH in toluene followed by reaction with chlorotrimethylsilane gave the corresponding (*Z*)-silyl enol ethers (*Z/E* = >99:1). After establishing an optimized experimental procedure and ratio of the reactants used, the chiral Lewis acid catalysts were prepared by stirring a mixture of the metal salt with the chiral ligand (1:1.2) in dichloromethane at room temperature for 2 h. After evaporation of the solvent and other volatile compounds, the solid complex thus obtained was employed as catalyst in the aldol reaction without further purification.

At first, (*Z*)-1-phenyl-1-trimethylsiloxypropene (**2a**) was reacted with benzaldehyde (**3a**) in aqueous ethanol ($C_2H_5OH/H_2O = 9:1$) in the presence of various Lewis acid catalysts (20 mol %), which were prepared from

$Sc(OTf)_3$, $Nd(OTf)_3$, $Pb(ClO_4)_2$, $Cu(OTf)_2$, $Zn(OTf)_2$, and $In(OTf)_3$ with the chiral semi-crown ligand (*S,S*)-**1a** (Scheme 1). Although, in all cases, the reaction proceeded smoothly to give the aldol product **4a** in good yields (75–90%) and diastereoselectivities (*syn:anti* > 80:20), the enantioselectivities of the formed *syn*-**4a** were very poor (0–5%). Fortunately, when a catalytic amount of $Ga(OTf)_3$ (20 mol %) was used under the same reaction conditions, the ee of *syn*-**4a** was increased remarkably to 80%. It is noteworthy to mention that although there are extensive reports on the use of chiral aluminium Lewis acids in asymmetric reactions, there are only few examples of chiral gallium-Lewis acid-catalyzed asymmetric reactions.^[21]

Subsequently, various gallium-Lewis acids prepared by chiral semi-crown ligands (**1a–g**) or mono-arm-type ligands (**1h, i**) with $Ga(OTf)_3$ were examined in the asymmetric aldol reaction of **2a** with **3a** in aqueous alcohol ($C_2H_5OH/H_2O = 9:1$) (Table 1). It is seen in Table 1 that the use of chiral ligand (*S,S*)-**1b** (*R* = *t*-butyl) provided a slightly higher enantioselectivity (87% ee) than chiral ligand (*S,S*)-**1a** (*R* = methyl) (80% ee) (entries 2 vs. 1). The use of chiral ligand (*S,S*)-**1c** (*R* = F) re-



Scheme 1.

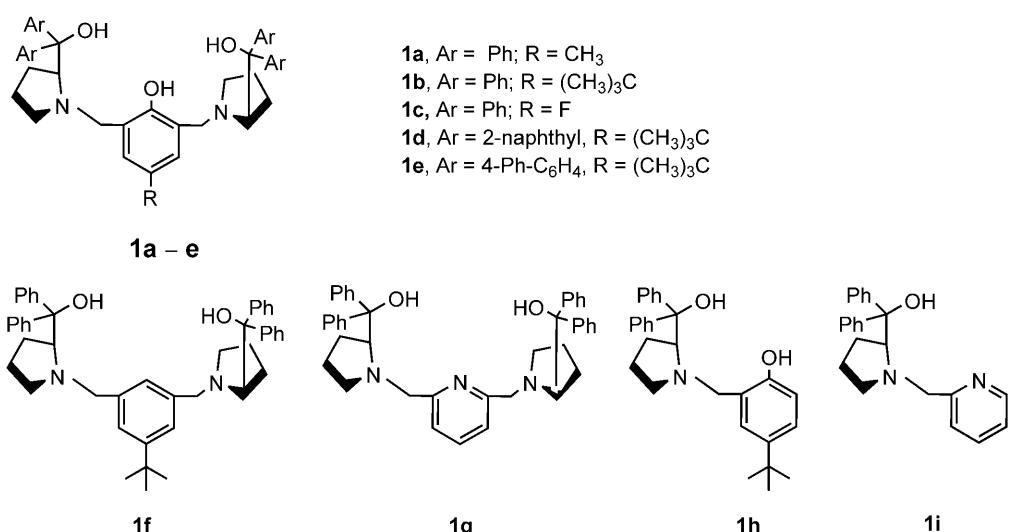


Figure 1. Chiral semi-crown type ligands **1a–g** and mono-arm-type ligands **1h, i**.

Table 1. The reaction of **2a** with **3a** in aqueous media.^[a]

Entry	Chiral catalyst ^[b] [L* + Ga(OTf) ₃]	Reaction time ^[c] [h]	Yield of 4a ^[d] [%] (syn/anti) ^[e]	ee of syn- 4a ^[f] [%]	Yield of 5 ^[d] [%]
1	1a	36	80 (87/13)	80	5
2	1b	36	89 (89/11)	87	trace
3	1b + GaCl ₃	36	61 (84/16)	78	—
4	1c	24	76 (88/12)	78	5
5	1d	8	81 (90/10)	87	—
6	1e	8	84 (95/5)	86	—
7	1f	36	—	—	98
8	1g	36	65 (85/15)	44	31
9	1h	36	72 (89/11)	5	20
10	1i	36	49 (90/10)	2	48
11	Ga(OTf) ₃	15 min	—	—	98
12	GaCl ₃	36	trace	—	—

^[a] In H₂O/C₂H₅OH (1:9).^[b] Catalyst loading: 20 mol %.^[c] Reaction temperature: 0–5 °C.^[d] Yield of isolated product.^[e] Determined by ¹H NMR.^[f] Determined by chiral HPLC.

sulted in a decrease in the enantioselectivity (78% ee, entry 4). The use of non-C₂-symmetrical mono-prolinol ligands (*S*)-**1h** and (*S*)-**1j** did not provide any significant enantioselectivity (entries 9 and 10).

There are two competing reactions in the aqueous reaction of silyl enol ether with aldehyde: the aldol reaction and hydrolysis of the silyl enol ether. If Ga(OTf)₃ (without the chiral ligand) was used alone in the aqueous aldol reaction, silyl enol ether **2a** hydrolyzed completely in only 15 min to give 1-phenylpropanone (**5**) (entry 11); whereas the use of GaCl₃ alone as catalyst, although no hydrolyzed product **5** was obtained, resulted in only trace amounts of aldol product after stirring for 36 h (entry 12). However, when the Ga-Lewis acid catalysts [prepared from semi-crown ligand **1b** and Ga(OTf)₃ or GaCl₃] were employed, the aqueous aldol reaction of **2a** with **3a** provided both good yield and enantioselectivity of the aldol product **4a** together with a trace amount of **5** (entries 2 and 3). These results suggested that the ligand played an important role in accelerating the aldol reaction and suppressing the hydrolysis of silyl enol ethers in aqueous media. The reaction was further accelerated with the use of ligands **1d** and **1e**, in which the phenyl group on the chiral ligand was replaced by 2-naphthyl and 4-biphenyl groups: the reaction time was shortened from 24 h to 8 h with a slightly higher diastereoselectivity (syn/anti = 95:5) and the same enantioselectivities of syn-**4a** (86% ee) (entries 5 and 6).

In order to elucidate the binding ability of the semi-crown ligands with Ga³⁺ in aqueous media, UV-vis titration of the chiral ligands with Ga(OTf)₃ was performed. The plotting of the change of optical density (C₀/ΔOD) against OD⁻¹ afforded a line with linear correlation coefficients (R) when mixing the chiral ligands with

Ga(OTf)₃ in H₂O/C₂H₅OH (1:9), indicating the formation of a 1 + 1 complex. The values of the corresponding R (0.9973–0.9999) (Table 2) indicated a very good linear relationship and also show the reliability of the plots in extracting the association constants. The introduction of a solution of the prepared complex **1b**/Ga(OTf)₃ in H₂O/C₂H₅OH (1:9) to an electrospray mass spectrometer provided two peaks at *m/e* = 748.8 (calcd. for C₄₆H₅₀GaN₂O₃: 748.6) and 899.8 (calcd. for C₄₇H₅₂F₃GaN₂O₆S: 899.6) that correspond to M + 1 and M + 1 + HOTf, respectively. The results also demonstrated the formation of a 1 + 1 complex in aqueous alcohol. However, no peak was observed in the electrospray mass spectrum of the complex **1f**/Ga(OTf)₃ under the same conditions. Based on the Benesi–Hidebrand relationship,^[22] the association constant could be determined by the UV-vis titration of chiral ligand with the solution of Ga(OTf)₃ in H₂O/C₂H₅OH (1:9) (Table 2). As shown in Table 2, the complex of the semi-crown li-

Table 2. Association constants of the complex in H₂O/C₂H₅OH (1:9).

Complex [ligand/Ga(OTf) ₃]	Association constant ^[a] [M ⁻¹]	R ^[b]
1a + Ga(OTf) ₃	5.89 × 10 ³	0.9973
1b + Ga(OTf) ₃	1.20 × 10 ⁴	0.9979
1c + Ga(OTf) ₃	4.44 × 10 ²	0.9997
1f + Ga(OTf) ₃	6.69 × 10 ²	0.9999
1g + Ga(OTf) ₃	3.73 × 10 ³	0.9998
1h + Ga(OTf) ₃	5.08 × 10 ²	0.9996

^[a] Measured by UV-vis titration.^[b] Linear correlation coefficient.

gand bearing a phenol hydroxy group and a *tert*-butyl group in the phenyl ring (**1b**) with $\text{Ga}(\text{OTf})_3$ has the largest association constant ($1.20 \times 10^4 \text{ M}^{-1}$), and exhibits the highest binding ability of the semi-crown ligand to Ga^{3+} in aqueous media. The ligand **1f** (with two alkyl hydroxy and without a phenol hydroxy group) and mono-arm ligand **1h** (with one alkyl hydroxy and one phenol hydroxy group) also have relatively low association constants (6.69×10^2 and 5.08×10^2 , respectively), which correspond to weak bonding. Thus, the Trost ligand has more binding sites and can generate a stronger [O–Ga] bond through the removal of HOTf from the reaction of OH with $\text{Ga}(\text{OTf})_3$. On the other hand, the complex of ligand **1g** (with a pyridine group) with Ga^{3+} , which generates a N···Ga coordination bond, has a slightly lower association constant (3.73×10^3). On the basis of these results, it can be postulated that there is a dynamic equilibrium between the complex and the gallium species as well as the ligand in aqueous media. For the complex (S,S) -**1b**/ $\text{Ga}(\text{OTf})_3$, the equilibrium shifted more to the side of forming the chiral and reactive catalyst complex, leading to a higher yield of aldol product and asymmetric induction (Table 1, entry 2). Whereas, since the complex **1f**/ $\text{Ga}(\text{OTf})_3$ has a low binding ability (lower value of R) in aqueous media, the equilibrium shifted towards the side of dissociation, generating a gallium species that is inactive in catalyzing the aldol reaction and leading to hydrolysis of the silyl enol ether (Table 1, entry 7).

In view of the above results, the chiral catalyst $[(S,S)$ -**1b**/ $\text{Ga}(\text{OTf})_3$] was selected for further studies. The effect of the reaction solvent on the reaction was also examined (Table 3). Since the complex **1b**/ $\text{Ga}(\text{OTf})_3$ has the strongest binding ability in aqueous media, both diastereo- and enantioselectivities remained high with an increase of the water content in the mixture-solvent and with water alone as the solvent (Table 3, entries 2–5). However, in water alone the reaction was slow and gave a lower yield of the aldol reaction product. In this

case, the addition of a surfactant (SDS) did not improve the yield of the reaction. On the other hand, the use of ethanol as solvent decreased the enantioselectivity of *syn*-**4a** significantly (entry 1). In anhydrous THF, the reaction offered the aldol product in a low yield (47%) together with lower diastereoselectivity (*syn/anti* = 77:23) and enantioselectivities (44% ee of *syn*-**4a**); the addition of a small amount of water dramatically improved the yield (80%), diastereoselectivity (88:12) and enantioselectivity (80% ee) (entries 6 and 7). Only a trace amount of the aldol product was detected when dichloromethane was used as solvent under the same reaction conditions (entry 8).

Subsequently, various aromatic aldehydes were employed in the asymmetric aldol reaction in water/ethanol (9:1) under the same reaction conditions catalyzed by the chiral gallium-Lewis acid [$\text{Ga}(\text{OTf})_3/(S,S)$ -**1b**]. In all cases, the reactions provided good yields (77–90%), diastereoselectivities (*syn/anti* = 80/20–90/10) and enantioselectivities of *syn*-products (78–88% ee) (Table 4). The presence of an electron-withdrawing group on the phenyl ring of the aldehyde (e.g., Cl) decreased the enantioselectivity (entry 4). The effect is more prominent in the case of *p*-nitrobenzaldehyde (**3g**), generating *syn*-**4g** in 62% ee (entry 7). The absolute configuration of *syn*-**4a** and its analogues were determined as *2R,3R* by comparing the optical rotation of *syn*-**4a** ($[\alpha]_D$: –11.5) and *syn*-**4f** ($[\alpha]_D$: –101.5) with those of the authentic compounds (*2S,3S* enantiomers: $[\alpha]_D$: +11.7 and +103.6, respectively).^[24] The reaction of an aliphatic aldehyde (**3h**) gave a lower ee (30%) (entry 8). No reaction was observed with simple ketones under the current conditions.

In order to investigate the relationship of the structure of silyl enol ether with the enantioselectivity, various silyl enol ethers **6a–e** and **2a–h** were synthesized and employed in aldol reactions with aldehydes (Scheme 2). Since **6a** is less stable in water, the yield of the aldol product is low (30%, Table 5, entry 1). The increase of the

Table 3. The reaction of **2a** with **3a** in various solvents.^[a]

Entry	Solvent	Reaction time ^[b]	Yield of 4a ^[c] [%] (<i>syn/anti</i>) ^[d]	ee of <i>syn</i> - 4a ^[e] [%]
1	$\text{C}_2\text{H}_5\text{OH}$	36 h	75 (88/12)	58
2	$\text{H}_2\text{O}/\text{C}_2\text{H}_5\text{OH}$ (1:9)	36 h	89 (89/11)	87
3	$\text{H}_2\text{O}/\text{C}_2\text{H}_5\text{OH}$ (1:1)	36 h	84 (82/18)	82
4	$\text{H}_2\text{O}/\text{C}_2\text{H}_5\text{OH}$ (9:1)	36 h	85 (85/15)	85
5	H_2O	3 d	41 (90/10)	84
6	THF	36 h	47 (77/23)	44
7	$\text{H}_2\text{O}/\text{THF}$ (1:4)	36 h	80 (88/12)	80
8	CH_2Cl_2	3 d	trace	

^[a] Catalyst: **1b**/ $\text{Ga}(\text{OTf})_3$ (20 mol %).

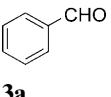
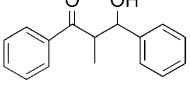
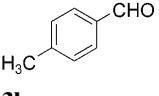
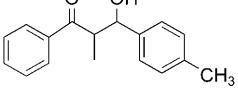
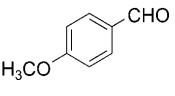
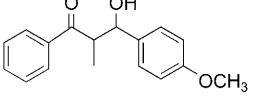
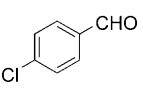
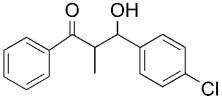
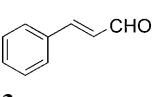
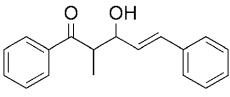
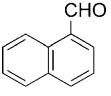
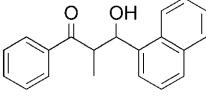
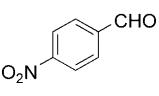
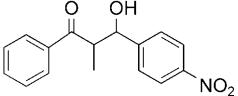
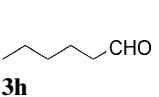
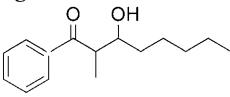
^[b] Reaction temperature: 0–5 °C.

^[c] Yield of isolated product.

^[d] Determined by ^1H NMR.

^[e] Determined by chiral HPLC.

Table 4. The reactions of **2a** with various aldehydes (**3a–h**) in aqueous media.^[a]

Entry	Aldehyde (R)	Product (R)	Yield of 4 ^[b] [%] (syn/anti) ^[c]	ee of syn- 4 ^[d] [%]
1			85 (85/15)	85
2			89 (90/10)	88
3			80 (88/12)	84
4			77 (82/18)	78
5			90 (90/10)	86
6			87 (80/20)	82
7			82 (77/23)	62
8			78 (87/18)	30

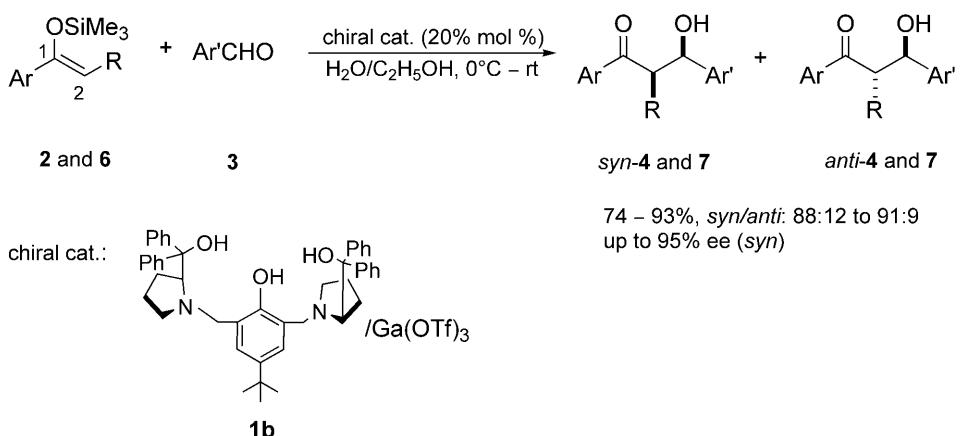
^[a] In H₂O/C₂H₅OH (9:1), reaction temperature: 0–5 °C.^[b] Yield of isolated product.^[c] Determined by ¹H NMR.^[d] Determined by chiral HPLC.

bulkiness of substituents at the 2-position of the silyl enol ether affected the stereochemistry of the reaction strongly, and resulted in low enantioselectivities (46–59% ee) (Table 5, entries 3–6).

However, variation of the aryl group at the 1-position of the silyl enol ethers gave very interesting results: when 1-(4'-biphenyl)-1-trimethylsiloxy-1-propene (**2h**) was used, the diastereoselectivity of the aldol reaction is *syn/anti*=90:10 and the enantioselectivity of the *syn*-aldol product (*syn*-**4p**) reached up to 95% ee (Table 6, entry 9); although the aldol reaction of aromatic aldehydes bearing an electron-withdrawing group [such as chloro (**3d**) and bromo (**3i**)] gave relatively

low enantioselectivities of the *syn*-aldol product in general, the reaction of **2h** with **3d** or **3i** gave >90% ee (entries 10 and 11). The high enantioselectivity can be attributed to the hydrophobic π–π stacking between the aromatic silyl enol ether and aromatic aldehyde in aqueous media.

The silyl enol ethers (**9a** and **9b**) prepared from aliphatic ketones are generally unstable in aqueous media and undergo hydrolysis readily to form ketones. In the current reaction, an excess amount of silyl enol ethers is required (**9a** or **9b**:**3a**=3:1) and the yields of aldol products are also relatively lower (Table 7, entries 1 and 2). The use of these compounds also led to lower

**Scheme 2.****Table 5.** The reaction of silyl enol ether **2a**, **6a–e** with benzaldehyde (**3a**) in aqueous media.^[a]

Entry	Silyl enol ether (R)	Product (R)	Yield of 7 ^[b] [%] (<i>syn/anti</i>) ^[c]	ee of <i>syn-7</i> [%] ^[d]
1			30	66
2			89 (89/11)	87
3			91 (83/17)	46
4			93 (71/29)	53
5			88 (82/18)	59
6			83 (58/42)	51

^[a] In $\text{H}_2\text{O}/\text{C}_2\text{H}_5\text{OH}$ (1:9), reaction temperature: room temperature.

^[b] Yield of isolated product.

^[c] Determined by ^1H NMR.

^[d] Determined by chiral HPLC.

enantioselectivity (71–73% ee) compared with the reaction of aromatic silyl enol ethers with benzaldehyde. Silylketene acetal **11** is even more unstable and only hydrolysis product was isolated after stirring for 24 h. Previously, Kobayashi^[14b] reported that the aqueous asym-

metric reactions of silyl ketene thioacetal with aldehyde gave optically active β -hydroxy thioesters in 78–83% ee of the *syn*-products, which are useful compounds for synthesizing optically pure alcohols. Because silylketene thioacetals are more sensitive to water, 2,6-di-*tert*-

Table 6. The reaction of aromatic silyl enol ethers with aldehydes in aqueous media.^[a]

Entry	Silyl enol ether	Aldehyde	Product	Yield [%] ^[b] (<i>syn/anti</i>) ^[c]	ee of <i>syn</i> - 4 ^[d] [%]
1				89 (89/11)	87
2				85 (88/12)	85
3				84 (90/10)	82
4				87 (90/10)	77
5				93 (92/8)	88
6				87 (90/10)	86
7				86 (95/5)	88
8				92 (91/9)	94
9				88 (90/10)	95
10				81 (89/11)	92
11				74 (90/10)	91

[a] In H₂O/C₂H₅OH (1:9), reaction temperature: room temperature.

[b] Yield of isolated product.

[c] Determined by ¹H NMR.

[d] Determined by chiral HPLC.

butylpyridine (30 mol %) must be added in order to suppress the competing hydrolysis reaction effectively. The addition of 2,6-di-*tert*-butylpyridine is not necessary in

the current reaction. By using the Trost ligand/Ga(OTf)₃ as chiral catalyst, the reaction of silylketene thioacetal **12** with aldehydes in aqueous alcohol (H₂O/C₂H₅

Table 7. The reaction of silyl substrates with aldehydes in aqueous media.^[a]

Entry	Silyl substrate	Aldehyde	Reaction time ^[b] [h]	Product	Yield ^[c] [%] (<i>syn/anti</i>) ^[d]	ee of <i>syn</i> -[%] ^[e]
1			16		66 (90/10)	73
2			16		64 (84/16)	71
3			24	—	—	—
4			48		67 (91/9)	84
5			72		64 (99/1)	87
6			72		69 (91/9)	88
7			72		70 (83/17)	80
8			72		76 (88/12)	90
9			72		72 (99/1)	96

[a] In H₂O/C₂H₅OH (1:9).

[b] Reaction temperature: room temperature.

[c] Yield of isolated product.

[d] Determined by ¹H NMR.

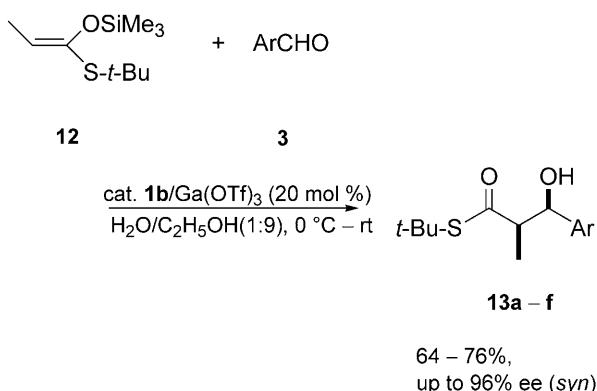
[e] Determined by chiral HPLC.

OH = 1:9) gave the corresponding aldol products **13a–f** in the reasonable yields 64–76% and high diastereoselectivities (*syn/anti* = 83:17 to 99:1) (Scheme 3). When 1-naphthylaldehyde (**3f**) was used, the enantioselectivity of the product *syn*-**13f** reached 96% ee (entry 9). The configuration of the *syn*-β-hydroxy thioesters was deduced as 2*R*,3*R* by comparing the retention time of authentic compound^[14b] with that of *syn*-**13c** on chiral HPLC (using the same column: Daicel Chiralcel OD):

*t*_R = 16.2 (major) and 26.2 min (minor) vs. *t*_R = 16.2 (major) and 25.0 min (minor).

Conclusion

Chiral gallium-Lewis acids with chiral semi-crown ligands (Trost's ligand) have been developed for catalytic asymmetric Mukaiyama aldol reactions in aqueous me-

**Scheme 3.**

dia. The strong binding of Ga³⁺ with the semi-crown ligands and the ligand acceleration effect of the chiral gallium catalysts exerted in the aldol reaction are responsible for the high enantioselectivities of the aqueous asymmetric reactions. The scope and applications of such chiral gallium catalysts in asymmetric C–C bond-forming reactions in aqueous media are under further investigation.

Experimental Section

General Remarks

IR spectra were recorded on a Perkin-Elmer 782 infra-red spectrometer. ¹H and ¹³C NMR spectra were measured with Varian XL-300 and Bruker DMX-300 (300 MHz) spectrometers in CDCl₃ with tetramethylsilane as an internal standard. Mass spectra were recorded on a Bruker APEX-2 spectrometer using the FBA technique. Electrospray ionization mass spectrometry (ESI-MS) analyses were performed using an LCMS-2010 mass spectrometer (Shimadzu, JAP). The sample solution (5 µL) was directly delivered into the ESI source with a syringe. The mobile phase was C₂H₅OH:H₂O (9:1, v/v). HPLC spectra were performed on a Shimadzu CTO-10ASVP equipped with the stated chiral columns. Optical rotation was measured on a Perkin-Elmer 241 (589 nm). The UV-vis titration was performed on a Techcomp UV-2410 spectrometer. Melting points were measured using a Beijing-Taike X-4 apparatus and are uncorrected. Sample **1i** is a gift kindly provided by Dr. H. Chen of Peking University.

Synthesis of the Chiral Ligands

Chiral ligands **1b–h** were synthesized according to the literature procedure for the synthesis of (*S,S*)-**1a**.^[17]

Ligand (S,S)-1b: A light yellow solid, mp 96–98 °C; [α]_D: +46.0 (c 1.0, CH₂Cl₂); IR: ν = 3424, 3058, 3028, 2960, 2870, 1600, 1485, 1448, 1116 cm⁻¹; ¹H NMR: δ = 1.24 (9H, s), 1.54–2.04 (8H, m), 2.42 (2H, m), 2.81 (4H, m), 3.26, 3.42 (4H, ABq, *J* = 12.7 Hz), 6.80 (2H, s), 7.12–7.35 (12H, m), 7.58 (4H, d, *J* = 7.8 Hz), 7.73 (4H, d, *J* = 7.8 Hz); ¹³C NMR: δ = 29.7, 23.5,

31.7, 34.0, 55.0, 57.7, 71.4, 78.9, 124.0, 125.9, 126.0, 126.4, 126.6, 127.1, 128.0, 128.2, 128.8, 146.4, 147.0, 152.6; HR-MS (FAB): *m/z* = 681.4066, calcd. for C₄₆H₅₂N₂O₃: 681.4066.

Synthesis of (Z)-Silyl Enol Ethers

To a suspension of sodium hydroxide (114 mg, 6 mmol) in toluene (25 mL), aryl ketone (4 mmol) and trimethylchlorosilane (0.76 mL, 6 mmol) were added dropwise, followed by refluxing for 12 h. Upon cooling to room temperature, triethylamine (0.83 mL, 6 mmol) was added, and the mixture was poured into a mixture of hexane/ice water. The organic layer was separated and dried over Na₂SO₄. After evaporation of solvent, the crude material was purified by flash chromatography on silica column (eluent: hexane) to give the product. All the prepared silyl enol ethers have predominantly the (Z)-configuration (Z/E = > 99:1) as determined by ¹H NMR.

Aldol Reaction of Silyl Enolate with Aldehydes in the Presence of a Chiral Catalyst

Preparation of the chiral catalyst: A solution of the chiral ligand (0.12 mmol) and Ga(OTf)₃ (51.7 mg, 0.1 mmol) in methylene chloride (1 mL) was stirred for 6 h at room temperature. The solvent was evaporated to give a slightly yellow solid that was used as the chiral catalyst directly.

Typical experimental procedure for the aldol reaction: Benzaldehyde (**3a**; 5 mL, 0.5 mmol) and silyl enol ether **2a** (154.5 mg, 0.75 mmol) were added into a solution of the above-prepared catalyst in a mixed solvent (H₂O/C₂H₅OH = 1:9) at 0–5 °C, followed by stirring for 36 h at 0 °C to room temperature. The reaction was quenched with aqueous NaHCO₃. The mixture was extracted with ether (3 ×), and the combined organic phase was dried over Na₂SO₄ and concentrated. The crude product was purified by flash chromatography on silica gel (eluent: ethyl acetate-petroleum ether = 1:10) to give a mixture of *syn*- and *anti*-**4a**. The *syn/anti* ratio was determined by ¹H NMR and the ee of *syn*-**4a** by chiral HPLC.

Characterization data of compounds **1**, **2**, **4**, and **13** can be found in the Supporting Information.

Acknowledgements

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Reductive Desymmetrization of 2-Alkyl-1,3-diketones Catalyzed by Optically Active β -Ketoiminato Cobalt Complexes

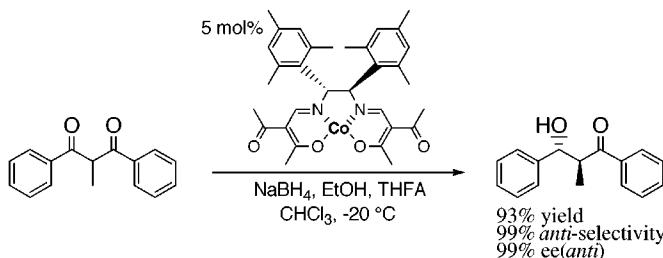
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ABSTRACT



The reductive desymmetrization of acyclic 1,3-diketones was achieved for the first time by catalytic borohydride reduction in the presence of optically active β -ketoiminato cobalt(II) complex catalysts. In this reaction, various 2-substituted-1,3-diaryl-1,3-propanediones were converted into the corresponding optically active 2-substituted-1,3-diaryl-3-hydroxypropanone in good-to-high yields with excellent diastereo- and enantioselectivities and high catalytic efficiencies.

The strategy of enantioselective desymmetrization is often used for the preparation of optically active compounds because two or more stereocenters can be generated in one reaction step.¹ For example, the optically active 2-substituted-3-hydroxyketones can be obtained by the enantioselective reduction of the corresponding symmetrical 2-substituted-1,3-diketones, which are readily prepared by Claisen condensation,² etc. Whereas various reductive desymmetrizations of symmetrical diketones have already been reported in enzymatic reactions,³ the applications of the asymmetric reduction catalyzed by metal complexes were limited to a few cyclic symmetrical imides,⁴ diamides,⁵ and diketones.⁶ For the synthesis of the optically active 2-substituted-3-

hydroxyketone units that often appear in various natural products,⁷ many studies have been conducted to develop the most efficient methods. An aldol reaction is one of the most reliable methods for this purpose, and its enantioselective and catalytic versions have been examined using various optically active transition metal complexes.⁸ In almost all

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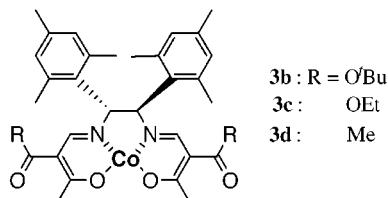
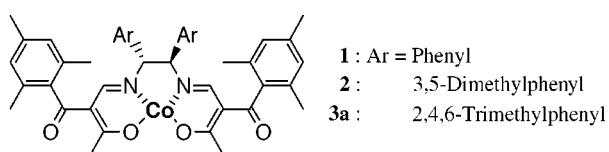
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Table 1. Various Catalysts^a for Enantioselective Desymmetrization

entry	catalyst	yield (%) ^b	anti-selectivity (%) ^c	ee (anti, %) ^d	recovery (%) ^b	diols yield (%) ^b
1	1	65	93	33	3	27
2	2	58	99	45		39
3	3a	65	94	89	24	11
4	3b	55	98	81	1	41
5	3c	71	96	87	1	28
6	3d	75	95	92	10	15
7 ^e	3d	93	99	99		7

^a Procedure A: to a solution of the modified borohydride was added a solution of the cobalt catalyst and the substrate; 0.5 mmol of substrate, 0.025 mmol (5 mol %) of cobalt catalyst, 0.5 mmol of NaBH₄, 1.5 mmol of EtOH, 7 mmol of tetrahydrofurfuryl alcohol (THFA) in CHCl₃ (total 28 mL) at 0 °C, 10 h.

^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d Determined by HPLC analysis. ^e Procedure B: to a solution of the cobalt catalyst and the substrate was added a solution of the modified borohydride; 0.25 mmol of substrate, 0.0125 mmol (5 mol %) of cobalt catalyst **3d**, 0.25 mmol of NaBH₄, 0.25 mmol of EtOH, 3.5 mmol of THFA in CHCl₃ (total 14 mL) at -20 °C, 10 h.



catalytic enantioselective aldol reactions, however, preparations of silyl or metal enolates^{8,9} are required in advance along with a relatively large amount of loading of the catalyst for high enantio- and/or diastereoselectivity. These disadvantages have made the enantioselective and catalytic aldol reactions difficult to use on a multigram scale in laboratory and manufacturing processes. The diastereo- and enantioselective reductions of the corresponding 2-substituted-1,3-diketones conventionally prepared by the Claisen condensation should be an alternative solution for synthesis of aldol-type compounds.

Recently, we developed optically active β-ketoiminato cobalt complex catalysts¹⁰ for the highly enantioselective borohydride reduction of ketones¹¹ and imines¹² to afford the corresponding secondary alcohol and amines with high catalytic efficiencies¹³ and reported that the 1,3-diaryl-1,3-diketones were converted by the catalytic system into the corresponding 1,3-diols with high enantioselectivity.¹⁴ In this communication, we would like to describe the first successful

reaction for the reductive desymmetrization of acyclic symmetrical diketones with high stereoselectivities and high catalytic efficiencies and to propose a new method for the preparation of optically active aldol-type compounds with high enantioselectivity.

The desymmetrization of 1,3-diphenyl-2-methyl-1,3-propanedione into optically active 1,3-diphenyl-3-hydroxy-2-methylpropanone was adopted as a model reaction for screening the various optically active β-ketoiminato cobalt complexes for the catalytic borohydride reduction (Table 1). Each ligand of the cobalt catalyst was prepared from the corresponding optically active 1,2-disubstituted-1,2-ethylenediamine and 1,3-dicarbonyl compound.¹³ Although the anti-selectivity of the resulting β-hydroxyketones was excellent in each case, the enantiomeric excesses of the anti products varied widely, being sensitive to the structure of the cobalt complex catalysts (entries 1–6). The catalyst **1** or **2** afforded a low or moderate ee of the anti product (entries 1 and 2), whereas the enantioselectivity was remarkably improved when employing the series **3** catalysts derived from the optically active 1,3-bis(2,4,6-trimethylphenyl)ethylenediamine (entries 3–6). Among the series **3** catalysts, it was found that catalyst **3d**, having acetyl groups on both side chains, was the most efficient catalyst for the reductive desymmetrization of the 1,3-diphenyl-2-methyl-1,3-propanedione (entry 6). After optimization of the reaction conditions, 99% ee of the anti product was isolated in 93% yield with 99% diastereoselection (entry 7).

The catalytic and enantioselective desymmetrization was successfully applied to the preparation of various optically active 2-substituted-1,3-diaryl-3-hydroxypropanones from the corresponding 1,3-diketones (Table 2). Various 2-methyl-

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Table 2. Catalytic Desymmetrization of Various 2-Alkyl-1,3-diaryl-1,3-propanediones^a

entry	β -hydroxyketones	yield/% ^b	anti-selectivity/% ^c	ee/% ^d
1		93	99	99
2		97	99	99
3		73	99	99
4		68	99	99
5		96	99	97
6		88	99	99
7		88	98	97
8		96	99	98
9		45	99	91

^a Procedure B (see Table 1). ^b Isolated yield. ^c Determined by ¹H NMR.
^d Values for ee's of anti products were determined by HPLC analysis.

1,3-diaryl-1,3-diketones, having *p*-methylphenyl-, 2-naphthyl-, *p*-bromophenyl-, or *p*-methoxyphenyl- as the aryl group, were converted into the corresponding anti-2-methyl-3-hydroxyketones in good-to-high yields with excellent anti-selectivity and excellent enantioselectivity (entries 2–5). For the catalytic and enantioselective desymmetrization of various 2-substituted-1,3-diketones, such as 2-ethyl-, 2-allyl-, 2-benzyl-, and 2-isopropyl-, the corresponding anti-2-alkyl-3-hydroxyketones were obtained with excellent anti-selectivity and excellent enantioselectivity (entries 6–9).

The excellent stereoselectivity in the present catalytic reduction system can be explained as follows (Figure 1). The hydride equivalent nucleophile should attack one of the carbonyl groups in the 1,3-diaryl-1,3-propanedione according to the Felkin–Anh model to afford the corresponding anti product with high selectivity. Concerning the excellent enantioselectivity, the optically active β -ketoiminato cobalt complex could distinctly recognize the *re/si* face of the carbonyl group similar to the cobalt-catalyzed borohydride reduction of the aryl ketones.^{11c} Since the reaction takes place with high enantioselectivity and the operation of path A appears as a consequence of the absolute configuration of

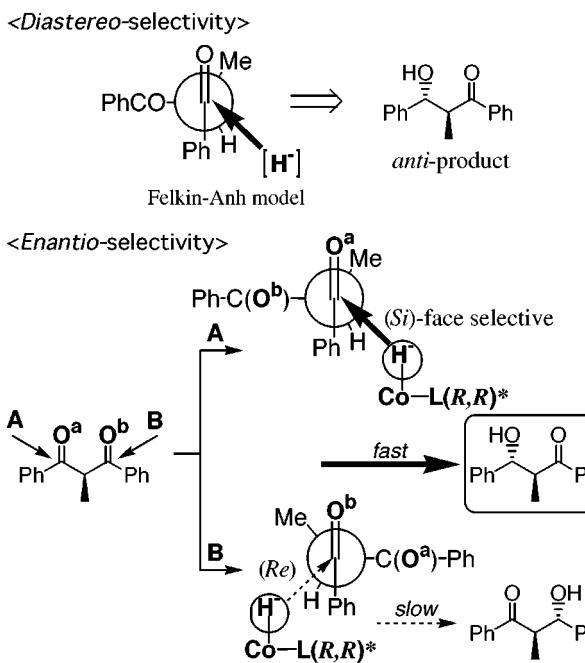


Figure 1. Diastereo- and enantioselectivity in the catalytic reduction system.

one of the products, the presentation in Figure 1 is fully supported by experimental results.

The absolute configuration of the resulting α -substituted- β -hydroxyketones was confirmed. The stereoselectively obtained product, the anti-1,3-di(*p*-bromophenyl)-3-hydroxy-2-methyl-1-propanone, was conventionally converted into the corresponding (*R*)- α -methoxyphenylacetate. As a result of the X-ray analysis, it was revealed that (2*S*,3*R*)-1,3-di(*p*-bromophenyl)-3-hydroxy-2-methyl-1-propanone was obtained, corresponding to the (*R,R*)-cobalt complex catalyst (Figure 2). The enantioselective sense in the present reduction of 1,3-diaryl-2-substituted-1,3-propanedione was in perfect accord with various examples of cobalt complex catalyzed

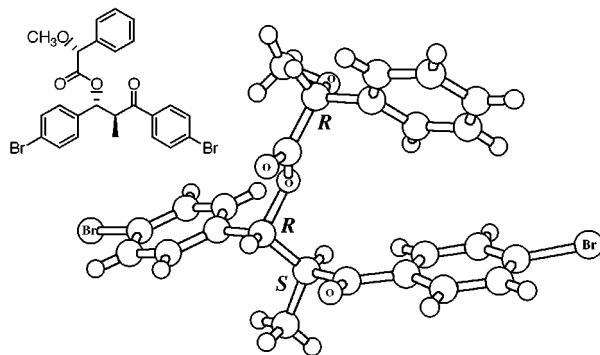


Figure 2. X-ray analysis of (R)- α -methoxyphenylacetate of anti-1,3-di(*p*-bromophenyl)-3-hydroxy-2-methyl-1-propanone corresponding to the (*R,R*)-cobalt catalyst.

reductions of carbonyl compounds reported by our research group.¹³ Also, this observation would support the above-mentioned mechanism for the highly diastereo- and enantioselection.

In summary, the successful reaction of the catalytic desymmetrization of acyclic symmetrical diketones was first achieved for the enantioselective reduction catalyzed by the optically active β -ketoiminato cobalt complexes. In the presence of a 5 mol % or less amount of the cobalt complex catalysts, various 2-substituted-1,3-diaryl-1,3-propanediones were transformed into the corresponding optically active 2-substituted-1,3-diaryl-3-hydroxypropanones with high di-

astereo- and enantioselectivities. These results indicated that enantioselective borohydride reduction catalyzed by cobalt complexes would provide a new method for preparing optically active aldol-type compounds. Further applications to other types of dicarbonyl compounds are currently underway.

Supporting Information Available: Experimental procedures, spectral data for new compounds, and X-ray analysis data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Enantioselective Borohydride Reduction Catalyzed by Optically Active Cobalt Complexes

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Abstract: The highly enantioselective borohydride reduction of aromatic ketones or imines to the corresponding alcohols was developed in the presence of a catalytic amount of an optically active cobalt(II) complex catalyst. This enantioselective reduction is carried out using a precisely premodified borohydride with alcohols such as tetrahydro-

furfuryl alcohol, ethanol and methanol. High optical yields are obtained by choosing the appropriate alcohol as

Keywords: asymmetric catalysis • diastereoselectivity • enantioselectivity • kinetic resolution • reduction

modifiers and a suitable β -ketoiminato ligand of the catalyst. The enantioselective borohydride reduction has been successfully applied to the preparation of optically active 1,3-diols, the stereoselective reduction of diarylferrocenes, and dynamic and/or kinetic resolution of 1,3-dicarbonyl compounds.

Introduction

The enantioselective reduction of prochiral ketones is one of the most reliable and efficient methods to obtain the corresponding optically active secondary alcohols,^[1] which are themselves found in various natural or medicinal com-

pounds and are readily converted to other useful functionalized compounds. Various methods involving chemical and biological procedures have been developed for the enantioselective reduction of ketones. High enantioselectivities were achieved in the asymmetric hydrogenation of functionalized ketones such as α -amino ketones and β -ketoesters by using the diphosphine complexes of rhodium^[2] and ruthenium.^[3] Recently, simple ketones were enantioselectively hydrogenated using iridium^[4] or ruthenium^[5] complex catalysts. In particular, the combined system of BINAP–ruthenium(II), optically active diamine and KOH acted as a highly efficient catalyst for the enantioselective hydrogenation of aromatic ketones.^[1a, 6] For the same purposes, metal hydride reagents modified with various optically active ligands have been alternatively proposed, such as lithium aluminum hydride,^[7] sodium borohydride,^[8] and borane with camphor, proline, and binaphthol derivatives.^[9] It is remarkable that in the presence of a catalytic amount of chiral oxazaborolidines,^[1b, 10] the asymmetric reduction of ketones was effectively achieved to obtain various optically active secondary alcohols. Many successful applications have been reported; for example, a prostaglandin precursor,^[11] potassium channel blockers^[12] and trichloromethyl alcohol used for the preparation of unnatural amino acids.^[13] Borohydrides including lithium borohydride and sodium borohydride are some of the most conventional reducing reagents in organic synthesis due to their stability, high selectivity, and ease of handling, therefore, the enantioselective reduction of ketones was proposed^[14] with the combined use of stoichiometric amounts of optically active *N*-benzoylcystine^[15] as a ligand; for example, it was reported that butyrophenone was converted to the corresponding

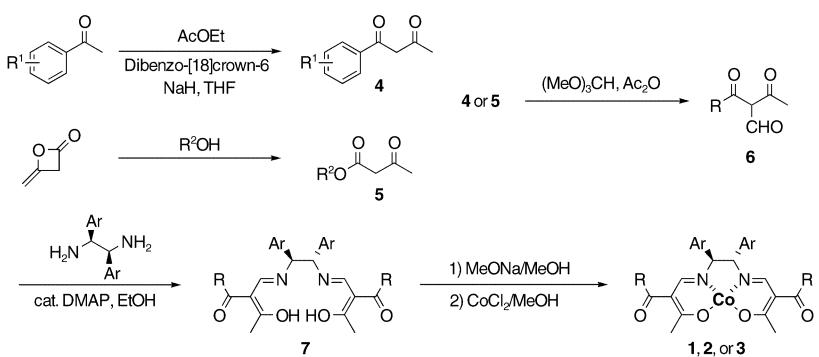
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optically active alcohol with 90% *ee* at -40°C . Although the lanthanoid complexes as a stoichiometric Lewis acid catalysts for the enantioselective reduction with sodium borohydride was reported,^[16] there are few reports of the enantioselective reduction of ketones with borohydrides and a catalytic amount of an optically active metal complex. The optically active semicorrin–cobalt(II) complexes were proposed for the enantioselective 1,4-reduction with sodium borohydride but no application to the 1,2-reduction version was found.^[17] Whereas the optically active β -ketoiminato cobalt(II) complexes proved to be efficient catalysts for the enantioselective borohydride reduction of aryl ketones and imines to obtain the corresponding optically active alcohols and amines in high yields with high *ee* values. In this article, we would like to fully disclose the highly enantioselective reduction of ketones and imines catalyzed by the optically active β -ketoiminatocobalt(II) complexes and its application to the highly stereoselective preparation of useful compounds.

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Results and Discussion

Preparation of the optically active β -ketoiminato cobalt(II) complexes: It has been already reported from our laboratory that manganese(II)–chloride complexes with optically active β -ketoiminato-type ligands function as a catalyst during the enantioselective aerobic epoxidation of simple olefins^[18] and the asymmetric oxidation of sulfides to optically active sulfoxides.^[19] The corresponding cobalt(II) complexes were found to catalyze the enantioselective reduction of ketones with sodium borohydride.^[20] Various optically active β -ketoiminato cobalt(II) complexes **1–3** (Figure 1) were synthe-



Scheme 1. Preparation of β -ketoiminato cobalt(II) complexes.

sized as follows (Scheme 1). The benzoyl acetone derivatives **4** were prepared from the corresponding acetophenone using the Claisen condensation. The acetoacetic ester derivatives **5** were prepared from diketene and the corresponding alcohol. The treatment of these 1,3-dicarbonyl compounds (**4** or **5**) with trimethyl orthoformate and acetic anhydride provided 2-formyl-1,3-dicarbonyl compounds **6**. The optically active β -ketoiminato ligand **7** was obtained by imine formation with the optically active 1,2-diaryl-1,2-ethanediamines. The ligand **7** was then treated with two equivalents of sodium methoxide and subsequently treated with one equivalent amount of cobalt(II) chloride under a nitrogen atmosphere to afford the cobalt(II) complex **1–3** as an orange-colored powder. A X-ray analysis of the molecular structure of the optically active β -ketoiminato cobalt complex was performed for the cobalt(III)-iodide (Figure 2) and bromide complexes derived from the corresponding cobalt(II) complex **1a**^[21] and **3b**,^[22] respectively.

Activation of borohydride with appropriate alcohols: Preliminary investigations suggested that the addition of an alcohol was indispensable for achieving a high enantioselectivity. As shown in Table 1, the enantioselective reduction of 6-methoxy-1-tetralone (**8a**) with or without ethanol indicated a significant improvement in both the chemical yield and enantioselectivity. Without ethanol, the alcohol **9a** was obtained in less than 10% yield and its enantiomeric excess was only 5%, whereas in the presence of ethanol, an 83% *ee* in 38% yield in 24 h (entries 1 and 2). A higher enantiomeric excess of 87% as well as a faster reaction rate were realized in the presence of tetrahydrofurfuryl alcohol (THFA) to afford the alcohol **9a** in 82% yield (entry 3). The combined use of ethanol and THFA allowed further improvement in the enantiomeric excess of the alcohol **9a** with 91% (entry 4). In the presence of structurally similar

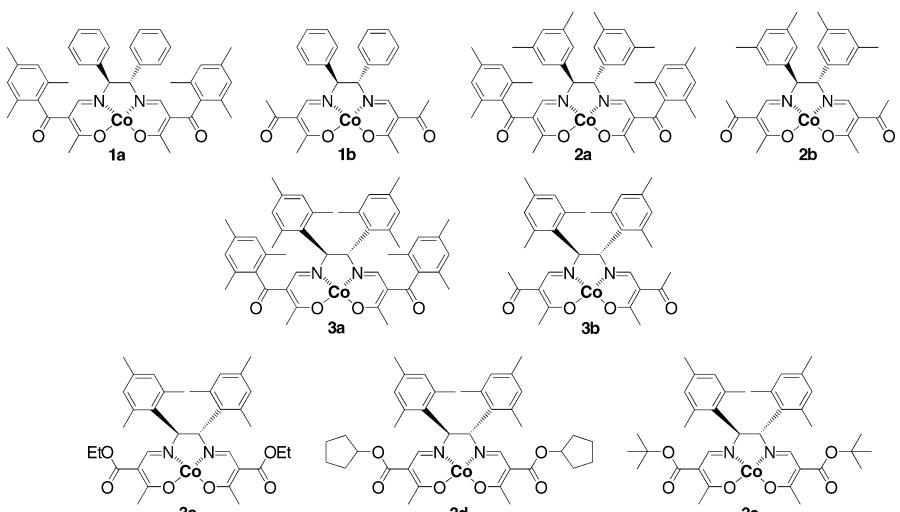


Figure 1. Various cobalt complex catalysts for enantioselective borohydride reduction.

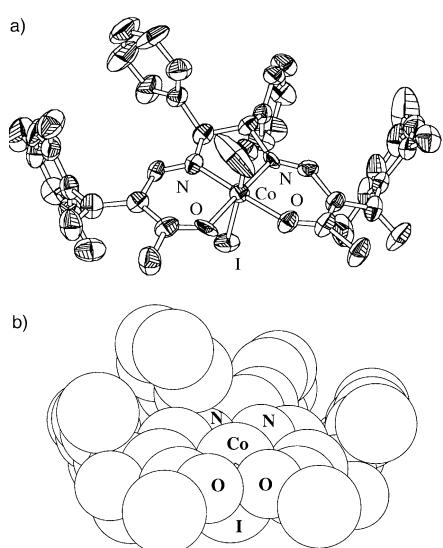


Figure 2. Crystal structure of $[N,N'$ -bis{2,4,6-trimethylbenzoyl}-3-oxobutylidene]-1(S,2S)-1,2-diphenylethylenediaminato)cobalt(II) iodide **1a-I**. a) ORTEP drawing. b) Space filling model based on the X-ray structure (MeOH was omitted).

Table 1. Effects of the various alcohol(s) on the enantioselective borohydride reduction catalyzed by cobalt(II) catalyst.^[a]

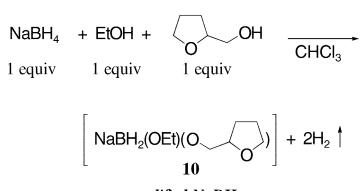
Entry	Alcohols (equiv vs NaBH ₄)	Yield [%]	<i>ee</i> [%] ^[b]	Reaction scheme:		
				NaBH ₄ , alcohol(s)	5 mol% Co catalyst 2a	Product: 6-methoxy-1-tetralone (8a) → 6-methoxy-1-tetralenol (9a)
1	none	<10	5			
2	EtOH (6)	38	83			
3		82	87			
4	THFA (6)+EtOH (6)	87	91			
5	THFA (1)+EtOH (1)	82	93			
6	THFA (14)+EtOH (3)	>98	93			
7		65	75			
8		27	70			

[a] Reaction conditions: 0.50 mmol substrate **8a**, 0.025 mmol Co catalyst **2a**, 0.75 mmol NaBH₄, in CHCl₃ (10 mL), at -20°C, 24 h. [b] Determined by HPLC analysis.

alcohols such as methoxymethanol and tetrahydro-3-furmethanol, the enantioselectivities were lower (75 and 70 % *ee*, entries 7 and 8, respectively). The molar ratios of THFA versus ethanol was systematically examined for the catalytic and enantioselective reduction of the ketone **8a**, and these surveys indicated that a 1 molar equivalent of both alcohols to NaBH₄ were at least required for achieving a high *ee* (91 % *ee*, entry 5). The best result was observed by adding 14 molar equivalents of THFA and 3 molar equivalent of ethanol (entry 6). In the optimized reaction conditions, 1 mol % of the cobalt(II) complex **2a** catalyzed the reaction to quantitatively afford the corresponding alcohol **9a** in 6 h with 93 % *ee*. The non-catalyzed reduction path was also examined by subjecting the modified borohydride to the ketone **8a** in the absence of

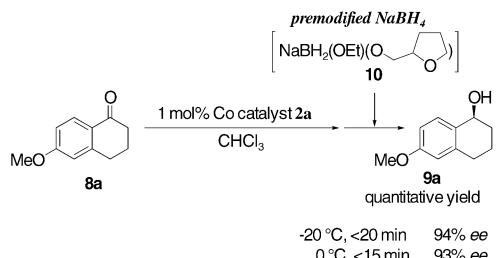
the cobalt(II) complex catalyst for 48 h, and the starting substrate was nearly quantitatively recovered (>95 %), thus the observation indicated a very small contribution of the non-catalyzed path in the present enantioselective reduction. The addition of THFA to this reaction system presented two interesting features; 1) THFA made the reaction mixture homogenous, and an appropriately activated borohydride was specifically formed in situ. 2) A modification protocol of the borohydride influenced the reactivity and enantioselectivity during the catalytic reduction of the ketones.

Although NaBH₄ is usually employed for the reduction of ketones in alcoholic solvents, the resulting activated borohydride has never been completely characterized.^[23] The pre-modification procedure for the formation of an active borohydride was then examined. The monitoring of the H₂ evolution during the treatment of the borohydride with alcohols revealed that nearly 2 molar equivalents of H₂ versus NaBH₄ was gradually liberated as the modification reaction proceeded. This implied that NaBH₄ consumed 2 molar equivalents of alcohols. Based on the multiplier effect of ethanol and tetrahydrofurfuryl alcohol mentioned in Table 1, the premodified borohydride in the present reaction is tentatively illustrated as formula **10** (Scheme 2).^[24] The



Scheme 2. Preparation of premodified activated borohydride.

borohydride thus modified with THFA/ethanol was subjected to the reduction of 6-methoxy-1-tetralone (**8a**) in the presence of a catalyst **2a**, and drastic acceleration of the enantioselective reduction was observed. When the premodified borohydride **10** solution was used at -20°C (Scheme 3),



Scheme 3. Efficient borohydride reductant.

the reaction was completed within 20 min even in the presence of 1 mol % of catalyst to afford in quantitative yield the corresponding alcohol **9a** with 94 % *ee*. The modification of the borohydride and the reduction were carried out at 0°C, and the reaction was completed within 15 min while maintaining the enantioselectivity (93 % *ee*).

The tentative structure of the modified borohydride **10** was supported by the experiments of the asymmetric reduction of

6-methoxy-1-tetralone with 5 mol % of a cobalt(II) catalyst **2a** by using the three kinds of premodified borohydrides treated with one, two, and three equivalent(s) of THFA, respectively (Figure 3). During the reaction of the borohydride with

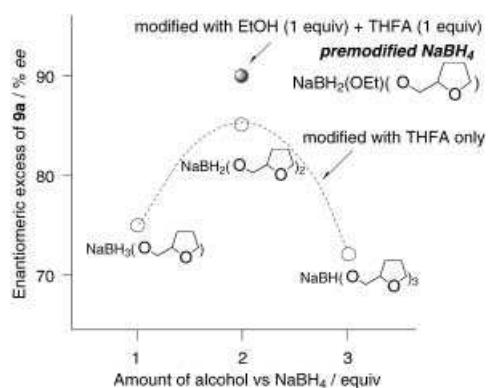


Figure 3. Relationship between the amount of alcohol vs NaBH_4 and enantiomeric excess.

THFA at room temperature, the corresponding amount of hydrogen gas was observed versus the amount of THFA employed. The premodified borohydride using one equivalent of THFA afforded the corresponding alcohol in 36% yield with 75% *ee* for 18 h at -20°C . For the premodified borohydride with two equivalents of THFA, the reduction slowly proceeded, but a better enantioselection was observed, that is, the optically active alcohol was obtained in 17% yield with 85% *ee* for 24 h. Both the reactivity and enantioselectivity were lower in the reaction system using the modified borohydride made from sodium borohydride and three equivalents of THFA; the ketone was converted to the corresponding alcohol in 10% yield with 72% *ee* for 24 h. Furthermore, by using one equivalent each of THFA and ethanol, the reactivity as well as the enantioselectivity were significantly improved; the reaction gave the alcohol in 65% yield with 90% *ee* for 20 h. This was consistent with the above-mentioned result using the in-situ-modified borohydride with one equivalent each of THFA and ethanol (entry 5 in Table 1).

The ^{13}C NMR analysis of the resulting borohydride also supported the tentative structure mentioned above. The sodium borohydride was treated with one equivalent of ethanol and four equivalents of THFA in CHCl_3 at 0°C . During the treatment, it was observed that almost two equivalents of hydrogen gas were released. Although the peaks for EtOH were not changed after borohydride treatment, a new set of peaks for THFA (peaks **a**, **b**, and **c** in Figure 4) was observed next to the original set of peaks (peaks **A**, **B**, and **C** in Figure 4). The intensity ratio of the unshifted peaks (**A**, **B**, and **C**) for the remaining THFA versus the shifted peaks (**a**, **b**, and **c**) after borohydride treatment was about 3:1. It is reasonable to assume that the borohydride reacted with one molar of EtOH and THFA each to afford $\text{NaBH}_2(\text{OEt})(\text{OTHFA})$. It was reported that the borohydrides substituted by two or three alcohols, such as MeOH and EtOH, were not stable and were readily disproportionalated to the starting borohydride BH_4^- and the borate

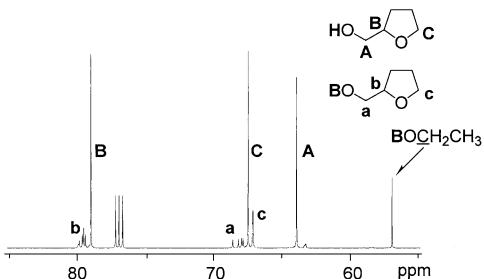


Figure 4. ^{13}C NMR spectra of modified NaBH_4 in CDCl_3 .

$[\text{B}(\text{OR})_4]^-$.^[23] On the contrary, the oxygen atom on tetrahydrofuran could partially coordinate to borate to form a five-membered chelate structure and stabilize the di-alkoxy-substituted borohydride. The interpretation is quite consistent with the ^{13}C NMR observation that the peak for the 5th position on tetrahydrofuran was significantly shifted after borohydride treatment.

It should be noted that the appropriate choice of alcohol in the combination with THFA was also significantly effective for tuning the enantioselectivity (Table 2). For example, when the borohydride was modified with the combined use of methanol and THFA, the aryl primary alkyl ketone **8b** was converted to the corresponding alcohol **9b** with 90% *ee*. The use of ethanol in place of methanol in this reaction improved the enantioselection to 97% *ee*. A similar effect was observed during the enantioselective reduction of the cyclopropyl phenyl ketone **8c** (76% *ee* with methanol versus 90% *ee* with ethanol). On the contrary, methanol was alternatively effective for the reduction of the aryl secondary alkyl ketones **8d** and **8e** (98 and 95% *ee*, respectively). The following notes for choosing the suitable additive alcohols to achieve a high enantioselection are described; 1) The use of the ethanol-THFA combination for the modification of borohydride is preferable when using sterically less demanding ketones

Table 2. Combination of additive alcohols with various aromatic ketones.^[a]

Entry	Ketone	ee [%] ^[b]	
		Activator ROH MeOH	Activator ROH EtOH
1		8b	90 97
2		8c	76 90
3		8d	98 77
4		8e	95 78

[a] Reaction conditions: 0.50 mmol substrate, 0.005 mmol Co catalyst **3a**, 0.75 mmol NaBH_4 , 2.25 mmol ROH, 10.3 mmol THFA, in CHCl_3 (10 mL), at -20°C , 12 h, quantitative yield. [b] Determined by HPLC analysis.

(primary alkyl or cyclopropyl ketone). 2) For the ketones with a more steric demand (secondary alkyl ketone), methanol is preferable for the combined use with THFA.^[25]

Combination of cobalt(II) complexes with various substituted ketones: The preliminary investigations of the asymmetric borohydride reduction of various ketones using the cobalt(II) complex catalysts **1a**, **2a**, or **3a** suggested that the suitable matching of catalyst and substrates is significant in order to achieve a high enantioselection (Table 3). For example, the

Table 3. Combination of cobalt(II) complex catalysts with various substituted ketones.^[a]

Entry	Ketone	ee [%] ^[b]		
		1a	2a	3a
1		8f 91 ^[c] (81) ^[a]	75	n.r. ^[d]
2		8g 65	90	60
3		8h 88	92	74
4		8b 63	87	97
5		8e 62	65	95 ^[e]

[a] Reaction conditions: 0.50 mmol substrate, 0.005 mmol Co catalyst, 0.75 mmol NaBH₄, 2.25 mmol EtOH, 10.3 mmol THFA, in CHCl₃ (10 mL), at –20 °C, 12 h, quantitative yield. [b] Determined by HPLC analysis. [c] Using MeOH instead of EtOH. [d] No reaction.

reduction of 2,2-dimethyl-1-tetralone (**8f**) with the combined use of MeOH/THFA or EtOH/THFA was catalyzed by the complex **1a** to afford the corresponding optically active alcohol in 91 or 81 % *ee*, respectively, whereas that it was 75 % *ee* when the complex **2a** was employed. On the contrary, the enantioselectivity during the reduction of 1-tetralone (**8g**) was observed to be higher when using complex **2a** (90 % *ee*) than that for the complex **1a** or **3a** (65 or 60 % *ee*, respectively). Similarly, 2,2-dimethyl-4-chromanone (**8h**) was converted to the corresponding alcohol by the enantioselective borohydride reduction catalyzed by complex **2a** (with 92 % *ee*) than by using complex **1a** (with 88 % *ee*) or **3a** (with 74 % *ee*). For the acyclic ketones such as butyrophenone (**8b**) and cyclohexyl phenyl ketone (**8e**), complex **3a** was the most matched catalyst to achieve a high enantioselectivity and afford the optically active alcohols with 95 and 97 % *ee*, respectively. Enantioselection ranging between 62–87 % *ee* in the same reaction was observed by using complex **1a** and **2a**.^[26]

A general rule to choose a matched catalyst was extracted as follows; 1) the complex **1a** having the chiral ligand derived from prototypical 1,2-diphenylethylenediamine was effective for the reduction of aryl ketones which are sterically hindered at the *α*-position of the carbonyl groups (entry 1). 2) The complex **2a** having the chiral ligand derived from 1,2-bis(3,5-dimethylphenyl)ethylenediamine was the most matched to the cyclic aryl ketones with less steric demand (entries 2 and 3). 3) The complex **3a** having the chiral ligand derived from the bulky 1,2-bis(2,4,6-trimethylphenyl)ethylenediamine was effectively employed during the enantioselective borohydride reduction of acyclic alkyl aryl ketones (entries 4 and 5). The present study indicated that highly enantioselective borohydride reductions of various aryl ketones are achieved by the appropriate choice of the optically active cobalt(II) catalysts and the matched combination of two alcohols used for modifying the borohydride. Various aromatic ketones were smoothly converted to the corresponding optically active alcohols in quantitative yield using 1 mol % of the cobalt(II) complex catalysts.

Catalytic enantioselective reduction of imine: In order to prepare the optically active alcohols with high efficiency, the catalytic enantioselective reduction of prochiral ketones had been extensively investigated. Likewise, analogous catalytic enantioselective reductions of imines to afford optically active amines have been reported in the literature, however, few examples are known for the syntheses of the optically active amines with satisfactory *ee* values. For examples, the recent achievements of the metal catalyzed enantioselective hydrogenations,^[27] transfer hydrogenation,^[28] hydrosilylations,^[29] and oxazaborolidine^[30] catalyzed enantioselective borane reduction of imines are not enough in terms of enantioselectivity or applicability. The development of a highly efficient enantioselective reduction of imines still remains as challenging topics in synthetic organic chemistry. The above-mentioned enantioselective borohydride reduction was applied to compounds with a C=N functionality, and it was found that the reduction of *N*-substituted ketimines were effectively catalyzed by the cobalt(II) complexes to form the corresponding optically active amines with high enantiomeric purity.

Preliminary experiments on the synthesis of the optically active primary amines from each aryl ketoximes and *N*-substituted ketimines by the enantioselective borohydride reductions using 1 mol % of the cobalt(II) complex **2a** were tried at 0 °C for 4 h (Table 4). The treatments of oxime **11a** or oxime methyl ether **11b** by the borohydride reductions using the cobalt(II) complex did not afford the optically active primary amines under the above conditions, and the starting substrates were completely recovered. On the contrary, when the reduction of the protected imines such as *N*-toluenesulfonyl imine **11c** (*N*-tosyl imine) or *N*-diphenylphosphinyl imine **11d** was tried, the reactions smoothly took place and the corresponding optically active amines were obtained in 95 and 85 % yields with 71 and 98 % *ee*, respectively. The observed differences in *ee* values of the resulting amines could be attributed to the competitive direct reduction of imines with borohydrides by a non-catalytic reduction pathway. When the *N*-tosyl imine **11c** was subjected to the reduction in

Table 4. Effects of the various substituents of imines.^[a]

Entry	$-X$	Yield [%]	ee [%] ^[b]
1	$-OH$	11a	n.r. ^[c]
2	$-OMe$	11b	n.r. ^[c]
3	$-Ts$	11c	95
4	$-P(O)Ph_2$	11d	85
			98

[a] Reaction conditions: 0.50 mmol substrate, 0.005 mmol Co catalyst **2a**, 0.75 mmol modified NaBH₄ (0.75 mmol NaBH₄, 0.75 mmol EtOH, 10.3 mmol THFA), in CHCl₃, at 0 °C, 4 h. [b] Determined by HPLC analysis. [c] No reaction.

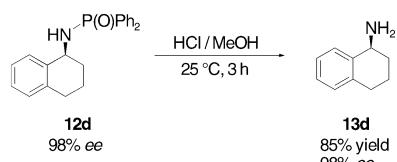
the absence of a catalyst, the corresponding racemic amine was obtained in 30% yield. On the other hand, *N*-phosphinyl imine **11d** was inert toward the premodified borohydride alone; this suggested that *N*-phosphinyl imines are suitable substrates for the present reductions. The enantioselective borohydride reduction using an optically active cobalt(II) complex catalyst (**1a**, **2a**, or **3a**) was then examined using various *N*-diphenylphosphinyl imines, and the results are summarized in Table 5.

In the presence of 1 mol % of the above-mentioned catalyst **1a**, **2a**, or **3a**, various aryl *N*-phosphinyl imines were smoothly converted to the corresponding optically active amines in good yields at 0 °C within 4 h. As shown in the enantioselective borohydride reduction of aryl ketones, a suitable combination of the cobalt(II) catalyst and aryl imine was one of the important factors in achieving high enantioselectivity (Table 5). When the cyclic aryl imine **11d** was subjected to the reductions, the cobalt(II) complex **2a** was the best choice, and the corresponding amine was obtained in 98% *ee* whereas complex **1a** gave 92% *ee* (entries 1 and 2). It should be noted that when complex **3a** was used, no reaction took place (entry 3). It may be attributed to the high degree of steric congestion for *N*-diphenylphosphinyl imines with cobalt(II) complexes. Complex **3a** gave the corresponding amine with the best enantiomeric excess (90% *ee*, entry 6) for the acyclic aryl imine **11e**. Complexes **1a** and **2a** gave lower yields as 77 and 80% *ee*, respectively (entries 4 and 5). The observed combinations of the catalyst and imine are similar to the suitable pairs found for the aryl ketone reduction, and thus the cyclic aryl substrates with complex **2a** and acyclic aryl substrates with complex **3a** are preferable. Accordingly, various cyclic *N*-phosphinyl imines **11f–i** were applied to the reductions using 1 mol % of complex **2a**, and the corresponding optically active amines were obtained in 91–99% *ee* (entries 7–10).^[31] The resulting *N*-phosphinyl amine represents an additional advantage over the *N*-sulfonyl amine, since the conversion to the optically active primary amine by subsequent removal of the diphenylphosphoryl group can be carried out under mild conditions; for example, using HCl/MeOH at 25 °C for 3 h, the optically active primary amine was obtained in good yield without racemization (Scheme 4).

Table 5. Enantioselective borohydride reduction of *N*-diphenylphosphinyl imines.^[a]

Entry	Imine	Catalyst	Yield [%]	ee [%] ^[b]
1		11d 1a	88	92
2		2a	85	98
3		3a	n.r. ^[c]	
4		11e 1a	96	77
5		2a	95	80
6		3a	97	90
7		11f 2a	86	91
8		11g 2a	81	94
9		11h 2a	97	99
10		11i 2a	81	92

[a] Reaction conditions: 0.50 mmol substrate, 0.005 mmol Co catalyst **2a**, 0.75 mmol modified NaBH₄ (0.75 mmol NaBH₄, 0.75 mmol EtOH, 10.3 mmol THFA), in CHCl₃, at 0 °C, 4 h. [b] Determined by HPLC analysis. [c] No reaction.



Scheme 4. Removal of diphenylphosphoryl group.

Preparation of optically active *C*₂-symmetrical diol compounds: Enantiomerically pure *C*₂-symmetrical 1,3-diaryl-1,3-propanediol could be employed as the essential component of chiral ligands in asymmetric syntheses;^[32] however, few reports have been published on the successful preparation of the optically active 1,3-diaryl-1,3-propanediols.^[33] The optically active ferrocene derivatives have been extensively employed as the powerful chiral ligands of transition-metal complexes for various enantioselective catalyses.^[34] The *C*₂-symmetrical chiral ferrocenyldiol is one of the most accessible precursors for the optically active ligands.^[35] Among several preparations,^[36] the enantioselective reduction with borane/THF catalyzed by the chiral oxazaborolidine (CBS reduc-

tion)^[9a, 10a, 11] of the corresponding diketones is the most reliable method.^[37] Though the protocol was effective for various 1,1'-diacylferrocenes, the loading of a large amount (60–200 mol %) of the oxazaborolidine catalyst was required for the high enantioselectivity. In this section, it was described that the efficient and highly asymmetric synthesis of *C*₂-symmetrical diol compounds from the corresponding diketones was achieved by the enantioselective borohydride reduction catalyzed by the optically active cobalt(II) complexes.

The enantioselective borohydride reduction of 1,3-diaryl-1,3-diketones was first examined using various optically active β -ketoiminato cobalt complex catalysts adopting 1,3-diphenyl-1,3-diketone (**14a**) as the model substrate (Table 6). It was

Table 6. Various cobalt(II) catalysts for enantioselective borohydride reduction of dibenzoylmethane.^[a]

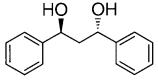
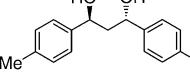
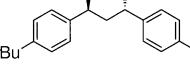
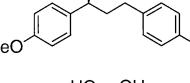
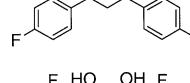
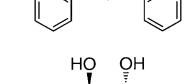
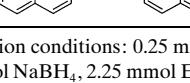
Entry	Catalyst	Yield [%]	dl:meso ^[b]		ee [%] ^[c]
			dl	meso	
1	1a	93	53:47		41
2	1b	93	29:71		61
3	2a	quant	56:44		64
4	3a	96	85:15		90
5	3b	93	81:19		98
6	3c	97	66:34		89
7	3d	90	72:28		94
8 ^[d]	3b	quant	84:16		98

[a] Reaction conditions: 0.50 mmol substrate **14a**, 0.005 mol % Co catalyst, 1.5 mmol NaBH₄, 4.5 mmol EtOH, 63 mmol THFA, in CHCl₃ (20 mL), at –20 °C, 24–48 h. [b] Determined by ¹H NMR analysis of diacylated 1,3-diols after the treatment with Ac₂O/pyridine. [c] Determined by HPLC analysis. [d] Using 0.005 mmol Co catalyst **3b**. [e] Using MeOH instead of EtOH.

found that the enantioselectivities in this reaction were sensitively affected by the steric demand of the chiral diamine part of the cobalt catalyst ligand. When complex **1a**, **1b** or **2a**, prepared from the optically active 1,2-diphenylethylenediamine or 1,2-bis(3,5-dimethylphenyl)ethylenediamine, was employed as a catalyst, the ee values of the product were moderate (entries 1–3). However, catalyst **3**, having the optically active 1,3-bis(2,4,6-trimethylphenyl)ethylenediamine unit, realized an excellent enantioselectivity and a good-to-high dl selectivity in each case (entries 4–7). Especially, catalyst **3b**, with attached acyl groups as the side chains, indicated a high dl selectivity (81 %) and excellent ee value (98 %) for the enantioselective reduction of 1,3-diphenyl-1,3-propanedione (**14a**).^[38] After optimizing the reaction conditions, it was found that the concentration of the reaction mixture depended on the stereoselectivity. In the 8.3 × 10^{–3} M solution (0.25 mmol substrate versus 30 mL chloroform), the dl selectivity was enhanced up to 84 % with 98 % ee (entry 8).

The optimized procedure was successfully applied to the preparation of various 1,3-diaryl-1,3-propanediols from the corresponding 1,3-diketones (Table 7). Diketones with alkyl, electron-donating, and -withdrawing groups were all smoothly reduced in high enantioselectivity with high dl selectivity. As

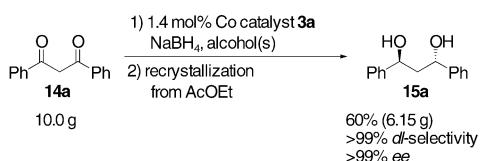
Table 7. Enantioselective preparation of various 1,3-diaryl-1,3-propanediols.^[a]

Entry	1,3-Diaryl-1,3-propandione	Yield [%]	dl:meso ^[b]	ee [%] ^[c]
1 ^[d]		15a quant	84:16	98
2		15b 94	85:15	97
3 ^[e]		15c 94 15d	80:20	96
4		99	84:16	98
5		15e 98	76:24	99
6		15f 99	90:10	97
7		15g 93	81:19	99

[a] Reaction conditions: 0.25 mmol substrate, 0.0125 mmol Co catalyst, **3b**, 0.75 mmol NaBH₄, 2.25 mmol EtOH, 10.5 mmol THFA, in CHCl₃ (30 mL), at –20 °C, 40–60 h. [b] Determined by ¹H NMR analysis of diacylated 1,3-diols after the treatment with Ac₂O/pyridine. [c] Determined by HPLC analysis. [d] Using 0.005 mmol Co catalyst **3b**. [e] Using MeOH instead of EtOH.

examples, the 1,3-diaryl-1,3-diols with *p*-methyl- (**15b**), *p*-methoxy- (**15d**), *p*-fluoro- (**15e**), and *o*-fluoro- (**15f**) substituents were obtained in 97, 98, 99, and 97 % ee, with 85, 84, 76, and 90 % dl selectivity, respectively (entries 2, and 4–6). For the reduction of 1,3-bis(4-*tert*-butylphenyl)-1,3-propanedione (**14c**), the addition of methanol instead of ethanol was effective in the reduction system (entry 3) for modification of the borohydride. Also, dinaphthylidione with a larger aromatic ring **14g** was smoothly reduced to the 1,3-diol **15g** with 81 % dl selectivity and 99 % ee (entry 7).^[39]

The present procedure could be readily used for the multigram preparation because one recrystallization of the crude products afforded the enantiomeric pure 1,3-diols. For example, dibenzoylmethane (10.0 g) was treated with the modified borohydride in the presence of a catalytic amount of the cobalt complex **3a** produced a quantitative yield of 1,3-diphenyl-1,3-propanediol. After rinsing the dl/meso mixture with ethyl acetate/hexane and simple recrystallization from ethyl acetate, optically pure 1,3-diphenyl-1,3-propanediol (6.15 g) was obtained in 60 % overall yield (Scheme 5). It should be noted that the obtained pure 1,3-propanediol was quantitatively converted to the optically pure 1,3-diphenyl-1,3-propanediamine by the conventional method.^[40]



Scheme 5. Preparation of enantiopure 1,3-diphenyl-1,3-propanediol.

The enantioselective reduction of 1,1'-dibenzoylferrocenes (**16a**) into optically active 1,1'-ferrocenyl diols was adopted as a model reaction for screening the various optically active β -ketoiminato cobalt complexes for the catalytic borohydride reduction (Table 8). When complex **1** or **2** was employed as a

Table 8. Various cobalt(II) catalysts for enantioselective borohydride reduction of 1,1'-dibenzoylferrocene.^[a]

Entry	Catalyst	<i>dl</i> : <i>meso</i> ^[b]	<i>ee</i> [%] ^[c]
1	1a	21:79	31
2	1b	22:78	21
3	2a	23:77	20
4	2b	25:75	32
5	3a	86:14	>99
6	3b	88:12	>99
7	3c	80:20	>99
8	3d	72:28	>99
9	3e	75:25	>99

[a] Reaction conditions: 0.125 mmol substrate **16a**, 0.00625 mmol Co catalyst, 0.50 mmol modified NaBH₄ (0.50 mmol NaBH₄, 0.50 mmol EtOH, 7.0 mmol THFA), in CHCl₃, at -20°C, 12 h, quantitative yield. [b] Determined by ¹³C NMR analysis. [c] Determined by HPLC analysis.

catalyst, the *ee* values of the product were very low (entries 1–4), whereas excellent *ee* values (>99% *ee*) were achieved by the bulky complex **3** (entries 5–9).^[38] Catalyst **3b** (entry 6), with attached acyl groups as the side chains, indicated the highest *dl* selectivity (88%) with excellent *ee* (>99%) for the enantioselective reduction of 1,1'-dibenzoylferrocene (**16a**). The solvent effect was subsequently surveyed and found that the reaction time significantly depended on the reaction solvent. In chloroform, a suitable solvent for the enantioselective borohydride reduction, and other typical solvents, the reduction was completed in 12–72 hours,^[41] whereas in diethyl ether, the enantioselective reduction was completed in 0.5 h at -20°C. In diethyl ether at 0°C, the reduction to afford 1,1'-bis(α -hydroxypropyl)ferrocene (**17a**) was finished within 15 min while maintaining high enantio- and *dl* selectivities.

The enantioselective borohydride reduction was successfully applied to the preparation of various optically active 1,1'-ferrocenyl diols using 5 mol % of a cobalt catalyst **3b** in diethyl ether at 0°C (Table 9). Various 1,1'-dibenzoylferrocene de-

Table 9. Enantioselective borohydride reduction of various 1,1'-diacylferrocenes.^[a]

Entry	1,1'-Diacylferrocene	Yield [%]	<i>ee</i> [%] ^[b]	<i>dl</i> : <i>meso</i> ^[c]
1	X = H	16a	92	>99 89:11
2	X = F	16b	90	>99 87:13
3	X = Cl	16c	89	99 87:13
4	X = Br	16d	88	>99 89:11
5	X = CH ₃	16e	90	>99 88:12
6	X = F	16f	94	>99 99:1
7	X = Cl	16g	87	>99 93:7
8 ^[d]	X = Br	16h	96	97 88:12
9 ^[e]	n = 1	16i	84	>99 82:18
10 ^[e]	n = 2	16j	80	>99 80:20
11 ^[e]	n = 4	16k	90	>99 87:13
12 ^[e]	n = 6	16l	69	>99 85:15

[a] Reaction conditions: 0.125 mmol substrate, 0.00625 mmol Co catalyst **3b**, 0.5 mmol modified NaBH₄, in Et₂O, at 0°C within 3 h. [b] Determined by HPLC analysis. [c] Determined by ¹H NMR analysis and/or ¹³C NMR analysis. [d] Et₂O reflux temperature, 0.5 h. [e] Using 0.0125 mmol Co catalyst **3b**, 1.25 mmol modified NaBH₄, at -40°C, 48 h.

rivatives, possessing *p*-fluorophenyl (**16b**), *p*-chlorophenyl (**16c**), *p*-bromophenyl (**16d**), *p*-methylphenyl (**16e**), *o*-fluorophenyl (**16f**), and *o*-chlorophenyl (**16g**) were converted to the corresponding *C*₂-symmetrical ferrocenyl diols **17** with excellent *ee* values and high *dl* selectivity (entries 2–7). The reaction of 1,1'-di(*o*-bromobenzoyl)ferrocene (**16h**) was very slow at 0°C due to steric hindrance. Therefore, the enantioselective reduction was carried out at the diethyl ether reflux temperature to afford the corresponding diols in 96% yield for 0.5 h with 87% *dl* selectivity and 97% *ee* (entry 8). The present enantioselective reduction could be applied to the 1,1'-dialkanoylferrocenes. Although the *dl* selectivity from 1,1'-dihexanoylferrocene (**16k**) was not sufficient at 0°C, the reduction was tried at -40°C to afford the corresponding diol with 87% *dl* selectivity and >99% enantioselectivity (entry 11). Also, the 1,1'-dipropanoyl- (**16i**), dibutanoyl- (**16j**), and dioctanoyl- (**16l**) ferrocenes were stereoselectively reduced to the corresponding ferrocenyl diols with high *dl* selectivity and excellent enantioselectivity (entries 9, 10, and 12).^[42] It is noted that the efficient and highly stereoselective preparation of the *C*₂-symmetrical chiral diol compounds was provided by the enantioselective borohydride reduction of the 1,3-diaryl-1,3-propanedione, 1,1'-dialkanoyl-, and 1,1'-dibenzoyl-ferrocenes catalyzed by the optically active β -ketoimino cobalt(II) complex.

Synthesis of optically active anti-alcohol compounds: The aldol reaction is one of the most useful and reliable methods in organic synthesis for new carbon–carbon bond formation accompanied by the preparation of 2-substituted-3-hydroxy-carbonyl units.^[43] Optically active 2-substituted-3-hydroxy-

carbonyl units are often observed in natural products and their hydroxy or carbonyl groups could be converted into various functionalities. Therefore, highly diastereoselective and/or enantioselective versions of the aldol reaction^[44] are indispensable for organic synthesis. A wide variety of enantioselective aldol reactions, especially the catalytic enantioselective version by optically active transition-metal complexes, have been dynamically studied for a decade.^[45] In almost all catalytic enantioselective aldol reactions, however, the preparation of silyl or metal enolates is required in advance along with a relatively large amount of loading of the catalyst for high enantio- and/or diastereoselectivity. These disadvantages have made the catalytic and enantioselective aldol reactions difficult to use for multigram scale laboratory and manufacturing processes. Alternatively, optically active 2-substituted-3-hydroxycarbonyl compounds could also be prepared from the corresponding 2-substituted-1,3-dicarbonyl compounds with catalytic and enantioselective reductions.

The symmetrical 2-substituted-1,3-diketones was first adopted as a model substrate for the demonstration of the reductive synthesis of optically active aldol compounds using the enantioselective borohydride reduction catalyzed by the optically active β -ketoimato cobalt complexes. Because the four isomers of the hydroxyketones and diol compounds could be produced in this reaction, the stereoselectivity and reactivity should be controlled at the same time. The enantioselective reduction of 1,3-diphenyl-2-methyl-1,3-propanedione (**18a**) into the optically active 1,3-diphenyl-3-hydroxy-2-methylpropanone (**19a**) was chosen as a model reaction for screening the suitable optically active β -ketoimato cobalt catalyst (Table 10). Although the *anti*-selectivity of the resulting β -hydroxyketones was excellent in each case, the *ee* values of the *anti*-products widely varied, being

Table 10. Various cobalt(II) catalysts for enantioselective borohydride reduction of 2-methyl-1,3-diphenyl-1,3-propanedione.^[a]

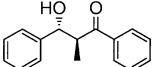
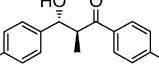
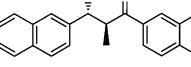
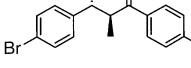
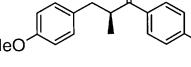
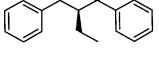
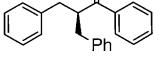
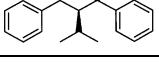
Entry	Catalyst	Yield [%]	<i>anti</i> -Selectivity [%] ^[b]	hydroxyketones 19a		Recovery [%]	Diol Yield [%]
				<i>ee</i> (anti) [%] ^[c]	ee (anti) [%] ^[d]		
1	1a	65	93	33	3	27	
2	2a	58	99	45	—	39	
3	3a	65	94	89	24	11	
4	3b	75	95	92	10	15	
5	3c	55	98	81	1	41	
6	3e	71	96	87	1	28	
7 ^[d]	3b	93	99	99	—	7	

[a] Procedure A: A solution of the Co catalyst and the substrate was added to the solution of the modified NaBH₄; 0.5 mmol substrate **18a**, 0.025 mmol Co catalyst, 0.5 mmol NaBH₄, 1.5 mmol oEtOH, 7 mmol THFA, in CHCl₃, at 0 °C, 10 h. [b] Determined by ¹H NMR analysis. [c] Determined by HPLC analysis. [d] Procedure B: To the solution of the Co catalyst and the substrate was added a solution of the modified NaBH₄; 0.25 mmol substrate **18a**, 0.0125 mmol Co catalyst **3b**, 0.25 mmol modified NaBH₄ (0.25 mmol NaBH₄, 0.25 mmol EtOH, 3.5 mmol THFA), in CHCl₃, at –20 °C, 10 h.

sensitive to the structure of the cobalt complex catalysts (entries 1–6). Catalyst **1a** or **2a** afforded a low or moderate *ee* of the *anti*-product (entries 1 and 2), whereas the enantioselectivity was remarkably improved when employing catalysts **3a–c** and **e** derived from the optically active 1,3-bis(2,4,6-trimethylphenyl)ethylenediamine (entries 3–6). Among these catalysts, it was found that catalyst **3b**, having acetyl groups on both side chains, was the most efficient catalyst for the enantioselective reduction of the 1,3-diphenyl-2-methyl-1,3-propanedione (entry 4). After optimization of the reaction temperature (–20 °C) and procedure, 99% *ee* of the *anti*-product was isolated in 93% yield with 99% diastereoselectivity (entry 7).

The catalytic and enantioselective reduction was successfully applied in the preparation of various optically active 2-substituted-1,3-diaryl-3-hydroxypropanones **19** from the corresponding 1,3-diketones **18** (Table 11). Various 2-methyl-1,3-diaryl-1,3-diketones, having *p*-methylphenyl- (**18b**), 2-naphthyl- (**18c**), *p*-bromophenyl- (**18d**), and *p*-methoxy-

Table 11. Enantioselective borohydride reduction of 2-alkyl-1,3-diaryl-1,3-propanediones.^[a]

Entry	Hydroxyketone	Yield [%]	<i>anti</i> -selectivity [%] ^[b]	<i>ee</i> (<i>anti</i>) [%] ^[c]	
1		19a	93	99	99
2		19b	97	99	99
3		19c	73	99	99
4		19d	68	99	99
5		19e	96	99	97
6		19f	88	99	99
7		19g	88	99	97
8		19h	96	99	98
9		19i	45	99	91

[a] Procedure B (see Table 10). [b] Determined by ¹H NMR. [c] Determined by HPLC analysis.

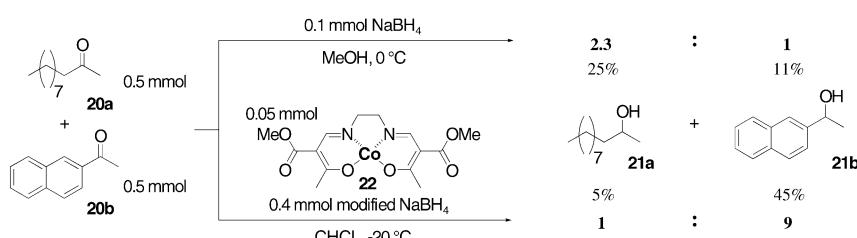
phenyl- (**18e**) as the aryl group, were converted into the corresponding *anti*-2-methyl-3-hydroxyketones **19b–e** in good-to-high yield with excellent *anti*-selectivity and excellent enantioselectivity (entries 2–5). For the catalytic and enantioselective reduction of various 2-substituted-1,3-diketones, such as 2-ethyl- (**18f**), 2-allyl- (**18g**), 2-benzyl- (**18h**), and 2-isopropyl- (**18i**), the corresponding *anti*-2-alkyl-3-hydroxyketones (**19f–i**) were obtained with excellent *anti*-selectivity and excellent enantioselectivity (entries 6–9).^[46]

In this reaction system, it is remarkable feature that the *anti*-selectivity is excellent. The highly *anti*-selective aldol reactions of the highly diastereoselective^[47] or enantioselective^[48] version were very limited. It was expected that the present catalytic reduction could provide an alternative potential for the preparation of optically active *anti*-aldol compounds. Recently, it was revealed in a preliminary examination of the borohydride reduction with a catalytic amount of the β -ketoiminato cobalt complexes that aromatic ketones were preferentially reduced in the presence of aliphatic ketones. As shown in Scheme 6, 0.1 mmol NaBH₄ was added to a solution of 0.5 mmol 2-undecanone (**20a**) and 0.5 mmol 2-acetonaphthone (**20b**) in methanol. After 8 h, 2-undecanone (**20a**) (as an alkyl ketone) was reduced to the corresponding alcohol **21a** in 25% yield and 2-acetonaphthone (**20b**) (as an aromatic ketone) in 11% yield. The chemoselectivity for the reduction of the aliphatic ketone was about 70%. In contrast, in the presence of 0.1 mmol of the β -ketoiminato cobalt complex **22**, the chemoselectivity was completely reversed. By treatment of the premodified borohydride, an aromatic ketone, 2-acetonaphthone (**20b**), was selectively reduced to 1-(2-naphthyl)-1-ethanol (**21b**) in 45% yield while the aliphatic ketone **20a** was reduced in only 5% yield. The chemoselectivity for the aromatic ketone was 90%.

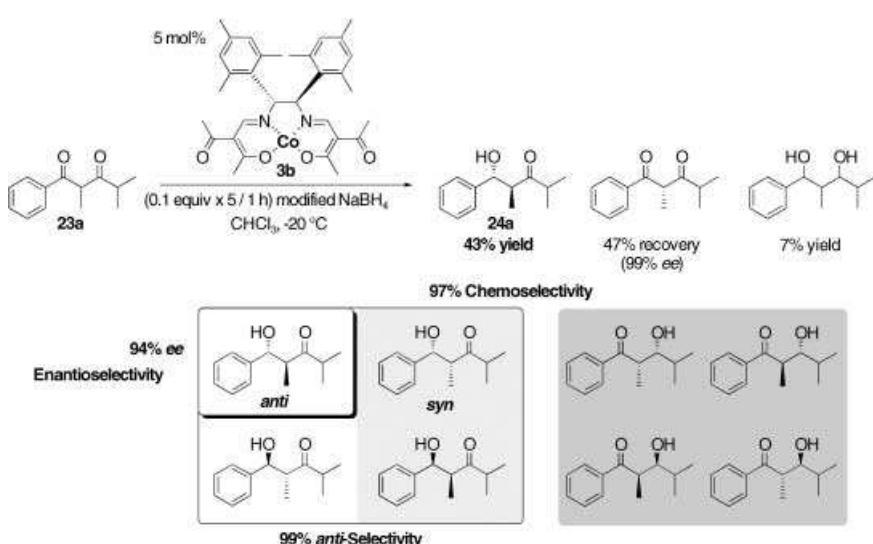
These observations encouraged us to apply the cobalt-catalyzed reduction to 1-alkyl-3-aryl-1,3-diketones to prepare the corresponding 1-alkyl-3-aryl-3-hydroxyketones. It was conventionally reported for the chemo- and enantioselective reduction of unsymmetrical 1-alkyl-3-aryl-1,3-diketones that the ketone neighboring alkyl group was selectively reduced because of the reduced bulkiness.^[33f] As the unsymmetrical 2-substituted-1,3-diketone model for the chemo-, diastereo- and enantioselective reduction, 2,4-dimethyl-1-phenyl-1,3-pentanedione (**23a**) was adopted. Because the kinetic resolu-

tion should be considered for the model substrate, 0.5 equivalent of the premodified borohydride was employed in the presence of 5 mol % of the optically active β -ketoiminato cobalt complex catalyst **3b**. After 24 h, the reaction was quenched to afford the corresponding hydroxyketones **24a** in 44% yield with 88% aromatic versus 12% aliphatic alcohol. Though the diastereoselectivity in the aromatic alcohol was determined to be 93% *anti*, the enantioselectivity of the *anti*-aromatic alcohol **24a** was 67% *ee*.

In the case of using only 0.25 equivalents of the premodified borohydride, it was found that an optically active hydroxyketone was obtained in 21% yield with high chemo- (98%), diastereo- (98%), and enantioselectivities (99% *ee*). These observations suggested that the excess hydride in the catalytic system caused a non-catalytic reduction thus resulting in low selectivities. In order to maintain the initial reaction conditions, therefore, five portions of the 0.1 equivalents premodified borohydride were successively added at one-hour intervals to the reaction to obtain the 3-aryl-3-hydroxyketones **24a** in 43% yield with 97% chemoselectivity, 99% *anti*-selectivity, and with 94% enantiomeric excess (Scheme 7). The *ee* values of the 2-methyl-1,3-diketone **23a** remaining after the kinetic resolution was determined by HPLC. Since racemization of the 2-substituted-1,3-diketones gradually proceeded at room temperature, the reaction mixture was directly injected into the HPLC chiral column (Daicel chiralpak AD, 5.0% propan-2-ol in *n*-hexane) to determine



Scheme 6. Chemoselective borohydride reduction of aromatic versus aliphatic ketones.



Scheme 7. Highly chemo-, diastereo-, and enantioselective borohydride reduction of 2-methyl-1,3-diketone.

Table 12. Highly chemo-, diastereo-, and enantioselective reduction of 2-alkyl-1,3-diketones.^[a]

Entry	Hydroxyketone	Yield [%]	Conversion [%]	Selectivity		
				Chemo- [%] ^[b]	anti- [%] ^[b]	Enantio- [%] ^[c]
1		24a	46	48	99	99
2		24b	41	42	99	99
3		24c	47	55	95	98
4		24d	48	49	99	99
5		24e	47	54	96	98
6		24f	47	54	99	98
7		24g	45	52	93	94

[a] Procedure: Four portions of the 0.1 equiv modified NaBH₄ were successively added at 2 h intervals to the solution of the Co catalyst and the substrate; 0.25 mmol substrate, 0.0125 mmol Co catalyst **3b**, 0.1 mmol modified NaBH₄ (0.1 mmol NaBH₄, 0.1 mmol EtOH, 1.4 mmol THFA), in CHCl₃, at -20 °C, 10 h.

[b] Determined by ¹H NMR analysis. [c] Determined by HPLC analysis.

the *ee* of 2,4-dimethyl-1-phenyl-1,3-pentanedione **23a** which was 99% *ee*.

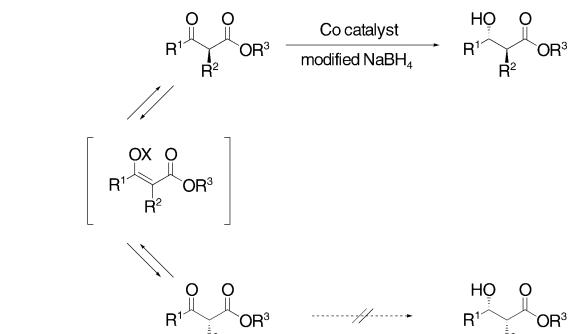
In order to reduce the excess hydride in the catalytic system and avoid any further non-catalytic reduction, four portions of the 0.1 equivalent premodified borohydride were successively added at two-hour intervals to the reaction mixture to produce a 46% yield, and 99% chemo-, 99% *anti*- and 96% enantioselectivities. These observations indicated that the cobalt-catalyzed reduction selectively afforded only one isomer among the possible eight isomers and that the kinetic resolution was excellent. The present kinetic resolution system was successfully applied to the enantioselective reduction of various 2-substituted-1-alkyl-3-aryl-1,3-diketones **23** to produce optically active 2-substituted-3-hydroxyketones **24** (Table 12). The 1,3-diketones having a 2-methyl- (**23a**), 2-ethyl- (**23b**) or 2-allyl- (**23c**) group were converted into the corresponding 3-aryl-3-hydroxyketones **24a–c** with high chemo-, diastereo- and enantioselectivities (entries 1–3). The kinetic resolution during the enantioselective reduction of the substrate containing a *tert*-butyl ketone **23d** afforded an excellent result such that the corresponding reduced product **24d** obtained in 48% yield indicated 99% chemoselectivity, 99% *anti*-selectivity, and 97% *ee* (entry 4). The present highly selective kinetic resolution could also be applied to the substrates with primary alkyl ketones, such as *n*-nonyl ketone

23e, isobutyl ketone **23f**, or benzyl ketone **23g** to obtain the corresponding *anti*-hydroxyketones **24e–g** with high selectivities (entries 5–7).^[49]

If the racemization equilibrium of the starting material, that is the 2-substituted 3-ketocarbonyl compound, would occur during the kinetic resolution of the enantioselective reaction, it should be a more efficient and promising method for the generation of the chiral centers at the α - and β -positions of the carbonyl compounds in one reaction step ideally in 100% chemical yield.^[50] Therefore, the dynamic kinetic resolution with an enantioselective reaction has been applied to the 2-substituted 3-ketoester for the preparation of optically active 2-substituted 3-hydroxyesters, *anti*-aldol-compounds in high yield and with high stereoselectivities (Scheme 8). Several trials of dynamic kinetic resolution during the enantioselective reduction of 2-substituted-3-ketoesters have already been reported; for example, the ruthenium complex catalyzed hydrogenation was successfully

applied to 2-substituted 3-ketoesters to obtain aldol products with high stereoselectivities; however, almost all the reactions using enantioselective hydrogenation were *syn*-selective.^[51]

For the screening of the reaction conditions for the dynamic kinetic resolution, the 2-methyl-3-(2-naphthyl)-3-oxopropionic acid ethyl ester (**25a**) was adopted as the model substrate and various bases were examined for racemization equilibrium (Table 13). In the presence of 4 mol % of the cobalt catalyst **3b**, the enantioselective borohydride reduction afforded the 3-hydroxy-2-methyl-3-(2-naphthyl)propionic acid ethyl ester (**26a**) with moderate *anti*-selectivity and enantio-



Scheme 8. Dynamic kinetic resolution with borohydride reduction.

Table 13. Various bases for kinetic resolution.^[a]

Entry	Base	Yield [%]	anti-Selectivity [%] ^[b]	ee [%] ^[c]	4 mol% Co catalyst 3b modified NaBH ₄		
					1.0 equiv base	25a	26a
1	–	99	69	83			
2	Na ₂ CO ₃	99	69	81			
3	Cs ₂ CO ₃	96	66	82			
4	Et ₃ N	95	79	87			
5	HN <i>i</i> Pr ₂	94	82	87			
6	NaOEt	86	88	91			
7	NaOMe	66	88	90			
8 ^[d]	NaOMe	91	92	95			

[a] Reaction conditions: 0.25 mmol substrate **25a**, 0.01 mmol catalyst **3b**, 0.25 mmol base, 0.30 mmol modified NaBH₄ (0.30 mmol NaBH₄, 0.30 mmol EtOH, 4.2 mmol THFA), in CHCl₃ at 0 °C, 24 h. [b] Determined by ¹H NMR analysis. [c] Determined by HPLC analysis. [d] At –10 °C, 15 h.

selectivity (entry 1). These observations indicated that the racemization equilibrium was not sufficient without any base. In order to accelerate the racemization equilibrium via its enolates, several bases were added to the reaction mixture. In the presence of alkali metal carbonates, the reduction smoothly proceeded though the *anti*-selectivity and enantioselectivity were not improved at all (entries 2 and 3). The addition of amine bases slightly improved the stereoselectivity, but their selectivities did not reach a satisfactory level (entries 4 and 5). The high diastereo- and enantioselectivities were achieved with the addition of an alkali metal alkoxide, though the isolated yields were low due to the *retro*-aldol reaction from the resulting products. To avoid any side reaction, the reaction was performed at –10 °C to improve the isolated yield to 91 % while maintaining high diastereo- and enantioselectivities.

Various 2-alkyl-3-aryl-3-ketoesters **25** were successfully subjected to the enantioselective reduction with dynamic kinetic resolution for the preparation of the *anti*-aldol-type compounds (Table 14). The optically active 3-hydroxy-2-methylesters containing 2-naphthyl (**26a**), phenyl (**26b**), *p*-bromophenyl (**26c**), *p*-methylphenyl (**26d**), or *p*-methoxyphenyl (**26e**) as a 3-aryl group could be prepared in the present dynamic kinetic resolution system with high diastereo- and enantioselectivities in high isolated yields (entries 1–5). The 3-phenyl-3-ketoesters, having an ethyl **25f** or allyl **25g** group on the active methyne, were also converted into the corresponding 3-aryl-3-hydroxyester **26f–g** with good diastereoselectivity and high ee values (entries 6 and 7).^[52] It was demonstrated that the optically active *anti*-2-substituted-3-hydroxy compounds could be prepared from the corresponding 2-substituted-3-ketocarbonyl compounds using enantioselective borohydride reduction. In contrast, the *syn*-aldol was generally produced in the transition-metal catalyzed reac-

Table 14. Dynamic kinetic resolution of enantioselective reduction for *anti*-aldol compounds.^[a]

Entry	Hydroxyester	Yield [%]	anti-Selectivity [%] ^[b]	ee (anti) [%] ^[c]
1		93	99	99
2		97	99	99
3		73	99	99
4		68	99	99
5		96	99	97
6		88	99	99 ^[d]
7		88	99	97

[a] Reaction conditions: 0.25 mmol substrate, 0.01 mmol Co catalyst **3b**, 0.25 mmol NaOMe, 0.30 mmol modified NaBH₄ (0.30 mmol NaBH₄, 0.30 mmol EtOH, 4.2 mmol THFA), in CHCl₃, at –10 °C, 10–15 h. [b] Determined by ¹H NMR analysis. [c] Determined by HPLC analysis. [d] Determined by HPLC analysis after acylation.

tions; the present enantioselective reduction would provide an alternative approach for the preparation of *anti*-aldol compounds.

Enantiofacial discrimination of asymmetric borohydride reduction: A possible catalytic cycle is explained as follows (Figure 5): When the modified NaBH₄ was added to the cobalt(II) complex solution, this reaction mixture was instantly turned from orange, the color of the original catalyst solution, to red. It was implied that new active species, probably cobalt–hydride intermediates were generated from the modified borohydride and cobalt(II) complexes.

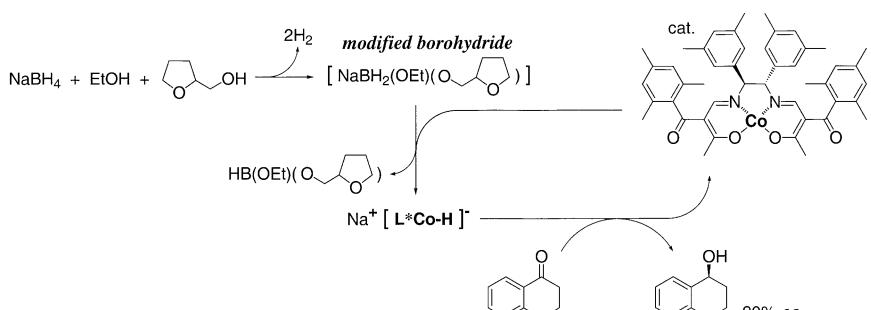


Figure 5. Overall reaction pathway of cobalt catalyzed enantioselective reduction.

The FAB mass analysis of the cobalt complex **1a** treated with borohydride was then examined. A peak at m/z 697 in the FAB MS spectra was observed under negative mode for the original cobalt complex **1a** (Figure 6a). After treatment of the cobalt complex **1a** with borohydride, the peak at m/z 697 vanished and a new peak was found at m/z 698, which can be assigned as a cobalt–hydride complex (Figure 6b).

When borodeuteride was employed in place of borohydride, the original peak at m/z 697 disappeared and a new peak at m/z 699 assigned to the cobalt–deuteride complex

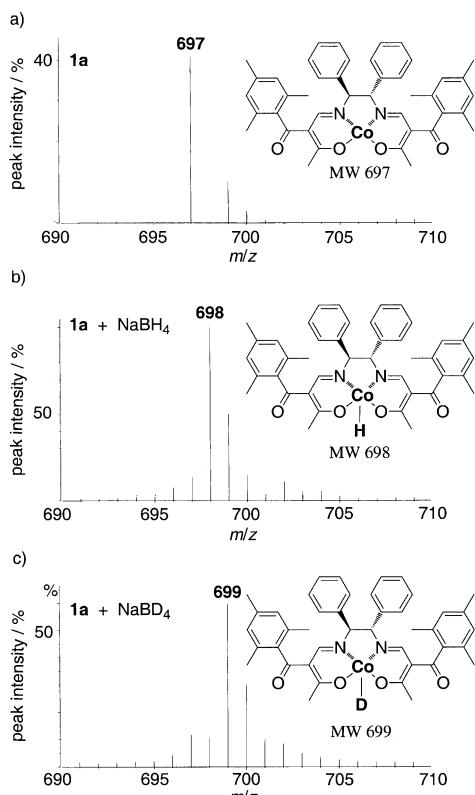
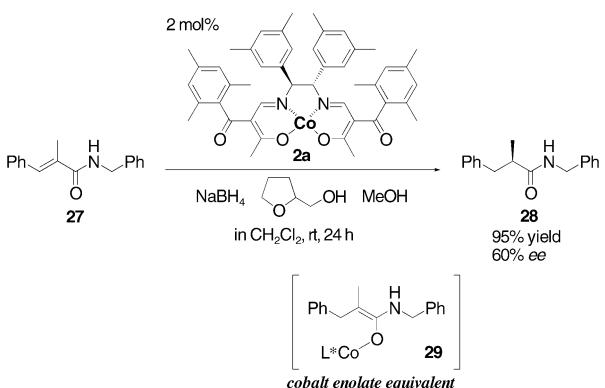


Figure 6. FAB mass spectra of the cobalt complex treated with borohydride.

appeared (Figure 6c). These results clearly indicated that the cobalt–hydride species would mainly exist in the reaction media and could act as the reactive intermediate. Optically active cobalt–hydride species then precisely reacted with the prochiral ketones recognizing the enantioface. As a result, an optically active alcohol was obtained and the cobalt complex was recycled. It was recently found that *N*-benzyl-(*E*)- α -methylcinnamic amide **27** was subjected to the enantioselective reduction system to obtain the optically active 2-methylcarboxamide **28** with 60% ee (Scheme 9)^[53]. This result suggested that the cobalt hydride generated in the reaction system would attack the cinnamic amide in a 1,4-reduction manner to form the cobalt-enolate equivalent **29**, which was then protonated *in situ* by THFA or methanol to afford the optically active carboxyamide.

As mentioned above, X-ray analysis of the molecular structure of the optically active β -ketiminato cobalt complex was performed for the cobalt(III)-iodide complex derived from



Scheme 9. Catalytic enantioselective protonation of cobalt enolate equivalent.

the corresponding cobalt(II) complex **1a** and **3b**. It revealed that the centered cobalt was surrounded by the square-planar ligand and that aryl groups in the optically active diamine and a mesityl group in the side chain were located nearby. The observed enantiofacial selection of the corresponding (*S*)-alcohols to the (*S,S*)-cobalt complexes (*Re* attack) can be explained by considering the favorable transition state illustrated in Figure 7; the substrates, aryl ketones, would

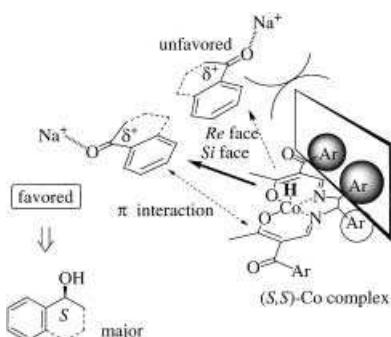


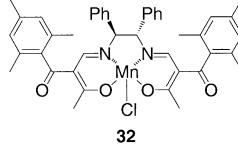
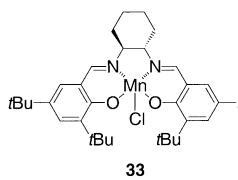
Figure 7. Possible mechanistic explanation for the observed enantioface selection in asymmetric reduction with (*S,S*)-cobalt complex.

approach the postulated cobalt-hydride through the open site (*Re* attack). The aromatic ring of the aryl ketone was placed parallel to the square delocalized π system plane of the cobalt complex by π interaction. Because $\pi-\pi$ interaction occurred efficiently between the catalyst and aromatic ketone, the reduction of the aryl ketone proceeded faster than the alkyl ketone in the catalytic system (Scheme 6). The approaching carbonyl group of the substrates was oriented away from the cobalt complex to avoid any steric hindrance by the bulky aryl groups. The alternative transition state (*Si* attack) is not rationalized because of the steric repulsion of the bulky aryl groups of the complex with the carbonyl group from the incoming ketones. These closely packed transition states could suggest that the enantiofacial selectivity was fairly dependent on these components as substrates, ligands, and additive alcohols as shown in Tables 1 and 2. Based on these observations, it could be assumed that sodium borohydride was modified *in situ* with the additive alcohols to form $\text{NaBH}_2(\text{OR}^1)(\text{OR}^2)$ ($\text{R}^1=\text{Me}$ or Et , $\text{R}^2\text{OH}=\text{THFA}$) and

then the modified borohydride was closely located to the cobalt complex and assisted the achieving a high enantioselectivity.

Recently, it was reported that Jacobsen's manganese(III) complexes as well as the β -ketoiminato cobalt(II) complexes could be used as catalysts for the enantioselective borohydride reduction of 2-phenacylpyridine (**30**).^[54] It should be pointed out here that (*S*)-1-phenyl-2-(2-pyridyl)ethanol (**31**) was obtained using the (*S,S*)-cobalt(II) complexes **1a**, **2a**, **3a**, or **3b**, whereas the (*R*)-product was obtained using (*S,S*)- β -ketoiminato manganese(III)-chloride complex **32** and Jacobsen's (*S,S*)-salen manganese(III)-chloride complex **33** (Table 15).^[55] It was proposed that Jacobsen's manganese(III) catalysts could be employed as a chiral Lewis acid to form a stable chelate complex with 2-phenacylpyridine, which was then enantioselectively reduced by the THFA-modified borohydride.^[54] On the other hand, the formation of a similar tight chelate with the cobalt(II) complexes could not be expected since the Lewis acidity of the cobalt(II) complex is presumed to be generally weak.^[56] Concerning the enantioselective sense, the manganese(III)-chloride complex with the β -ketoiminato ligand afforded the opposite enantiomer against the corresponding β -ketoiminato cobalt(II) complex although both structures of the manganese and cobalt complexes were very similar based on an X-ray analysis.^[19] The enantioselective sense in the present reduction of 2-phenacylpyridine was in accord with the cobalt complex catalyzed reductions of carbonyl compounds. These observations should suggest that the enantioselective borohydride reductions with the cobalt(II) and manganese(III) complex catalysts proceeded by different mechanisms. Therefore, it is reasonable to assume that the "cobalt–hydride equivalent"

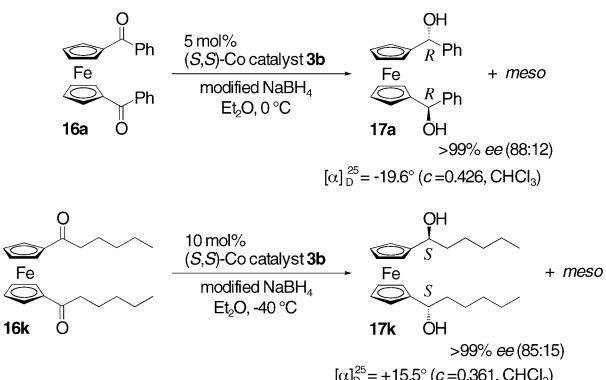
Table 15. Enantioselective reduction of 2-phenacylpyridine with cobalt(II) or manganese(III) catalysts.^[a]

Entry	(<i>S,S</i>)-catalyst	Yield [%]	<i>ee</i> [%] ^[b]	Absolute configuration
1	1a	89	22	<i>S</i>
2	2a	93	39	<i>S</i>
3	3a	93	64	<i>S</i>
4	3b	92	86	<i>S</i>
5		90	5	<i>R</i>
6		82	85	<i>R</i>

[a] Reaction conditions: 0.50 mmol substrate, 0.01 mmol Co catalyst, 0.75 mmol NaBH₄, 0.75 mmol EtOH, 10.5 mmol THFA, in CHCl₃ (10 mL), at 0 °C, 12 h. [b] Determined by HPLC analysis.

generated from the optically active cobalt catalyst and premodified borohydride could react with carbonyl compounds in a highly enantioselective manner. As mentioned above, all simple ketones **8a–g** were converted to the (*S*)-alcohol **9a–g** in the presence of the (*S,S*)-cobalt complexes. Various (*S*)-amines **12d–i** were also obtained corresponding to the (*S,S*)-cobalt catalyst. These results indicated that optically active β -ketoiminato cobalt complexes could recognize the prochiral face of imines as well as ketones in the same mechanism.

It was revealed that (*S,S*)-1,3-diphenyl-1,3-propanediol (**15a**) was obtained using to the (*S,S*)-cobalt catalyst when compared with the previously reported optical rotation.^[39] The enantioselective sense was in accord with the various cobalt-catalyzed reductions of the aryl ketones. The enantioselective sense was also determined for the enantioselective reduction of 1,1'-dibenzoylferrocene (**16a**) in the presence of the (*S,S*)-cobalt complex which afforded the (*R,R*)-ferrocenyldiol, whereas the (*S,S*)-diol was obtained from the 1,1'-dialkanoylferrocene (**16k**) (Scheme 10).^[42] The enantioselective sense in the reduction of the 1,1'-dibenzoylferrocene



Scheme 10. Enantioselective sense for dialkanoylferrocene vs dibenzoylferrocene.

(**16a**) was in accord with that^[26] of the acetophenone derivatives. As for the enantioselective reduction of 1,1'-dialkanoylferrocene (**16k**), it is reasonable to consider that the cobalt complex catalyst should recognize the ferrocenyl group as the π system similar to the reduction of phenyl ketone to achieve a high enantioselection. The *anti*-1,3-di(*p*-bromophenyl)-3-hydroxy-2-methyl-1-propanone (**19d**) was converted to (*R*)- α -methoxyphenylacetate for the X-ray analysis. It was found that the (*R*)-alcohol *anti*-form, (2*S*,3*R*)-1,3-di(*p*-bromophenyl)-3-hydroxy-2-methyl-1-propanone (**19d**), was obtained corresponding to the (*R,R*)-cobalt complex catalyst (Figure 8).^[46] Thus, the excellent stereoselectivity in the present catalytic reduction system can be explained as follows (Figure 9): The hydride equivalent nucleophile should attack one of the carbonyl groups in the 1,3-diaryl-1,3-propanedione according to the Felkin–Anh model to afford the corresponding *anti*-product with high diastereoselectivity. Concerning the excellent enantioselectivity, the optically active β -ketoiminato cobalt complex could

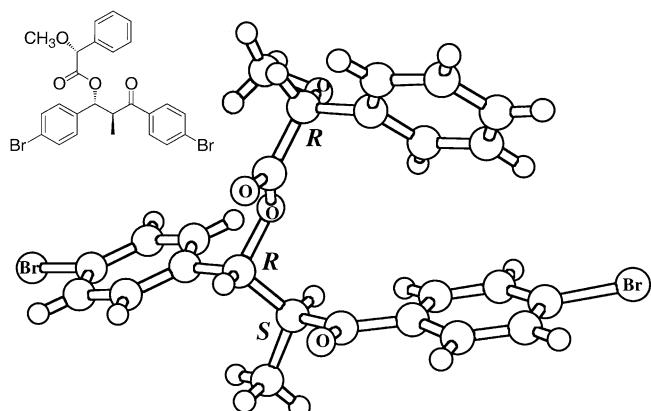


Figure 8. X-ray analysis of *(R)*- α -methoxyphenylacetate of *anti*-1,3-di(*p*-bromophenyl)-3-hydroxy-2-methyl-1-propanone corresponding to the (*R,R*)-cobalt catalyst.

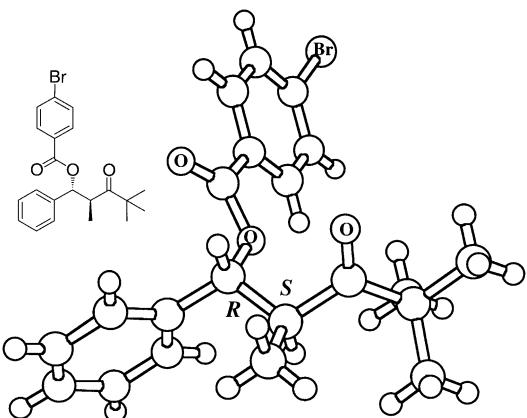


Figure 10. The absolute configuration of *p*-bromobenzoate of *anti*-1-hydroxy-2,4,4-trimethyl-1-phenyl-3-pentanone corresponding to the (*R,R*)-cobalt catalyst was determined by X-ray analysis.

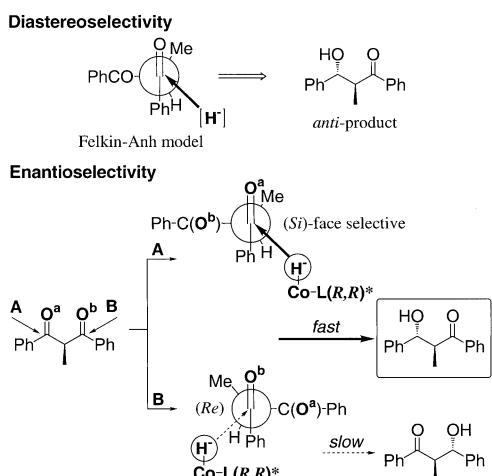


Figure 9. Diastereo- and enantioselectivities in the catalytic reduction system.

distinctly recognize the *Si* face of the carbonyl group using the (*R,R*)-cobalt complex catalyst. Therefore, the (*R*)-alcohol *anti*-form was obtained in the presence of the (*R,R*)-cobalt catalyst.

The *anti*-1-hydroxy-2,4,4-trimethyl-1-phenyl-3-pentanone (**24d**) was conventionally transformed into the corresponding *p*-bromobenzoate. As a result of the X-ray analysis, it was revealed that the (*1R,2S*)-form was obtained corresponding to the (*R,R*)-cobalt complex catalyst (Figure 10).^[49] The obtained *anti*-3-hydroxy-2-methyl-3-phenylpropionic acid ethyl ester (**26b**) was treated with lithium aluminum hydride for conversion into the corresponding *anti*-1-phenyl-2-methyl-1,3-propanediols. The optical rotation of the resulting 1,3-diol was compared with the previously reported result. It was revealed to be the (*2R,3R*)-*anti*-1,3-diol, therefore, the (*2S,3R*)-*anti*-3-hydroxyester should be generated and correspond to the (*R,R*)-catalyst. The absolute configurations of the obtained products could be fully explained by the above-mentioned surveys, that is, the presentation in Figure 7.

Conclusion

We have developed a novel method of the enantioselective borohydride reduction in which aromatic ketones are smoothly and quantitatively converted into the corresponding alcohols in the presence of a catalytic amount of the optically active cobalt(II) complex catalyst. This enantioselective reduction is carried out using a precisely premodified borohydride with alcohols such as tetrahydrofurfuryl alcohol, ethanol and methanol, and high *ee* values are obtained by choosing the appropriate alcohols as modifiers and a suitable β -ketoimato ligand of the catalyst. The enantioselective borohydride reduction has been successfully applied to the reduction of imines protected by a phosphinyl group. The optically active amines are obtained with high chemical yields and high *ee* values. The subsequent hydrolysis smoothly gives the corresponding primary amine while maintaining a high enantioselective excess. In the catalytic system, optically active C_2 -symmetrical diols, 1,3-diaryl-1,3-propanediols and 1,1'-ferrocenyldiols were prepared with high stereoselectivities and a high catalytic efficiency. Also, it was demonstrated that the optically active *anti*-2-substituted-3-hydroxycarbonyl compounds could be prepared from the corresponding 2-substituted 3-ketocarbonyl compounds using enantioselective borohydride reduction. In contrast, the *syn*-aldol was generally produced by the transition-metal catalyzed reactions; the present enantioselective reduction could provide an alternative approach for the preparation of the *anti*-aldol-type compounds.

Experimental Section

General: ^1H NMR spectra were measured on a JOEL model FX-270 (270 MHz) or GX-400 (400 MHz) spectrometer using CDCl_3 as a solvent with tetramethylsilane (0.00 ppm) as an internal standard. ^{13}C NMR spectra (100 MHz) were measured on a JOEL model GX-400 spectrometer using CDCl_3 (77.0 ppm) or C_6D_6 (128.0 ppm) as a solvent. Infrared spectra were recorded on a JASCO model IR-700 or FTIR-410 infrared spec-

trometer on 3M IR card (Type 61 and 62) or as KBr pellets. The melting points (m.p.) were measured on a Mettler FP62 apparatus, an Electro-thermal IA9100 apparatus, a Seiko Densi Kogyo Ltd. DSC-100 apparatus (DSC), or Shimadzu DSC-60 apparatus (DSC) and were uncorrected. Elemental analyses were determined with an Elemental Vario EL apparatus. High-resolution mass spectra (HRMS) were obtained with a HITACHI M-80B. FAB mass spectra were obtained with JOEL JMS-700 mass spectrometer using 3-nitrobenzyl alcohol as matrix with 10 kV acceleration voltage. High-performance liquid chromatography (HPLC) analyses were performed with a Shimadzu LC-6A chromatograph using an optically active column (Daicel Chiralcel OB, Chiralcel OD-H, Chiralpak AD, or Chiralpak AD-H); the peak areas were obtained with a Shimadzu Chromatopack CR-4A or Varian Dynamax MacIntegrator. Optical rotations were measured with a JASCO DIP-360 or DIP-370 digital polarimeter.

General procedure for preparation of optically active cobalt complexes: These ligands were prepared by the reported method^[18] from 3-oxo-2-(2,4,6-trimethylbenzoyl)butanal and the corresponding (1S,2S)-1,2-diarylenediamines. The optically active cobalt(II) complexes were prepared by the reported method.^[21, 57]

[N,N'-Bis[2-(2,4,6-trimethylbenzoyl)-3-oxobutylidene]-1S,2S]-1,2-bis(2,4,6-trimethylphenyl)ethylenediaminato]iodocobalt(III) (1a-I): Cobalt(II) complex **1a-I** was prepared by adding 0.5 equiv iodine to a dichloromethane solution of the cobalt(II) complex **1a** at room temperature. The crystal appropriate for X-ray analysis was obtained as dark brown plate by recrystallization (dichloromethane/Et₂O/hexane 1:1:4) at room temperature.

X-ray Crystallography of complex 1a-I: Accurate unit cell parameters were obtained on a Rigaku AFC-6R diffractometer with Cu_{Kα} radiation ($\lambda = 1.54178 \text{ \AA}$). The structure was solved by direct methods and refined by full-matrix least squares calculations.

Crystal data of 1a-I (C₄₈H₅₄N₂O₄ICo·H₂O): $F_w = 926.78$, monoclinic, space group $P2_1$, $a = 17.432(2)$, $b = 18.096(2)$, $c = 16.4(10) \text{ \AA}$, $\beta = 113.725(8)^\circ$, $V = 4744(289) \text{ \AA}^3$, $Z = 4$, $\rho = 1.298 \text{ Mg m}^{-3}$, $F(000) = 1912$, crystal size $0.25 \times 0.30 \times 0.03 \text{ mm}$, $T = 298 \text{ K}$, $\mu = 8.291 \text{ mm}^{-1}$, no. of reflections measured 8133 (total) and 7834 (unique), $R = 0.1242$ and $wR = 0.3113$.

X-ray Crystallography of complex 3b-Br: The complex **3b-Br** was prepared from the complex **3b** and bromine similarly to the complex **1a-I**. Accurate unit cell parameters were obtained on a Rigaku AFC-7R diffractometer with Mo_{Kα} radiation ($\lambda = 0.7107 \text{ \AA}$). The structure was solved by direct methods and refined by full-matrix least squares calculations.

Crystal data of 3b-Br (C₃₂H₃₈N₂O₄BrCo·H₂O·C₄H₈O): $F_w = 743.62$, monoclinic, space group $P2_1$, $a = 13.667(2)$, $b = 15.046(2)$, $c = 17.764(2) \text{ \AA}$, $\beta = 100.32(1)^\circ$, $V = 3593.8(8) \text{ \AA}^3$, $Z = 4$, $D = 1.374 \text{ Mg m}^{-3}$, $F(000) = 1552$, crystal size $0.50 \times 0.30 \times 0.1 \text{ mm}$, $T = 297 \text{ K}$, $\mu = 1.64 \text{ mm}^{-1}$, no. of reflections measured 12278 (total) and 11744 (unique), $R = 0.064$ and $wR = 0.186$.

Preparation of ketones: The chromanone derivative **8h** was prepared according to the literature method.^[58] Tetralone derivatives **8a** and **8g** were purchased from Tokyo Kasei Kogyo (TCI), and the ketones **8f**^[59] was prepared by reported procedure. Alkyl phenyl ketones **8b**, **8e**, **8c**, and **8d** were purchased from Tokyo Kasei Kogyo (TCI).

General procedure for enantioselective reduction of aromatic ketones using premodified borohydride

Exclusive formation of premodified dialkoxyborohydride 10: Under argon atmosphere, in a precooled vessel at 0 °C, were placed fine grained NaBH₄ (29 mg, 0.75 mmol), CHCl₃ (5.0 mL), EtOH (0.44 mL, 0.75 mmol) and THFA (1.0 mL, 10.3 mmol), and the mixture was continued to stir for 3 h.

Catalytic enantioselective borohydride reduction: The solution of **10** was added (while maintaining the solution at 0 °C) to the solution of (S,S)-cobalt(II) catalyst **2b** (3.7 mg, 0.005 mmol, 1 mol %) and 6-methoxy-1-tetralone (**8a**, 88 mg, 0.50 mmol) in CHCl₃(5.0 mL), and the mixture was continued to stir for 30 min at 0 °C. The reaction was quenched by the addition of saturated aqueous ammonium chloride, and extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and then the excess solvent were removed under reduced pressure. The purification by column chromatography on silica gel (hexane/ethyl acetate 4:1) gave the corresponding alcohol **9a** as colorless oil (99 %, 88 mg). The enantiomeric excess was determined to be

93 % by HPLC analysis using Daicel Chiralpak AD (2.0 % propan-2-ol in hexane, flow 1.0 mL min⁻¹); $[\alpha]_D^{28} = +29.7^\circ$ ($c = 0.81$, Et₂O).

6-Methoxy-1-tetralol (9a): ¹H NMR (CDCl₃): $\delta = 1.74 - 1.92$ (m, 5H), 2.65 – 2.87 (m, 2H), 3.78 (s, 3H), 4.73 (br, 1H), 6.62 (d, 1H, $J = 2.6 \text{ Hz}$), 6.76 (dd, 1H, $J = 2.6, 8.6 \text{ Hz}$), 7.33 (d, 1H, $J = 8.6 \text{ Hz}$); IR: $\tilde{\nu} = 3392, 2930, 1609, 1577, 1501, 1457 \text{ cm}^{-1}$. Enantiomeric excess was determined to be 93 % by HPLC analysis (Chiralpak AD; 2.0 % propan-2-ol in hexane, flow 1.0 mL min⁻¹, 44.1 min (major), 47.7 min (minor)); $[\alpha]_D^{28} = +29.7^\circ$ ($c = 0.81$ in Et₂O).

1-Phenyl-1-butanol (9b): ¹H NMR (CDCl₃): $\delta = 0.88$ (t, 3H, $J = 7.25 \text{ Hz}$), 1.26 – 1.35 (m, 2H), 1.68 – 1.81 (m, 2H), 1.91 (m, 1H), 4.62 (t, 1H, $J = 6.6 \text{ Hz}$), 7.23 – 7.34 (m, 5H); IR: $\tilde{\nu} = 3356, 2956, 2870, 1492, 1454 \text{ cm}^{-1}$. Enantiomeric excess was determined to be 97 % by HPLC analysis (Chiralcel OB; 1.0 % propan-2-ol in hexane, flow 1.0 mL min⁻¹, 14.2 min (major), 16.8 min (minor)); $[\alpha]_D^{28} = -47.9^\circ$ ($c = 0.34$ in benzene). (lit.^[60] $[\alpha]_D = +43.4^\circ$ (benzene), 96 % ee (*R*)).

Cyclopropylphenylmethanol (9c): ¹H NMR (CDCl₃): $\delta = 0.32 - 0.68$ (m, 4H), 1.15 – 1.28 (m, 1H), 2.00 (d, 1H, $J = 3.0 \text{ Hz}$), 4.00 (dd, 1H, $J = 3.0, 8.3 \text{ Hz}$), 7.25 – 7.44 (m, 5H); IR: $\tilde{\nu} = 3384, 3080, 3004, 1493, 1452 \text{ cm}^{-1}$. Enantiomeric excess was determined to be 90 % by HPLC analysis (Chiralpak AD; 2.0 % propan-2-ol in hexane, flow 0.7 mL min⁻¹, 36.5 min (minor), 38.2 min (major)); $[\alpha]_D^{28} = +22.6^\circ$ ($c = 0.234$ in CHCl₃).

2-Methyl-1-phenyl-1-propanol (9d): ¹H NMR (CDCl₃): $\delta = 0.80$ (d, 3H, $J = 6.93 \text{ Hz}$), 1.00 (d, 3H, $J = 6.9 \text{ Hz}$), 1.83 (br, 1H), 1.92 – 2.02 (m, 1H), 4.36 (dd, 1H, $J = 3.3, 6.9 \text{ Hz}$), 7.26 – 7.37 (m, 5H); IR: $\tilde{\nu} = 3422, 2958, 2872, 1492, 1453 \text{ cm}^{-1}$. Enantiomeric excess was determined to be 98 % by HPLC analysis (Chiralcel OB; 0.5 % propan-2-ol in hexane, flow 1.0 mL min⁻¹, 18.0 min (major), 19.1 min (minor)); $[\alpha]_D^{34} = -48.6^\circ$ ($c = 0.288$, Et₂O). (lit.^[61] $[\alpha]_D^{20} = -47.7^\circ$ ($c = 5.80$ in Et₂O), (*S*)).

Cyclohexylphenylmethanol (9e): ¹H NMR (CDCl₃): $\delta = 0.89 - 1.84$ (m, 11H), 1.97 (br, 1H), 4.35 (dd, 1H, $J = 3.0, 7.3 \text{ Hz}$), 7.22 – 7.35 (m, 5H); IR: $\tilde{\nu} = 3362, 3070, 3006, 1492, 1452 \text{ cm}^{-1}$. Enantiomeric excess was determined to be 95 % by HPLC analysis (Chiralcel OD-H; 10.0 % propan-2-ol in hexane, flow 0.5 mL min⁻¹, 11.8 min (major), 13.3 min (minor)); $[\alpha]_D^{31} = -21.8^\circ$ ($c = 0.461$ in EtOH). (lit.^[61] $[\alpha]_D^{20} = +22.5^\circ$ ($c = 5.13$ in EtOH), (*R*)).

2,2-Dimethyl-1-tetralol (9f): ¹H NMR (CDCl₃): $\delta = 0.98$ (s, 3H), 1.00 (s, 3H), 1.50 – 1.58 (m, 1H), 1.62 (br, 1H), 1.76 – 1.86 (m, 1H), 2.75 – 2.83 (m, 2H), 4.26 (s, 1H), 7.08 – 7.15 (m, 1H), 7.17 – 7.24 (m, 2H), 7.41 – 7.46 (m, 1H); IR: $\tilde{\nu} = 3388, 3020, 2918, 1453 \text{ cm}^{-1}$. Enantiomeric excess was determined to be 94 % by HPLC analysis (Chiralcel OD-H; 1.0 % propan-2-ol in hexane, flow 0.5 mL min⁻¹, 30.2 min (minor), 33.7 min (major)); $[\alpha]_D^{28} = +21.6^\circ$ ($c = 0.817$ in CHCl₃). (lit.^[62] $[\alpha]_D^{25} = +23.5^\circ$ ($c = 3.37$ in CHCl₃), (*S*)).

1-Tetralol (9g): ¹H NMR (CDCl₃): $\delta = 1.71 - 2.00$ (m, 4H), 2.01 – 2.10 (br, 1H), 2.69 – 2.85 (m, 2H), 4.74 (t, 1H, $J = 4.6 \text{ Hz}$), 7.05 – 7.14 (m, 1H), 7.16 – 7.21 (m, 2H), 7.36 – 7.41 (m, 1H); IR: $\tilde{\nu} = 3348, 2930, 2860, 1489, 1453 \text{ cm}^{-1}$. Enantiomeric excess was determined to be 90 % by HPLC analysis (Chiralpak AD; 2.5 % propan-2-ol in hexane, flow 1.0 mL min⁻¹, 18.4 min (major), 20.1 min (minor)); $[\alpha]_D^{24} = +28.8^\circ$ ($c = 0.55$ in CHCl₃). (lit.^[63] $[\alpha]_D^{17} = +32.7^\circ$ ($c = 10.7$ in CHCl₃), >99 % ee (*S*)).

2,2-Dimethyl-4-hydroxychroman (9h): ¹H NMR (CDCl₃): $\delta = 1.32$ (s, 3H), 1.43 (s, 3H), 1.58 – 1.77 (br, 1H), 1.87 (dd, 1H, $J = 8.4, 14.3 \text{ Hz}$), 2.18 (dd, 1H, $J = 8.4, 14.3 \text{ Hz}$), 4.87 (d, 1H, $J = 8.4 \text{ Hz}$), 6.77 – 6.83 (m, 1H), 6.90 – 6.97 (m, 1H), 7.14 – 7.21 (m, 1H), 7.42 – 7.48 (m, 1H); IR: $\tilde{\nu} = 3230, 2976, 1608, 1580, 1484, 1456 \text{ cm}^{-1}$. Enantiomeric excess was determined to be 92 % by HPLC analysis (Chiralpak AD; 2.5 % propan-2-ol in hexane, flow 1.0 mL min⁻¹, 20.5 min (major), 21.7 min (minor)); $[\alpha]_D^{28} = +49.0^\circ$ ($c = 1.00$ in CHCl₃). (lit.^[64] $[\alpha]_D = +51.5^\circ$ ($c = 1.12$ in CHCl₃), (*S*)).

Preparation of aryl N-diphenylphosphinyl imines: Aryl N-diphenylphosphinyl imines **1d-i** were prepared from the corresponding oxime and chlorodiphenylphosphine according to the literature method.^[65]

N-(1,2,3,4-Tetrahydro-1-naphthylidene)-P,P-diphenylphosphinamide (11d): ¹H NMR (CDCl₃): $\delta = 2.07 - 2.13$ (m, 2H), 2.67 (t, 2H, $J = 7.8 \text{ Hz}$), 4.76 (d, 1H, $J = 7.8 \text{ Hz}$), 5.91 (d, 1H, $J = 4.9 \text{ Hz}$), 7.13 – 7.28 (m, 3H), 7.58 – 7.52 (m, 7H), 7.89 – 7.94 (m, 4H); ¹³C NMR (CDCl₃): $\delta = 22.0, 27.8, 113.2$ (d, $J_{CP} = 5.0 \text{ Hz}$), 120.2, 126.4, 127.5, 127.8, 128.6 (d, $J_{CP} = 13.3 \text{ Hz}$), 131.7 (d, $J_{CP} = 10.0 \text{ Hz}$), 131.9 (d, $J_{CP} = 2.5 \text{ Hz}$), 132.0 (d, $J_{CP} = 130.2 \text{ Hz}$), 132.2 (d, $J_{CP} = 8.3 \text{ Hz}$), 133.0 (d, $J_{CP} = 1.7 \text{ Hz}$), 137.4; IR (KBr): $\tilde{\nu} = 3051, 2871, 1462$,

1438, 1201, 1123, 1109, 694 cm^{-1} ; m.p. 156.3–156.6 $^{\circ}\text{C}$; HRMS: m/z : calcd for $\text{C}_{22}\text{H}_{20}\text{NOP}$: 345.1283; found: 345.1276 [M^+].

N-(1-Phenylethylidene)-*P,P*-diphenylphosphinamide (11e):^[66] ^1H NMR (CDCl_3): δ = 2.96 (s, 3 H), 7.39–7.54 (m, 9 H), 7.97–8.09 (m, 6 H); ^{13}C NMR (CDCl_3): δ = 23.0 (d, $J_{\text{C},\text{P}}=12.4$ Hz), 127.7, 128.2 (d, $J_{\text{C},\text{P}}=12.4$ Hz), 128.3, 131.2 (d, $J_{\text{C},\text{P}}=2.5$ Hz), 131.4 (d, $J_{\text{C},\text{P}}=9.1$ Hz), 132.2, 133.5 (d, $J_{\text{C},\text{P}}=131.0$ Hz), 139.1 (d, $J_{\text{C},\text{P}}=24.0$ Hz), 181.2 (d, $J_{\text{C},\text{P}}=7.5$ Hz); IR (KBr): $\tilde{\nu}$ = 3060, 1642, 1438, 1200, 1125, 1109, 727, 715, 694, 550 cm^{-1} ; m.p. 139.6–140.4 $^{\circ}\text{C}$.

N-(1-Indanylidene)-*P,P*-diphenylphosphinamide (11f):^[67] ^1H NMR (CDCl_3): δ = 3.08 (t, 2 H, $J=5.6$ Hz), 3.24–3.27 (m, 2 H), 7.33–7.52 (m, 9 H), 7.97–8.03 (m, 5 H); ^{13}C NMR (CDCl_3): δ = 28.5, 34.9 (d, $J_{\text{C},\text{P}}=11.6$ Hz), 123.7, 125.8 (d, $J_{\text{C},\text{P}}=1.7$ Hz), 127.0, 128.1 (d, $J_{\text{C},\text{P}}=12.4$ Hz), 131.1 (d, $J_{\text{C},\text{P}}=2.5$ Hz), 131.3 (d, $J_{\text{C},\text{P}}=9.1$ Hz), 133.9, 134.6 (d, $J_{\text{C},\text{P}}=12.7$ Hz), 140.0 (d, $J_{\text{C},\text{P}}=23.2$ Hz), 153.1, 190.5 (d, $J_{\text{C},\text{P}}=7.5$ Hz); IR (KBr): $\tilde{\nu}$ = 1637, 1436, 1199, 1122, 870, 762, 519 cm^{-1} ; m.p. 165.3–166.6 $^{\circ}\text{C}$.

N-(6,7,8,9-Tetrahydro-5*H*-benzocyclohepten-5-ylidene)-*P,P*-diphenylphosphinamide (11g): ^1H NMR (CDCl_3): δ = 1.63 (q, 2 H, $J=7.6$ Hz), 1.99 (quintet, 2 H, $J=7.6$ Hz), 2.57 (t, 2 H, $J=7.6$ Hz), 4.70 (d, 1 H, $J=7.6$ Hz), 5.88 (t, 1 H, $J=7.6$ Hz), 7.18–7.33 (m, 3 H), 7.42–7.61 (m, 7 H), 7.92–7.97 (m, 4 H); ^{13}C NMR (CDCl_3): δ = 23.3, 32.2, 35.1, 112.4 (d, $J_{\text{C},\text{P}}=5.0$ Hz), 125.5, 126.2, 127.9, 128.5 (d, $J_{\text{C},\text{P}}=12.4$ Hz), 129.1, 131.7 (d, $J_{\text{C},\text{P}}=10.0$ Hz), 131.8 (d, $J_{\text{C},\text{P}}=3.3$ Hz), 131.9 (d, $J_{\text{C},\text{P}}=129.4$ Hz), 135.6 (d, $J_{\text{C},\text{P}}=1.6$ Hz), 138.3 (d, $J_{\text{C},\text{P}}=8.3$ Hz), 142.0; IR (KBr): $\tilde{\nu}$ = 3054, 2873, 1438, 1206, 1190, 692, 526 cm^{-1} ; m.p. 165.5–166.7 $^{\circ}\text{C}$; HRMS: m/z : calcd for $\text{C}_{22}\text{H}_{22}\text{NOP}$: 359.1439; found: 359.1458 [M^+].

N-(6-Methoxy-1,2,3,4-tetrahydro-1-naphthylidene)-*P,P*-diphenylphosphinamide (11h): ^1H NMR (CDCl_3): δ = 1.96 (quin, 2 H, $J=6.2$ Hz), 2.84 (t, 2 H, $J=6.2$ Hz), 3.23–3.27 (m, 2 H), 3.85 (s, 3 H), 6.67 (d, 1 H, $J=2.7$ Hz), 6.87 (dd, 1 H, $J=2.7, 8.8$ Hz), 7.38–7.45 (m, 6 H), 7.95–8.00 (m, 4 H), 8.40 (d, 1 H, $J=8.8$ Hz); ^{13}C NMR (CDCl_3): δ = 23.0, 30.1, 35.4 (d, $J_{\text{C},\text{P}}=12.4$ Hz), 55.4, 112.4, 113.4, 127.3 (d, $J_{\text{C},\text{P}}=24.1$ Hz), 128.2 (d, $J_{\text{C},\text{P}}=12.4$ Hz), 129.7, 131.0 (d, $J_{\text{C},\text{P}}=2.5$ Hz), 131.3 (d, $J_{\text{C},\text{P}}=9.1$ Hz), 135.3 (d, $J_{\text{C},\text{P}}=130.2$ Hz), 145.9 (d, $J_{\text{C},\text{P}}=1.7$ Hz), 163.1, 181.2 (d, $J_{\text{C},\text{P}}=6.6$ Hz); IR (KBr): $\tilde{\nu}$ = 1627, 1587, 1569, 1252, 1205, 813, 726, 550, 517 cm^{-1} ; m.p. 172.4–174.7 $^{\circ}\text{C}$; HRMS: m/z : calcd for $\text{C}_{23}\text{H}_{22}\text{NO}_2\text{P}$: 375.1388; found: 375.1366 [M^+].

N-(Chroman-4-ylidene)-*P,P*-diphenylphosphinamide (11i): ^1H NMR (CDCl_3): δ = 3.50–3.54 (m, 2 H), 4.35 (t, 2 H, $J=6.3$ Hz), 6.92 (d, 1 H, $J=7.9$ Hz), 7.04 (t, 1 H, $J=7.9$ Hz), 7.41–7.48 (m, 7 H), 7.95–8.01 (m, 4 H), 8.26 (dd, 1 H, $J=1.7, 7.9$ Hz); ^{13}C NMR (CDCl_3): δ = 33.8 (d, $J_{\text{C},\text{P}}=12.4$ Hz), 124.4, 126.2, 127.9, 128.3 (d, $J_{\text{C},\text{P}}=12.4$ Hz), 131.3 (d, $J_{\text{C},\text{P}}=2.5$ Hz), 131.3 (d, $J_{\text{C},\text{P}}=9.2$ Hz), 134.5 (d, $J_{\text{C},\text{P}}=131.0$ Hz), 160.5 (d, $J_{\text{C},\text{P}}=1.7$ Hz), 175.1 (d, $J_{\text{C},\text{P}}=6.6$ Hz); IR (KBr): $\tilde{\nu}$ = 1629, 1604, 1481, 1457, 1438, 1190, 1126, 1108, 896, 760, 728, 703, 551 cm^{-1} ; m.p. 161.3–163.0 $^{\circ}\text{C}$; HRMS: m/z : calcd for $\text{C}_{21}\text{H}_{18}\text{NO}_2\text{P}$: 347.1075; found: 347.1057 [M^+].

Typical procedure for enantioselective reduction of aryl *N*-diphenylphosphinyl imines

Formation of premodified borohydride: Under argon atmosphere, in a precooled vessel at 0 $^{\circ}\text{C}$ were placed fine grained NaBH_4 (29 mg, 0.75 mmol), CHCl_3 (5.0 mL), EtOH (0.044 mL, 0.75 mmol) and THFA (1.0 mL, 10.3 mmol), and the mixture was continued to stir for 3 h.

Catalytic enantioselective borohydride reduction: While maintaining solution of premodified borohydride at 0 $^{\circ}\text{C}$, its solution was slowly added to the solution of (*S,S*)-cobalt(ii) catalyst **2a** (3.7 mg, 0.005 mmol, 1 mol %) and *N*-diphenylphosphinyl imine (**11d**, 172.6 mg, 0.50 mmol) in CHCl_3 (5.0 mL), and the mixture was continued to stir for 4 h at 0 $^{\circ}\text{C}$. The reaction was quenched by the addition of saturated aqueous ammonium chloride, and extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and then the excess solvents were removed under reduced pressure. The purification by column chromatography on silica gel (hexane/ethyl acetate/dichloromethane 1:2:1) gave the corresponding amine **12d** as white solid (148.0 mg, 85%). Enantiomeric excess was determined to be 98% by HPLC analysis using Daicel Chiralpak AD (20.0% propan-2-ol in hexane, flow 1.0 mL min⁻¹); $[\alpha]_D^{28} = -65.2^{\circ}$ ($c = 0.43$ in MeOH).

Removal of diphenylphosphinyl group: Aryl *N*-diphenylphosphinyl amine (−)**12d** (191.6 mg, 0.55 mmol) was mixed with 5% HCl/methanol solution (15 mL). The solution was stirred for 3 h at ambient temperature. It was

evaporated, and treated with aqueous NaOH, extracted with Et₂O, dried with anhydrous sodium sulfate, to quantitatively provide the free amine (*S*)-(+)**13d** as a white solid, $[\alpha]_D^{26} = +47.8^{\circ}$ ($c = 0.68$ in benzene) (lit.^[68] $[\alpha]_D^{21} = -47.6^{\circ}$ ($c = 0.47$ in benzene), (*R*)).

N-(Diphenylphosphinyl)-1,2,3,4-tetrahydro-1-naphthylamine (**12d**):

^1H NMR (CDCl_3): δ = 1.63–1.98 (m, 3 H), 2.04–2.18 (m, 1 H), 2.60–2.85 (m, 2 H), 3.15–3.26 (m, 1 H), 4.24–4.38 (m, 1 H), 7.04 (d, 1 H, $J=7.3$ Hz), 7.12–7.26 (m, 2 H), 7.38–7.56 (m, 6 H), 7.71 (d, 1 H, $J=7.6$ Hz), 7.93–8.02 (m, 4 H); ^{13}C NMR (CDCl_3): δ = 19.9, 29.2, 33.4 (d, $J_{\text{C},\text{P}}=2.5$ Hz), 49.8 (d, $J_{\text{C},\text{P}}=1.7$ Hz), 126.2, 127.0, 128.4 (d, $J_{\text{C},\text{P}}=12.4$ Hz), 128.5 (d, $J_{\text{C},\text{P}}=12.4$ Hz), 128.9 (d, $J_{\text{C},\text{P}}=1.7$ Hz), 131.8 (d, $J_{\text{C},\text{P}}=1.7$ Hz), 132.1 (d, $J_{\text{C},\text{P}}=10.0$ Hz), 132.1 (d, $J_{\text{C},\text{P}}=9.1$ Hz), 132.4 (d, $J_{\text{C},\text{P}}=126.1$ Hz), 132.9 (d, $J_{\text{C},\text{P}}=128.5$ Hz), 137.3, 138.5, 138.6; IR (KBr): $\tilde{\nu}$ = 3120, 2925, 2860, 1438, 1196, 1182, 1118, 750, 736, 694, 531 cm^{-1} ; m.p. 132.1–136.7 $^{\circ}\text{C}$; HRMS: m/z : calcd for $\text{C}_{22}\text{H}_{22}\text{NOP}$: 347.1439; found: 347.1411 [M^+]. Enantiomeric excess was determined to be 98% by HPLC analysis (Chiralpak AD; 20.0% propan-2-ol in hexane, flow 1.0 mL min⁻¹, 12.9 min (major), 16.3 min (minor)); $[\alpha]_D^{28} = -65.2^{\circ}$ ($c = 0.43$ in MeOH). The corresponding free amine was assigned as (*S*) configuration as mentioned above.

N-(Diphenylphosphinyl)-1-phenylethylamine (**12e**):

^1H NMR (CDCl_3): δ = 1.57 (d, 3 H, $J=6.6$ Hz), 3.14–3.23 (m, 1 H), 4.31–4.47 (m, 1 H), 7.20–7.52 (m, 11 H), 7.77–7.96 (m, 4 H); ^{13}C NMR (CDCl_3): δ = 26.0, 51.0, 125.8, 127.0, 128.2 (d, $J_{\text{C},\text{P}}=12.4$ Hz), 128.3 (d, $J_{\text{C},\text{P}}=12.4$ Hz), 128.4, 131.6 (d, $J_{\text{C},\text{P}}=2.5$ Hz), 131.7 (d, $J_{\text{C},\text{P}}=2.5$ Hz), 131.8 (d, $J_{\text{C},\text{P}}=9.1$ Hz), 131.9 (d, $J_{\text{C},\text{P}}=130.2$ Hz), 132.3 (d, $J_{\text{C},\text{P}}=9.1$ Hz), 133.0 (d, $J_{\text{C},\text{P}}=127.7$ Hz), 144.9 (d, $J_{\text{C},\text{P}}=6.6$ Hz); IR (KBr): $\tilde{\nu}$ = 3431, 3165, 2974, 2869, 1437, 1181, 1126, 1109, 727, 692, 545 cm^{-1} ; m.p. 182.7–194.3 $^{\circ}\text{C}$; HRMS: m/z : calcd for $\text{C}_{20}\text{H}_{20}\text{NOP}$: 321.1283; found: 321.1263 [M^+]. Enantiomeric excess was determined to be 90% by HPLC analysis (Chiralpak AD; 10.0% propan-2-ol in hexane, flow 0.5 mL min⁻¹, 47.7 min (minor), 50.0 min (major)). The corresponding free amine was assigned as (*S*) configuration, $[\alpha]_D^{28} = -20.0^{\circ}$ ($c = 0.13$ in EtOH) (lit.^[69] $[\alpha]_D^{20} = -31.0^{\circ}$ ($c = 2.1$ in EtOH), (*S*)).

N-(Diphenylphosphinyl)-1-indanamine (**12f**):

^1H NMR (CDCl_3): δ = 1.87–1.99 (m, 1 H), 2.49–2.97 (m, 3 H), 3.24 (dd, 1 H, $J=6.3, 11.2$ Hz), 4.54–4.69 (m, 1 H), 7.14–7.27 (m, 3 H), 7.40–7.55 (m, 6 H), 7.67 (d, 1 H, $J=7.3$ Hz), 7.91–8.03 (m, 4 H); ^{13}C NMR (CDCl_3): δ = 30.0, 37.2 (d, $J_{\text{C},\text{P}}=4.1$ Hz), 56.8 (d, $J_{\text{C},\text{P}}=1.7$ Hz), 124.4, 126.6, 127.6, 128.4 (d, $J_{\text{C},\text{P}}=13.3$ Hz), 128.4 (d, $J_{\text{C},\text{P}}=12.4$ Hz), 131.68 (d, $J_{\text{C},\text{P}}=1.7$ Hz), 131.70 (d, $J_{\text{C},\text{P}}=2.5$ Hz), 132.0 (d, $J_{\text{C},\text{P}}=9.1$ Hz), 132.1 (d, $J_{\text{C},\text{P}}=9.1$ Hz), 132.4 (d, $J_{\text{C},\text{P}}=129.4$ Hz), 132.6 (d, $J_{\text{C},\text{P}}=125.2$ Hz), 142.6, 144.6 (d, $J_{\text{C},\text{P}}=6.6$ Hz); IR (KBr): $\tilde{\nu}$ = 3434, 3175, 1438, 1182, 1126, 1108, 1165, 744, 727 cm^{-1} ; m.p. 119.1–122.4 $^{\circ}\text{C}$; HRMS: m/z : calcd for $\text{C}_{21}\text{H}_{20}\text{NOP}$: 333.1283; found: 333.1284 [M^+]. Enantiomeric excess was determined to be 91% by HPLC analysis (Chiralpak AD; 20.0% propan-2-ol in hexane, flow 1.0 mL min⁻¹, 12.3 min (minor), 14.9 min (major); $[\alpha]_D^{30} = +36.5^{\circ}$ ($c = 0.663$ in MeOH). The corresponding free amine was assigned as *S* configuration, $[\alpha]_D^{30} = +9.9^{\circ}$ ($c = 0.19$ in MeOH) (lit.^[70] $[\alpha]_D^{20} = +15^{\circ}$ ($c = 1.7$ in MeOH), (*S*)).

N-(Diphenylphosphinyl)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ylamine (**12g**):

^1H NMR (CDCl_3): δ = 1.45–2.19 (m, 6 H), 2.57–2.86 (m, 2 H), 3.43 (dd, 1 H, $J=5.4, 10.7$ Hz), 4.37–4.52 (m, 1 H), 7.01–7.20 (m, 3 H), 7.22–7.56 (m, 7 H), 7.75–7.98 (m, 4 H); ^{13}C NMR (CDCl_3): δ = 27.3, 27.7, 36.1, 37.4, 55.5, 126.1, 126.9, 128.3 (d, $J_{\text{C},\text{P}}=11.6$ Hz), 128.4 (d, $J_{\text{C},\text{P}}=12.4$ Hz), 129.8, 131.6 (d, $J_{\text{C},\text{P}}=3.3$ Hz), 131.7 (d, $J_{\text{C},\text{P}}=9.1$ Hz), 131.7 (d, $J_{\text{C},\text{P}}=2.5$ Hz), 131.9 (d, $J_{\text{C},\text{P}}=140.1$ Hz), 133.2 (d, $J_{\text{C},\text{P}}=136.0$ Hz), 140.8, 143.0 (d, $J_{\text{C},\text{P}}=6.6$ Hz); IR (KBr): $\tilde{\nu}$ = 3432, 2098, 2923, 2858, 1438, 1198, 1182, 1112, 749, 720, 695, 537 cm^{-1} ; m.p. 214.7–215.0 $^{\circ}\text{C}$; HRMS: m/z : calcd for $\text{C}_{23}\text{H}_{24}\text{NOP}$: 361.1596; found: 361.1582 [M^+]. Enantiomeric excess was determined to be 94% by HPLC analysis (Chiralcel OD-H; 30.0% propan-2-ol in hexane, flow 0.5 mL min⁻¹, 9.9 min (major), 13.5 min (minor)); $[\alpha]_D^{30} = -40.8^{\circ}$ ($c = 0.556$ in MeOH).

N-(Diphenylphosphinyl)-6-methoxy-1,2,3,4-tetrahydro-1-naphthylamine (**12h**):

^1H NMR (CDCl_3): δ = 1.60–2.13 (m, 4 H), 2.57–2.88 (m, 2 H), 3.12–3.25 (m, 1 H), 3.76 (s, 3 H), 4.20–4.34 (m, 1 H), 6.56 (d, 1 H, $J=2.6$ Hz), 6.78 (dd, 1 H, $J=2.6, 8.6$ Hz), 7.37–7.53 (m, 6 H), 7.62 (d, 1 H, $J=8.6$ Hz), 7.89–8.00 (m, 4 H); ^{13}C NMR (CDCl_3): δ = 19.8, 29.5, 33.4 (d, $J_{\text{C},\text{P}}=2.5$ Hz), 49.2 (d, $J_{\text{C},\text{P}}=1.7$ Hz), 55.1, 112.5, 113.0, 128.3 (d, $J_{\text{C},\text{P}}=12.4$ Hz), 128.4 (d, $J_{\text{C},\text{P}}=12.4$ Hz), 130.3, 130.7 (d, $J_{\text{C},\text{P}}=7.5$ Hz), 131.6 (d, $J_{\text{C},\text{P}}=1.7$ Hz), 131.6 (d, $J_{\text{C},\text{P}}=2.5$ Hz), 132.0 (d, $J_{\text{C},\text{P}}=9.1$ Hz), 132.5 (d, $J_{\text{C},\text{P}}=127.8$ Hz), 132.9 (d, $J_{\text{C},\text{P}}=129.4$ Hz), 138.5, 158.2; IR (KBr): $\tilde{\nu}$ = 3210, 1607, 1500, 1436, 1255, 1181, 1107, 703, 529 cm^{-1} ; m.p. 156.1–157.3 $^{\circ}\text{C}$.

HRMS: *m/z*: calcd for C₂₃H₂₄NO₂P: 377.1545; found: 377.1521 [M⁺]. Enantiomeric excess was determined to be 99% by HPLC analysis (Chiralpak AD; 20.0% propan-2-ol in hexane, flow 1.0 mL min⁻¹, 15.2 min (minor), 18.5 min (major)); [α]_D²⁸ = -50.8° (*c* = 1.560 in MeOH).

N-(Diphenylphosphinyl)-chroman-4-ylamine (12i): ¹H NMR (CDCl₃): δ = 2.13–2.30 (m, 2H), 3.31 (dd, 1H, *J* = 6.9, 10.2 Hz), 4.10–4.41 (m, 3H), 6.74–6.79 (m, 1H), 6.89–6.97 (m, 1H), 7.10–7.18 (m, 1H), 7.39–7.58 (m, 7H), 7.89–8.04 (m, 4H); ¹³C NMR (CDCl₃): δ = 32.1 (d, J_{CP} = 2.5 Hz), 45.5, 63.2, 116.9, 120.6, 123.9, 124.0, 128.5, (d, J_{CP} = 13.3 Hz), 128.6, (d, J_{CP} = 13.3 Hz), 129.4, 131.8 (d, J_{CP} = 9.1 Hz), 131.9 (d, J_{CP} = 3.3 Hz), 131.9 (d, J_{CP} = 128.5 Hz), 132.1 (d, J_{CP} = 10.0 Hz), 132.6 (d, J_{CP} = 128.5 Hz), 154.6; IR (KBr): ν = 3432, 3196, 1438, 1177, 1126, 1077, 747, 701, 694, 533 cm⁻¹; m.p. 239.1–241.2°C; HRMS: *m/z*: calcd for C₂₁H₂₆NO₂P: 349.1232; found: 349.1223 [M⁺]. Enantiomeric excess was determined to be 92% by HPLC analysis (Chiralpak AD; 20.0% propan-2-ol in hexane, flow 1.0 mL min⁻¹, 9.8 min (minor), 11.4 min (major)); [α]_D²⁸ = -64.3° (*c* = 1.130 in CHCl₃).

Preparation of 1,3-diaryl-1,3-propanedione: 1,3-Diaryl-1,3-propanediones **14a** and **14d** are commercially available. 1,3-Diaryl-1,3-propanediones **14b**, **14c**, **14e**, **14f**, and **14g** were prepared by the conventional Claisen condensation reaction.

1,3-Bis(*p*-methylphenyl)-1,3-propanedione (14b): ¹H NMR (CDCl₃): δ = 2.43 (s, 6H), 6.82 (s, 1H), 7.29 (d, 4H, *J* = 8.3 Hz), 7.89 (d, 4H, *J* = 8.3 Hz); ¹³C NMR (CDCl₃): δ = 21.8, 92.4, 127.0, 129.3, 132.8, 143.0, 185.3; IR (KBr): ν = 1608, 1527, 1481, 1184, 1120, 1014, 773 cm⁻¹; m.p. 127.0–127.4°C; elemental analysis calcd (%) for C₁₇H₁₆O₂: C 80.93, H 6.39; found: C 80.76, H 6.32.

1,3-Bis(*p*-tert-butylphenyl)-1,3-propanedione (14c): ¹H NMR (CDCl₃): δ = 1.36 (s, 18H), 6.82 (s, 1H), 7.50 (d, 2H, *J* = 8.2 Hz), 7.92 (d, 2H, *J* = 8.2 Hz); ¹³C NMR (CDCl₃): δ = 31.2, 35.2, 92.6, 125.5, 126.9, 132.8, 155.9, 185.3; IR (KBr): ν = 2960, 1606, 1495, 1362, 1296, 1109, 796, 546 cm⁻¹; m.p. 107.3–107.7°C; elemental analysis calcd (%) for C₂₃H₂₈O₂: C 82.10, H 8.39; found: C 82.00, H 8.37.

1,3-Bis(*p*-fluorophenyl)-1,3-propanedione (14e): ¹H NMR (CDCl₃): δ = 6.75 (s, 1H), 7.11–7.24 (m, 4H), 7.93–8.12 (m, 4H); ¹³C NMR (CDCl₃): δ = 92.5, 115.8 (d, J_{CF} = 21.6 Hz), 129.5 (d, J_{CF} = 9.1 Hz), 131.5 (d, J_{CF} = 3.3 Hz), 165.3 (d, J_{CF} = 253.7 Hz), 184.3; IR (KBr): ν = 1599, 1481, 1223, 1157, 850, 785, 567, 488 cm⁻¹; m.p. 171.8–172.0°C; HRMS: *m/z*: calcd for C₁₅H₁₀O₂F₂: 260.0649; found: 260.0675 [M⁺].

1,3-Bis(*o*-fluorophenyl)-1,3-propanedione (14f): ¹H NMR (CDCl₃): δ = 7.07 (s, 1H), 7.10–7.21 (m, 2H), 7.22–7.33 (m, 2H), 7.44–7.56 (m, 2H), 7.94–8.04 (m, 2H); ¹³C NMR (CDCl₃): δ = 102.4, 116.6 (d, J_{CF} = 23.2 Hz), 123.7 (d, J_{CF} = 9.7 Hz), 124.4 (d, J_{CF} = 4.1 Hz), 130.1 (d, J_{CF} = 1.6 Hz), 133.7 (d, J_{CF} = 9.1 Hz), 161.1 (d, J_{CF} = 256.3 Hz), 182.1; IR (KBr): ν = 1612, 1487, 1219, 1153, 820, 762, 602 cm⁻¹; m.p. 101.6–102.6°C; HRMS: *m/z*: calcd for C₁₅H₁₀O₂F₂: 260.0649; found: 260.0618 [M⁺].

1,3-Bis(2-naphthyl)-1,3-propanedione (14g): ¹H NMR (CDCl₃): δ = 7.17 (s, 1H), 7.53–7.66 (m, 4H), 7.87–8.12 (m, 8H), 8.60 (s, 2H); ¹³C NMR (CDCl₃): δ = 93.8, 123.2, 126.7, 127.7, 128.1, 128.3, 128.4, 129.3, 132.66, 132.73, 135.2, 185.3; IR (KBr): ν = 1599, 1523, 1496, 1429, 1190, 951, 789, 478 cm⁻¹; m.p. 171.8–172.0°C; HRMS: *m/z*: calcd for C₂₃H₁₆O₂: 324.1150; found: 324.1156 [M⁺].

Typical procedure for enantioselective reduction of 1,3-diaryl-1,3-propanedione: Under a dry nitrogen atmosphere in a vessel at -20°C, ethanol (0.13 mL, 2.25 mmol) and tetrahydrofurfuryl alcohol (THFA, 1.0 mL, 10.5 mmol) were added to the suspension of NaBH₄ (28 mg, 0.75 mmol) in CHCl₃ (22 mL). After 15 min, to the solution was added a CHCl₃ solution (4 mL) of a cobalt catalyst (complex (S,S)-**3b**, 1.4 mg, 0.0025 mmol) and then dibenzoylmethane (56 mg, 0.25 mmol) in CHCl₃ (4 mL) was added and stirred for 40 h at -20°C. The reaction was quenched by pH 7 buffer solution and the crude products were extracted with CH₂Cl₂. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After evaporation, the residue was purified by silica gel column chromatography (hexane/AcOEt) to give (1S,3S)-1,3-diphenyl-1,3-propanediol in quantitative yield. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD, Hexane/EtOH) to be 98%. The ratio of *dl/meso* was determined by ¹H NMR analysis of the corresponding diacetate after treatment with Ac₂O/pyridine to be 84:16.

dl-1,3-Diphenyl-1,3-propanediol (15a):^[33c] HPLC: Daicel Chiralpak AD (5% ethanol in hexane, flow 1.0 mL min⁻¹), 25.9 min (*meso*), 29.4 min (minor), 46.6 min (major).

dl-1,3-Bis(*p*-methylphenyl)-1,3-propanediol (15b): ¹H NMR (CDCl₃): δ = 2.16 (t, 2H, *J* = 5.2 Hz), 2.35 (s, 6H), 2.72 (d, 2H, *J* = 5.2 Hz), 4.94 (q, 2H, *J* = 5.2 Hz), 7.15–7.17 (m, 4H), 7.24–7.26 (m, 4H); ¹³C NMR (CDCl₃): δ = 21.2, 46.4, 71.6, 125.5, 129.1, 137.0, 141.1; IR (KBr): ν = 3562, 2939, 1512, 1063, 812, 517 cm⁻¹; m.p. 108.9–109.4°C; HRMS: *m/z*: calcd for C₁₇H₂₀O₂: 256.1463; found: 256.1444 [M⁺]. HPLC: Daicel chiralpak AD (1 mL min⁻¹, 5% propan-2-ol in hexane), 25.9 min (*meso*), 29.4 min (minor), 46.6 min (major); [α]_D²³ = -27.6° (*c* = 0.56 in CHCl₃).

dl-1,3-Bis(*p*-tert-butylphenyl)-1,3-propanediol (15c): ¹H NMR (CDCl₃): δ = 1.32 (s, 18H), 2.19 (t, 2H, *J* = 5.1 Hz), 2.66 (d, 2H, *J* = 5.1 Hz), 4.98 (q, 2H, *J* = 5.1 Hz), 7.29–7.31 (m, 4H), 7.37–7.39 (m, 4H); ¹³C NMR (CDCl₃): δ = 31.4, 34.6, 46.3, 71.5, 125.3, 141.1, 150.3; IR (KBr): ν = 3450, 2962, 1363, 1269, 1049, 823, 588 cm⁻¹; m.p. 174.1–176.3°C; HRMS: *m/z*: calcd for C₂₃H₃₂O₂: 340.2402; found: 340.2411 [M⁺]. HPLC: Daicel chiralpak AD (1 mL min⁻¹, 2% ethanol in hexane), 31.0 min (*meso*), 49.4 min (minor), 55.9 min (major); [α]_D²³ = -16.9° (*c* = 1.01 in CHCl₃).

dl-1,3-Bis(*p*-methoxylphenyl)-1,3-propanediol (15d): ¹H NMR (CDCl₃): δ = 2.14 (t, 2H, *J* = 4.9 Hz), 2.72 (d, 2H, *J* = 4.9 Hz), 3.81 (s, 6H), 4.91 (q, 2H, *J* = 4.9 Hz), 6.88 (d, 4H, *J* = 8.5 Hz), 7.28 (d, 4H, *J* = 8.5 Hz); ¹³C NMR (CDCl₃): δ = 46.4, 55.3, 71.3, 113.7, 126.8, 136.2, 158.8; IR (KBr): ν = 3357, 2949, 1612, 1512, 1250, 1039, 822 cm⁻¹; m.p. 79.7–81.3°C; HRMS: *m/z*: calcd for C₁₇H₂₀O₄: 288.1361; found: 288.1405 [M⁺]. HPLC: Daicel chiralpak AD (1 mL min⁻¹, 4% 2-propanol in hexane), 90.0 min (*meso*), 98.1 min (minor), 118.5 min (major); [α]_D²³ = -20.7° (*c* = 0.86 in CHCl₃).

dl-1,3-Bis(*p*-fluorophenyl)-1,3-propanediol (15e): ¹H NMR (CDCl₃): δ = 2.12 (t, 2H, *J* = 5.0 Hz), 2.76 (d, 2H, *J* = 5.0 Hz), 4.97 (q, 2H, *J* = 5.0 Hz), 6.99–7.09 (m, 4H), 7.29–7.38 (m, 4H); ¹³C NMR (CDCl₃): δ = 46.6, 71.1, 115.3 (d, J_{CF} = 21.6 Hz), 127.1 (d, J_{CF} = 7.5 Hz), 139.7 (d, J_{CF} = 3.3 Hz), 162.0 (d, J_{CF} = 245.5 Hz); IR (KBr): ν = 3421, 3301, 2943, 1604, 1152, 1221, 831, 553 cm⁻¹; m.p. 122.0–123.5°C; HRMS: *m/z*: calcd for C₁₅H₁₄F₂O₂: 264.0962; found: 264.0951 [M⁺]. HPLC after acetylation: Daicel chiralpak AD (1 mL min⁻¹, 2% ethanol in hexane), 11.4 min (major), 15.1 min (*meso*), 22.2 min (minor); [α]_D²³ = -52.3° (*c* = 0.61 in CHCl₃).

dl-1,3-Bis(*o*-fluorophenyl)-1,3-propanediol (15f): ¹H NMR (CDCl₃): δ = 2.27 (t, 2H, *J* = 5.4 Hz), 2.91 (d, 2H, *J* = 5.4 Hz), 5.29 (q, 2H, *J* = 5.4 Hz), 6.97–7.05 (m, 2H), 7.14–7.20 (m, 2H), 7.21–7.30 (m, 2H), 7.52–7.61 (m, 2H); ¹³C NMR (CDCl₃): δ = 43.2, 66.4, 115.2 (d, J_{CF} = 21.6 Hz), 124.1 (d, J_{CF} = 3.3 Hz), 127.1 (d, J_{CF} = 4.1 Hz), 128.8 (d, J_{CF} = 8.3 Hz), 130.7 (d, J_{CF} = 13.3 Hz), 159.2 (d, J_{CF} = 244.6 Hz); IR (KBr): ν = 3462, 3348, 1493, 1219, 1049, 752 cm⁻¹; m.p. 79.6–80.6°C; HRMS: *m/z*: calcd for C₁₅H₁₄F₂O₂: 264.0962; found: 264.0959 [M⁺]. HPLC: Daicel chiralpak AD (1 mL min⁻¹, 5% ethanol in hexane), 18.4 min (*meso*), 22.3 min (minor), 38.9 min (major); [α]_D²³ = -47.2° (*c* = 0.29 in CHCl₃).

dl-1,3-Bis(2-naphthyl)-1,3-propanediol (15g): ¹H NMR (CDCl₃): δ = 2.38 (t, 2H, *J* = 4.9 Hz), 3.00 (d, 2H, *J* = 4.9 Hz), 5.19 (q, 2H, *J* = 4.9 Hz), 7.43–7.50 (m, 6H), 7.79–7.87 (m, 8H); ¹³C NMR (CDCl₃): δ = 46.1, 72.1, 123.8, 124.2, 125.8, 126.2, 127.6, 127.9, 128.3, 132.3, 141.4; IR (KBr): ν = 3390, 3311, 3053, 1398, 1034, 814 cm⁻¹; m.p. 198.5–200.2°C; HRMS: *m/z*: calcd for C₂₃H₂₀O₂: 328.1463; found: 328.1450 [M⁺]. HPLC after acetylation: Daicel chiralpak AD (1 mL min⁻¹, 10% ethanol in hexane), 13.5 min (major), 15.1 min (*meso*), 44.7 min (minor); [α]_D²³ = 47.1° (*c* = 0.13 in CHCl₃).

Typical procedure for multigram preparation of optically pure 1,3-diaryl-1,3-diols: Ethanol (15.5 mL, 268 mmol) and tetrahydrofurfuryl alcohol (90.7 mL, 936 mmol) were added at -20°C to the suspension of NaBH₄ (5.06 g, 134 mmol) and CHCl₃ (350 mL). After stirring for 15 min, to the solution was added a CHCl₃ solution (25 mL) of cobalt catalyst (complex (S,S)-**3a**, 500 mg, 0.64 mmol) and then dibenzoylmethane (10.0 g, 44.6 mmol) in CHCl₃ (25 mL). The solution was stirred for 3 d at -20°C. The reaction mixture was quenched by pH 7 buffer solution and extracted with CH₂Cl₂. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. Solvent and tetrahydrofurfuryl alcohol were removed under reduced pressure. The crude products were rinsed with ethyl acetate/hexane and recrystallized from ethyl acetate to obtain the optically pure (1S,3S)-1,3-diphenyl-1,3-propanediol (6.15 g, 60%). Optically pure 1,3-diaryl-1,3-propanediols were quantitatively converted to the corresponding 1,3-diamines without racemization.^[40]

Preparation of 1,1'-diacylferrrocenes: 1,1'-Diacylferrrocenes were prepared by the conventional Friedel-Crafts reaction from ferrocene and acyl chlorides.^[37c]

1,1'-Dibenzoylferrocene (16a):^[37c] ^1H NMR (CDCl_3): $\delta = 4.56\text{--}4.62$ (m, 4H), 4.90–4.96 (m, 4H), 7.39–7.46 (m, 4H), 7.51–7.58 (m, 2H), 7.76–7.82 (m, 4H).

1,1'-Bis(*p*-fluorobenzoyl)ferrocene (16b):^[37c] ^1H NMR (CDCl_3): $\delta = 4.57\text{--}4.61$ (m, 4H), 4.86–4.90 (m, 4H), 7.06–7.14 (m, 4H), 7.77–7.84 (m, 4H).

1,1'-Bis(*p*-chlorobenzoyl)ferrocene (16c): ^1H NMR (CDCl_3): $\delta = 4.58\text{--}4.61$ (m, 4H), 4.85–4.88 (m, 4H), 7.37–7.42 (m, 4H), 7.67–7.72 (m, 4H); ^{13}C NMR (CDCl_3): $\delta = 73.2, 74.5, 79.4, 128.5, 129.4, 137.1, 138.3, 196.3$; IR (KBr): $\tilde{\nu} = 1631, 1444, 1288, 1087, 836, 763 \text{ cm}^{-1}$; m.p. 187.4–187.7°C; elemental analysis calcd (%) for $\text{C}_{24}\text{H}_{16}\text{O}_2\text{Cl}_2\text{Fe}$: C 62.24, H 3.48; found: C 61.99, H 3.26.

1,1'-Bis(*p*-bromobenzoyl)ferrocene (16d): ^1H NMR (CDCl_3): $\delta = 4.58\text{--}4.62$ (m, 4H), 4.84–4.88 (m, 4H), 7.54–7.58 (m, 4H), 7.60–7.64 (m, 4H); ^{13}C NMR (CDCl_3): $\delta = 73.2, 74.5, 79.3, 126.9, 129.5, 131.5, 137.5, 196.4$; IR (KBr): $\tilde{\nu} = 1631, 1442, 1286, 1010, 835, 760, 504 \text{ cm}^{-1}$; m.p. 196.3–197.2°C; elemental analysis calcd (%) for $\text{C}_{24}\text{H}_{16}\text{O}_2\text{Br}_2\text{Fe}$: C 52.22, H 2.92; found: C 52.04, H 3.16.

1,1'-Bis(*p*-methylbenzoyl)ferrocene (16e): ^1H NMR (CDCl_3): $\delta = 2.43$ (s, 6H), 4.54–4.57 (m, 4H), 4.89–4.92 (m, 4H), 7.20–7.24 (m, 4H), 7.69–7.74 (m, 4H); ^{13}C NMR (CDCl_3): $\delta = 21.7, 73.1, 74.5, 79.7, 128.3, 128.9, 136.3, 142.4, 197.3$; IR (KBr): $\tilde{\nu} = 1628, 1446, 1288, 1165, 760, 505 \text{ cm}^{-1}$; m.p. 178.5–178.9°C; elemental analysis calcd (%) for $\text{C}_{26}\text{H}_{22}\text{O}_2\text{Fe}$: C 73.95, H 5.25; found: C 73.82, H 5.06.

1,1'-Bis(*o*-fluorobenzoyl)ferrocene (16f): ^1H NMR (CDCl_3): $\delta = 4.61\text{--}4.64$ (m, 4H), 4.82–4.85 (m, 4H), 7.09–7.16 (m, 2H), 7.18–7.23 (m, 2H), 7.44–7.52 (m, 4H); ^{13}C NMR (CDCl_3): $\delta = 72.5, 75.0, 79.8, 116.3$ (d, $J_{\text{C},\text{F}} = 21.6 \text{ Hz}$), 123.9 (d, $J_{\text{C},\text{F}} = 4.2 \text{ Hz}$), 128.0 (d, $J_{\text{C},\text{F}} = 15.8 \text{ Hz}$), 129.1 (d, $J_{\text{C},\text{F}} = 3.3 \text{ Hz}$), 132.3 (d, $J_{\text{C},\text{F}} = 8.3 \text{ Hz}$), 159.1 (d, $J_{\text{C},\text{F}} = 251.3 \text{ Hz}$), 195.1; IR (KBr): $\tilde{\nu} = 1638, 1455, 1301, 836, 754, 649, 492 \text{ cm}^{-1}$; m.p. 154.3–154.8°C; HRMS: m/z : calcd for $\text{C}_{24}\text{H}_{16}\text{O}_2\text{F}_2\text{Fe}$: 430.0468; found: 430.0438 [M^+].

1,1'-Bis(*o*-chlorobenzoyl)ferrocene (16g): ^1H NMR (CDCl_3): $\delta = 4.68\text{--}4.71$ (m, 4H), 4.80–4.83 (m, 4H), 7.30–7.36 (m, 2H), 7.39–7.42 (m, 4H), 7.44–7.47 (m, 2H); ^{13}C NMR (CDCl_3): $\delta = 72.4, 74.7, 79.7, 126.3, 128.7, 130.3, 130.9, 131.1, 138.5, 197.3$; IR (KBr): $\tilde{\nu} = 1638, 1447, 1297, 1064, 837, 755 \text{ cm}^{-1}$; m.p. 162.2–162.4°C; elemental analysis calcd (%) for $\text{C}_{24}\text{H}_{16}\text{O}_2\text{Cl}_2\text{Fe}$: C 62.24, H 3.48; found: C 62.14, H 3.43.

1,1'-Bis(*o*-bromobenzoyl)ferrocene (16h): ^1H NMR (CDCl_3): $\delta = 4.70\text{--}4.73$ (m, 4H), 4.81–4.84 (m, 4H), 7.30–7.41 (m, 4H), 7.44–7.48 (m, 2H), 7.58–7.62 (m, 2H); ^{13}C NMR (CDCl_3): $\delta = 72.5, 74.7, 79.5, 119.4, 126.9, 128.8, 131.2, 133.5, 140.4, 198.2$; IR (KBr): $\tilde{\nu} = 1650, 1444, 1291, 1036, 839, 742 \text{ cm}^{-1}$; m.p. 196.0–196.7°C; elemental analysis calcd (%) for $\text{C}_{24}\text{H}_{16}\text{O}_2\text{Br}_2\text{Fe}$: C 52.22, H 2.92; found: C 52.07, H 2.96.

1,1'-Dipropanoylferrocene (16i): ^1H NMR (CDCl_3): $\delta = 1.19$ (t, 6H, $J = 7.3 \text{ Hz}$), 2.68 (q, 4H, $J = 7.3 \text{ Hz}$), 4.44–4.49 (m, 4H), 4.75–4.80 (m, 4H); ^{13}C NMR (CDCl_3): $\delta = 8.2, 33.0, 70.4, 73.2, 80.2, 203.8$; IR (KBr): $\tilde{\nu} = 2935, 1673, 1458, 1243, 1102, 1050, 808 \text{ cm}^{-1}$; m.p. 53.8–55.2°C; elemental analysis calcd (%) for $\text{C}_{16}\text{H}_{18}\text{O}_2\text{Fe}$: C 64.45, H 6.08; found: C 64.53, H 6.12.

1,1'-Dibutanoylferrocene (16j): ^1H NMR (CDCl_3): $\delta = 1.01$ (t, 6H, $J = 7.3 \text{ Hz}$), 1.73 (sextet, 4H, $J = 7.3 \text{ Hz}$), 2.64 (t, 4H, $J = 7.3 \text{ Hz}$), 4.47–4.50 (m, 4H), 4.76–4.79 (m, 4H); ^{13}C NMR (CDCl_3): $\delta = 14.0, 17.7, 41.8, 70.5, 73.3, 80.4, 203.3$; IR (KBr): $\tilde{\nu} = 2968, 1662, 1456, 1242, 840, 507 \text{ cm}^{-1}$; m.p. 75.7–76.4°C; elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{22}\text{O}_2\text{Fe}$: C 66.27, H 6.80; found: C 66.28, H 6.57.

1,1'-Dihexanoylferrocene (16k):^[37c] ^1H NMR (CDCl_3): $\delta = 0.93$ (t, 6H, $J = 6.6 \text{ Hz}$), 1.31–1.43 (m, 8H), 1.70 (quintet, 4H, $J = 7.3 \text{ Hz}$), 2.65 (t, 4H, $J = 7.3 \text{ Hz}$), 4.45–4.51 (m, 4H), 4.74–4.80 (m, 4H).

1,1'-Diocanoylferrocene (16l): ^1H NMR (CDCl_3): $\delta = 0.90$ (t, 6H, $J = 7.1 \text{ Hz}$), 1.22–1.43 (m, 16H), 1.67 (quintet, 4H, $J = 7.3 \text{ Hz}$), 2.65 (t, 4H, $J = 7.3 \text{ Hz}$), 4.46–4.49 (m, 4H), 4.76–4.79 (m, 4H); ^{13}C NMR (CDCl_3): $\delta = 14.1, 22.7, 24.4, 29.2, 29.5, 31.8, 40.0, 70.5, 73.3, 80.4, 203.6$; IR (KBr): $\tilde{\nu} = 2925, 1681, 1464, 1241, 824 \text{ cm}^{-1}$; m.p. 55.8–57.5°C; elemental analysis calcd (%) for $\text{C}_{26}\text{H}_{38}\text{O}_2\text{Fe}$: C 71.23, H 8.74; found: C 71.42, H 8.63.

Typical procedure of the stereoselective reduction of 1,1'-diacylferrocenes

Preparation of the modified borohydride solution: EtOH (0.11 mL, 2 mmol) and tetrahydrofurfuryl alcohol (THFA) (2.71 mL, 28 mmol) were added at 0°C under a dry nitrogen atmosphere to a suspension of NaBH_4 (75.7 mg, 2 mmol) in CHCl_3 (13.3 mL). The mixture was stirred for 3 h at 0°C and then cooled at –20°C.

Enantio- and diastereoselective reduction of the 1,1'-dibenzoylferrocene (16a): 1,1'-Dibenzoylferrocene (16a) (0.125 mmol) and (S,S)-cobalt complex catalyst **3b** (3.6 mg, 0.00625 mmol, 5.0 mol % against 1,1'-dibenzoylferrocene) were dissolved in Et_2O (10 mL) and cooled to 0°C under a dry nitrogen atmosphere. The modified borohydride solution (4 mL, 0.5 mmol) was added to the reaction mixture and stirred for 0.5 h at 0°C. The reaction was quenched by drop-wise addition of ice-cold water (10 mL). The reaction mixture was extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation, the residue was purified by silica gel column chromatography (hexane/AcOEt) to afford the corresponding 1,1'-ferrocenyl diols **17a** and *meso*-form. The *dl/meso* selectivity was determined by ^{13}C NMR analysis and the enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, propan-2-ol/hexane).

dl-1,1'-Bis(α -hydroxyphenylmethyl)ferrocene (17a):^[37c] HPLC: Daicel Chiralpak AD-H (10% propan-2-ol in hexane, flow 1.0 mL min^{−1}), 9.6 min (minor), 11.2 min (major), 12.6 min (*meso*).

dl-1,1'-Bis(α -hydroxy-*p*-fluorophenylmethyl)ferrocene (17b):^[37c] HPLC: Daicel Chiralpak AD-H (10% propan-2-ol in hexane, flow 0.5 mL min^{−1}), 21.1 min (minor), 25.9 min (*meso*), 31.9 min (major).

dl-1,1'-Bis(α -hydroxy-*p*-chlorophenylmethyl)ferrocene (17c): ^1H NMR (CDCl_3): $\delta = 4.12\text{--}4.19$ (m, 4H), 4.21–4.30 (m, 4H), 4.34–4.38 (m, 2H), 5.49 (s, 2H), 7.17–7.24 (m, 8H); ^{13}C NMR (CDCl_3): $\delta = 66.5, 66.8, 68.1, 68.4, 72.1, 93.2, 127.4, 128.3, 128.4, 133.2, 142.5$; IR (KBr): $\tilde{\nu} = 3267, 1289, 1012, 811, 517 \text{ cm}^{-1}$; m.p. 130.8–132.1°C; elemental analysis calcd (%) for $\text{C}_{24}\text{H}_{20}\text{O}_2\text{Cl}_2\text{Fe}$: C 61.70, H 4.32; found: C 61.99, H 4.39. HPLC: Daicel Chiralcel OD-H (10% propan-2-ol in hexane, flow 1.0 mL min^{−1}), 7.0 min (minor), 7.6 min (major), 9.1 min (*meso*); $[\alpha]_D^{23} = -34.1^\circ$ ($c = 0.73$ in CHCl_3).

dl-1,1'-Bis(α -hydroxy-*p*-bromophenylmethyl)ferrocene (17d): ^1H NMR (CDCl_3): $\delta = 4.12\text{--}4.17$ (m, 4H), 4.21–4.26 (m, 2H), 4.33–4.37 (m, 2H), 4.52–4.58 (m, 2H), 5.44 (s, 2H), 7.08–7.14 (m, 4H), 7.32–7.37 (m, 4H); ^{13}C NMR (CDCl_3): $\delta = 66.5, 66.7, 68.1, 68.4, 72.1, 93.1, 121.3, 127.7, 131.3, 143.0$; IR (KBr): $\tilde{\nu} = 3281, 1486, 1009, 756, 494 \text{ cm}^{-1}$; m.p. 129.6–130.3°C; elemental analysis calcd (%) for $\text{C}_{24}\text{H}_{20}\text{O}_2\text{Br}_2\text{Fe}$: C 51.84, H 3.63; found: C 51.65, H 3.64. HPLC: Daicel Chiralcel OD-H (10% propan-2-ol in hexane, flow 1.0 mL min^{−1}), 8.3 min (minor), 10.9 min (major), 15.3 min (*meso*); $[\alpha]_D^{23} = -39.2^\circ$ ($c = 2.08$ in CHCl_3).

dl-1,1'-Bis(α -hydroxy-*p*-methylphenylmethyl)ferrocene (17e): ^1H NMR (CDCl_3): $\delta = 2.29$ (s, 6H), 3.68 (br, 2H), 4.12–4.15 (m, 2H), 4.16–4.19 (m, 2H), 4.21–4.24 (m, 2H), 4.38–4.42 (m, 2H), 5.55 (s, 2H), 7.06–7.10 (m, 4H), 7.19–7.23 (m, 4H); ^{13}C NMR (CDCl_3): $\delta = 21.1, 66.7, 66.8, 67.9, 68.2, 72.6, 93.7, 126.1, 128.9, 137.0, 141.4$; IR (KBr): $\tilde{\nu} = 3253, 1511, 1015, 806, 529 \text{ cm}^{-1}$; m.p. 129.5–130.5°C; elemental analysis calcd (%) for $\text{C}_{26}\text{H}_{20}\text{O}_2\text{Fe}$: C 73.25, H 6.15; found: C 73.08, H 5.95. HPLC: Daicel Chiralpak AD-H (10% propan-2-ol in hexane, flow 1.0 mL min^{−1}), 11.5 min (major), 15.1 min (*meso*), 16.9 min (minor); $[\alpha]_D^{23} = -13.5^\circ$ ($c = 0.66$ in CHCl_3).

dl-1,1'-Bis(α -hydroxy-*o*-fluorophenylmethyl)ferrocene (17f): ^1H NMR (CDCl_3): $\delta = 4.10\text{--}4.15$ (m, 2H), 4.20–4.27 (m, 4H), 4.32–4.38 (m, 2H), 4.39–4.44 (m, 2H), 5.88 (s, 2H), 6.86–6.96 (m, 2H), 6.99–7.08 (m, 2H), 7.10–7.19 (m, 2H), 7.32–7.41 (m, 2H); ^{13}C NMR (CDCl_3): $\delta = 66.0$ (d, $J_{\text{C},\text{F}} = 3.3 \text{ Hz}$), 66.8 (d, $J_{\text{C},\text{F}} = 11.6 \text{ Hz}$), 68.1 (d, $J_{\text{C},\text{F}} = 21.6 \text{ Hz}$), 92.6, 115.1 (d, $J_{\text{C},\text{F}} = 21.6 \text{ Hz}$), 124.1 (d, $J_{\text{C},\text{F}} = 3.3 \text{ Hz}$), 127.3 (d, $J_{\text{C},\text{F}} = 4.1 \text{ Hz}$), 128.8 (d, $J_{\text{C},\text{F}} = 8.3 \text{ Hz}$), 131.2 (d, $J_{\text{C},\text{F}} = 13.3 \text{ Hz}$), 159.5 (d, $J_{\text{C},\text{F}} = 245.5 \text{ Hz}$); IR (KBr): $\tilde{\nu} = 3271, 1485, 1221, 1044, 756, 494 \text{ cm}^{-1}$; m.p. 132.6–133.3°C; HRMS: m/z : calcd for $\text{C}_{24}\text{H}_{20}\text{O}_2\text{F}_2\text{Fe}$: 434.0781; found: 434.0786 [M^+]. HPLC: Daicel Chiralpak AD-H (10% propan-2-ol in hexane, flow 0.5 mL min^{−1}), 16.7 min (major), 18.8 min (minor), 23.8 min (*meso*); $[\alpha]_D^{23} = -31.2^\circ$ ($c = 1.75$ in CHCl_3).

dl-1,1'-Bis(α -hydroxy-*o*-chlorophenylmethyl)ferrocene (17g): ^1H NMR (CDCl_3): $\delta = 4.10\text{--}4.17$ (m, 2H), 4.22–4.30 (m, 2H), 4.33–4.46 (m, 4H), 4.60–4.68 (m, 2H), 5.99 (s, 2H), 7.06–7.14 (m, 2H), 7.14–7.28 (m, 4H), 7.41–7.49 (m, 2H); ^{13}C NMR (CDCl_3): $\delta = 66.8, 66.9, 68.0, 68.2, 68.6, 92.7, 127.0, 127.6, 128.5, 129.1, 131.9, 141.3$; IR (KBr): $\tilde{\nu} = 3271, 1469, 1434, 1016, 821, 747 \text{ cm}^{-1}$; m.p. 159.9–160.6°C; elemental analysis calcd (%) for $\text{C}_{24}\text{H}_{20}\text{O}_2\text{Cl}_2\text{Fe}$: C 61.70, H 4.32; found: C 61.71, H 4.09. HPLC: Daicel Chiralpak AD-H (5% propan-2-ol in hexane, flow 1.0 mL min^{−1}), 12.2 min (minor), 13.1 min (major), 15.5 min (*meso*); $[\alpha]_D^{23} = -47.3^\circ$ ($c = 1.61$ in CHCl_3).

dl-1,1'-Bis(α-hydroxy-o-bromophenylmethyl)ferrocene (17h): ^1H NMR (CDCl_3): $\delta = 3.94 - 3.99$ (m, 2H), 4.14–4.19 (m, 2H), 4.26–4.30 (m, 2H), 4.39–4.45 (m, 4H), 6.00 (s, 2H), 7.03–7.10 (m, 2H), 7.21–7.28 (m, 2H), 7.44–7.49 (m, 4H); ^{13}C NMR (CDCl_3): $\delta = 67.0, 67.2, 68.0, 68.4, 71.2, 92.8, 122.3, 127.7, 128.1, 128.9, 132.5, 143.0$; IR (KBr): $\tilde{\nu} = 3284, 1467, 1434, 1015, 745 \text{ cm}^{-1}$; m.p. 150.4–151.3 °C; elemental analysis calcd (%) for $\text{C}_{24}\text{H}_{20}\text{O}_2\text{Br}_2\text{Fe}$: C 51.84, H 3.63; found: C 51.58, H 3.61. HPLC: Daicel Chiralpak AD-H (10% propan-2-ol in hexane, flow 0.5 mL min⁻¹), 13.2 min (minor), 15.5 min (major), 17.9 min (*meso*); $[\alpha]_D^{23} = -10.6^\circ$ ($c = 0.72$ in CHCl_3).

dl-1,1'-Bis(α-hydroxypropyl)ferrocene (17i): ^1H NMR (CDCl_3): $\delta = 0.90$ (t, 6H, $J = 7.3$ Hz), 1.52–1.72 (m, 4H), 3.65 (br, 2H), 4.10–4.18 (m, 6H), 4.20–4.24 (m, 2H), 4.40 (t, 2H, $J = 6.3$ Hz); ^{13}C NMR (CDCl_3): $\delta = 9.9, 32.7, 66.2, 66.6, 67.48, 67.51, 71.4, 93.7$; IR (neat): $\tilde{\nu} = 3340, 2965, 1463, 1036, 810, 489 \text{ cm}^{-1}$; elemental analysis calcd (%) for $\text{C}_{16}\text{H}_{22}\text{O}_2\text{Fe}$: C 63.59, H 7.34; found: C 63.83, H 7.31. HPLC: Daicel Chiralpak AD-H (10% Ethanol in hexane, flow 1.0 mL min⁻¹), 7.2 min (minor), 14.9 min (*meso*), 25.3 min (major); $[\alpha]_D^{23} = +49.9^\circ$ ($c = 1.33$ in CHCl_3).

dl-1,1'-Bis(α-hydroxybutyl)ferrocene (17j): ^1H NMR (CDCl_3): $\delta = 0.89$ (t, 6H, $J = 7.3$ Hz), 1.24–1.72 (m, 8H), 3.26 (br, 2H), 4.11–4.19 (m, 6H), 4.20–4.24 (m, 2H), 4.44 (dd, 2H, $J = 5.4, 7.3$ Hz); ^{13}C NMR (CDCl_3): $\delta = 14.0, 18.9, 42.1, 66.1, 66.5, 67.51, 67.55, 69.9, 94.2$; IR (neat): $\tilde{\nu} = 3339, 2957, 1465, 1020, 810, 488 \text{ cm}^{-1}$; elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{26}\text{O}_2\text{Fe}$: C 65.47, H 7.94; found: C 65.43, H 7.88. HPLC: Daicel Chiralpak AD-H (10% Ethanol in hexane, flow 1.0 mL min⁻¹), 6.6 min (minor), 13.5 min (*meso*), 24.4 min (major); $[\alpha]_D^{23} = +33.9^\circ$ ($c = 1.29$ in CHCl_3).

dl-1,1'-Bis(α-hydroxyhexyl)ferrocene (17k):^[37c] HPLC: Daicel Chiralpak AD-H (2% Ethanol in hexane, flow 1.0 mL min⁻¹), 13.8 min (minor), 28.2 min (major), 33.8 min (*meso*).

dl-1,1'-Bis(α-hydroxyoctyl)ferrocene (17l): ^1H NMR (CDCl_3): $\delta = 0.87$ (t, 6H, $J = 6.8$ Hz), 1.08–1.46 (m, 20H), 1.48–1.70 (m, 4H), 3.27 (br, 2H), 4.10–4.17 (m, 6H), 4.19–4.22 (m, 2H), 4.43 (dd, 2H, $J = 5.6, 7.1$ Hz); ^{13}C NMR (CDCl_3): $\delta = 14.1, 22.7, 25.7, 29.3, 29.6, 31.9, 40.0, 66.1, 66.6, 67.50, 67.54, 71.1, 94.2$; IR (neat): $\tilde{\nu} = 3339, 2926, 1465, 1044, 809, 488 \text{ cm}^{-1}$; elemental analysis calcd (%) for $\text{C}_{26}\text{H}_{42}\text{O}_2\text{Fe}$: C 70.58, H 9.57; found: C 70.48, H 9.28. HPLC: Daicel Chiralpak AD-H (2% Ethanol in hexane, flow 1.0 mL min⁻¹), 11.0 min (minor), 18.1 min (major), 21.6 min (*meso*); $[\alpha]_D^{23} = +16.4^\circ$ ($c = 1.55$ in CHCl_3).

Preparation of 1,3-diaryl-2-alkyl-1,3-propanediones: The 1,3-dialkyl-1,3-propanediones were prepared by conventional Claisen condensation of the corresponding ArCOMe and ArCO₂Et, and then their sodium enolates were treated with the corresponding alkyl halide (RX) to obtain the 1,3-diaryl-2-alkyl-1,3-propanediones.

1,3-Diphenyl-2-methyl-1,3-propanedione (18a):^[71] ^1H NMR (CDCl_3): $\delta = 1.61$ (d, 3H, $J = 6.9$ Hz), 5.27 (q, 1H, $J = 6.9$ Hz), 7.41–7.50 (m, 4H), 7.53–7.60 (m, 2H), 7.90–8.01 (m, 4H).

1,3-Di(*p*-methylphenyl)-2-methyl-1,3-propanedione (18b): ^1H NMR (CDCl_3): $\delta = 1.58$ (d, 3H, $J = 6.9$ Hz), 2.39 (s, 6H), 5.21 (q, 1H, $J = 6.9$ Hz), 7.24 (d, 4H, $J = 8.3$ Hz), 7.86 (d, 4H, $J = 8.3$ Hz); ^{13}C NMR (CDCl_3): $\delta = 14.5, 21.7, 50.9, 128.5, 129.4, 133.0, 144.2, 196.6$; IR (KBr): $\tilde{\nu} = 2992, 2944, 1684, 1664, 1605, 1336, 1294, 1238, 1179, 966, 824, 565 \text{ cm}^{-1}$; m.p. 132.8–133.7 °C; elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{18}\text{O}_2$: C 81.17, H 6.81; found: C 81.25, H 6.59.

1,3-Di(2-naphthyl)-2-methyl-1,3-propanedione (18c): ^1H NMR (CDCl_3): $\delta = 1.75$ (d, 3H, $J = 7.0$ Hz), 5.57 (q, 1H, $J = 7.0$ Hz), 7.51–7.57 (m, 2H), 7.58–7.64 (m, 2H), 7.84–7.93 (m, 6H), 8.02–8.07 (m, 2H), 8.54 (s, 2H); ^{13}C NMR (CDCl_3): $\delta = 14.8, 51.4, 124.0, 126.8, 127.6, 128.6, 128.7, 129.6, 130.2, 132.4, 132.9, 135.6, 197.0$; IR (KBr): $\tilde{\nu} = 3058, 2985, 2937, 1687, 1675, 1623, 1361, 1315, 1280, 1171, 801, 760 \text{ cm}^{-1}$; m.p. 132.3–132.9 °C; HRMS: *m/z*: calcd for $\text{C}_{24}\text{H}_{18}\text{O}_2$: 338.1307; found: 338.1329 [M^+].

1,3-Di(*p*-methoxyphenyl)-2-methyl-1,3-propanedione (18d): ^1H NMR (CDCl_3): $\delta = 1.58$ (d, 3H, $J = 6.9$ Hz), 3.85 (s, 6H), 5.13 (q, 1H, $J = 6.9$ Hz), 6.92 (d, 4H, $J = 9.3$ Hz), 7.95 (d, 4H, $J = 9.3$ Hz); ^{13}C NMR (CDCl_3): $\delta = 14.6, 51.1, 55.5, 113.9, 128.6, 130.7, 163.5, 195.6$; IR (KBr): $\tilde{\nu} = 2973, 2940, 2917, 1674, 1658, 1598, 1570, 1511, 1338, 1263, 1169, 1021, 973, 855, 565 \text{ cm}^{-1}$; m.p. 78.4–79.4 °C; elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{18}\text{O}_4$: C 72.47, H 6.08; found: C 72.41, H 5.85.

1,3-Di(*p*-bromophenyl)-2-methyl-1,3-propanedione (18e): ^1H NMR (CDCl_3): $\delta = 1.59$ (d, 3H, $J = 7.1$ Hz), 5.12 (q, 1H, $J = 7.1$ Hz), 7.60 (d,

4H, $J = 8.5$ Hz), 7.79 (d, 4H, $J = 8.5$ Hz); ^{13}C NMR (CDCl_3): $\delta = 14.4, 51.4, 128.9, 129.9, 132.2, 134.1, 195.7$; IR (KBr): $\tilde{\nu} = 2986, 2935, 1697, 1671, 1583, 1281, 1195, 1068, 970, 797, 590 \text{ cm}^{-1}$; m.p. 112.9–113.8 °C; elemental analysis calcd (%) for $\text{C}_{16}\text{H}_{12}\text{Br}_2\text{O}_2$: C 48.52, H 3.05; found: C 48.24, H 2.77.

1,3-Diphenyl-2-ethyl-1,3-propanedione (18f): ^1H NMR (CDCl_3): $\delta = 1.06$ (t, 3H, $J = 7.3$ Hz), 2.13–2.23 (m, 2H), 5.12 (t, 1H, $J = 6.4$ Hz), 7.41–7.49 (m, 4H), 7.53–7.60 (m, 2H), 7.93–8.01 (m, 4H); ^{13}C NMR (CDCl_3): $\delta = 13.0, 23.0, 58.7, 128.4, 128.7, 133.3, 136.0, 195.9$; IR (KBr): $\tilde{\nu} = 2972, 2941, 1686, 1665, 1595, 1578, 1448, 1355, 1281, 1226, 1201, 991, 701, 692 \text{ cm}^{-1}$; m.p. 88.1–88.6 °C; elemental analysis calcd (%) for $\text{C}_{17}\text{H}_{16}\text{O}_2$: C 80.93, H 6.39; found: C 80.88, H 6.17.

2-Allyl-1,3-diphenyl-1,3-propanedione (18g): ^1H NMR (CDCl_3): $\delta = 2.88$ (t, 2H, $J = 6.8$ Hz), 5.04 (dd, 1H, $J = 1.5, 10.3$ Hz), 5.11 (dd, 1H, $J = 1.5, 17.1$ Hz), 5.30 (t, 1H, $J = 6.8$ Hz), 5.81–5.94 (m, 1H), 7.42–7.50 (m, 4H), 7.55–7.60 (m, 2H), 7.92–7.99 (m, 4H); ^{13}C NMR (CDCl_3): $\delta = 33.6, 56.8, 117.2, 128.5, 128.8, 133.4, 135.0, 135.8, 195.3$; IR (KBr): $\tilde{\nu} = 3060, 2916, 1695, 1671, 1594, 1447, 1333, 1208, 908, 761, 685 \text{ cm}^{-1}$; m.p. 65.9–66.6 °C; elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{16}\text{O}_2$: C 81.79, H 6.10; found: C 82.01, H 6.01.

2-Benzyl-1,3-diphenyl-1,3-propanedione (18h): ^1H NMR (CDCl_3): $\delta = 3.45$ (d, 2H, $J = 6.5$ Hz), 5.52 (t, 1H, $J = 6.5$ Hz), 7.13–7.26 (m, 5H), 7.36–7.45 (m, 4H), 7.50–7.56 (m, 2H), 7.85–7.92 (m, 4H); ^{13}C NMR (C_6D_6): $\delta = 35.6, 59.6, 126.7, 128.7, 128.80, 128.82, 129.4, 133.1, 136.6, 139.7, 194.9$; IR (KBr): $\tilde{\nu} = 3037, 2905, 1695, 1664, 1594, 1446, 1350, 1214, 948, 760, 711, 696 \text{ cm}^{-1}$; m.p. 106.4–107.4 °C; elemental analysis calcd (%) for $\text{C}_{22}\text{H}_{18}\text{O}_2$: C 84.05, H 5.77; found: C 84.24, H 5.82.

1,3-Diphenyl-2-isopropyl-1,3-propanedione (18i): ^1H NMR (CDCl_3): $\delta = 1.02$ (d, 6H, $J = 6.4$ Hz), 2.85–2.98 (m, 1H), 5.05 (d, 1H, $J = 9.3$ Hz), 7.39–7.49 (m, 4H), 7.51–7.59 (m, 2H), 7.96–8.05 (m, 4H); ^{13}C NMR (CDCl_3): $\delta = 21.4, 30.4, 64.9, 128.55, 128.64, 133.2, 136.9, 195.4$; IR (KBr): $\tilde{\nu} = 2965, 2935, 2876, 1696, 1657, 1448, 1292, 1224, 1204, 998, 705, 685 \text{ cm}^{-1}$; m.p. 82.1–83.0 °C; elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{18}\text{O}_2$: C 81.17, H 6.81; found: C 81.10, H 6.63.

Typical procedure for the reductive desymmetrization of 1,3-diaryl-2-alkyl-1,3-propanedione: Under a dry nitrogen atmosphere in a precooled vessel at –20 °C were placed the (*R,R*)-**3b** catalyst (7.2 mg, 0.0125 mmol), 1,3-diphenyl-2-methyl-1,3-propanedione (59.4 mg, 0.25 mmol), and CHCl_3 (12 mL). To this solution was added the solution of premodified NaBH_4 (2.0 mL), and stirred for 10 h at –20 °C. The reaction was quenched by precooled aqueous THF solution at –20 °C and pH 7 buffer solution and the crude products were extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After evaporation, the residue was purified by silica gel column chromatography (hexane/AcOEt) to give 1,3-diphenyl-3-hydroxy-2-methyl-1-propanone (55.5 mg, 93%). The *anti*-selectivity was determined by ^1H NMR analysis to be 99 %. The enantiomeric excess was determined by HPLC analysis to be 99 % ee.

anti-1,3-Diphenyl-3-hydroxy-2-methyl-1-propanone (19a):^[72, 73] ^1H NMR (CDCl_3): $\delta = 1.05$ (d, 3H, $J = 7.6$ Hz), 3.05 (br, 1H), 3.83 (quin, 1H, $J = 7.6$ Hz), 4.98 (d, 1H, $J = 7.6$ Hz), 7.24–7.49 (m, 7H), 7.52–7.59 (m, 1H), 7.93–7.99 (m, 2H); HPLC: Daicel Chiralpak AD (5% propan-2-ol in hexane, flow 1.0 mL min⁻¹), 23.6 min (major), 26.4 min (minor); $[\alpha]_D^{24} = +111.4^\circ$ ($c = 0.489$ in CHCl_3).

anti-1,3-Di(*p*-methylphenyl)-3-hydroxy-2-methyl-1-propanone (19b): ^1H NMR (CDCl_3): $\delta = 1.05$ (d, 3H, $J = 7.4$ Hz), 2.34 (s, 3H), 2.41 (s, 3H), 2.94 (d, 1H, $J = 4.6$ Hz), 3.79 (quin, 1H, $J = 7.4$ Hz), 4.95 (dd, 1H, $J = 4.6, 7.4$ Hz), 7.17 (d, 2H, $J = 7.9$ Hz), 7.27 (d, 2H, $J = 7.9$ Hz), 7.30 (d, 2H, $J = 7.9$ Hz), 7.88 (d, 2H, $J = 7.9$ Hz); ^{13}C NMR (CDCl_3): $\delta = 15.9, 21.2, 21.7, 47.8, 76.6, 126.5, 128.5, 129.0, 129.2, 134.1, 137.4, 139.1, 144.0, 204.3$; IR (KBr): $\tilde{\nu} = 3385, 2980, 2950, 1663, 1605, 1453, 1186, 999, 966, 818 \text{ cm}^{-1}$; m.p. 95.0–95.6 °C; elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{20}\text{O}_2$: C 80.56, H 7.51; found: C 80.57, H 7.62. HPLC: Daicel Chiralpak AD-H (15% propan-2-ol in hexane, flow 1.0 mL min⁻¹), 13.7 min (minor), 15.5 min (major); $[\alpha]_D^{24} = +126.1^\circ$ ($c = 1.077$ in CHCl_3).

anti-1,3-Di(2-naphthyl)-3-hydroxy-2-methyl-1-propanone (19c): ^1H NMR (CDCl_3): $\delta = 1.17$ (d, 3H, $J = 7.6$ Hz), 3.12 (d, 1H, $J = 4.4, 7.6$ Hz), 4.11 (quin, 1H, $J = 7.6$ Hz), 5.24 (dd, 1H, $J = 4.4, 7.6$ Hz), 7.45–7.66 (m, 5H), 7.81–7.93 (m, 6H), 7.95–7.99 (m, 1H), 8.03–8.08 (m, 1H), 8.52 (s, 1H); ^{13}C NMR (CDCl_3): $\delta = 16.2, 48.0, 77.1, 124.0, 124.3, 125.88, 125.92, 126.1, 126.7, 127.59, 127.65, 127.9, 128.3, 128.49, 128.53, 129.6, 130.2, 132.4, 133.05, 133.08, 133.9,$

135.6, 139.4, 204.5; IR (KBr): $\bar{\nu}$ = 3446, 3052, 2980, 1664, 1188, 823, 748, 477 cm^{-1} ; m.p. 120.7–121.6 $^{\circ}\text{C}$; HRMS: m/z : calcd for $\text{C}_{24}\text{H}_{20}\text{O}_2$: 340.1463; found: 340.1456 [M^+]. HPLC: Daicel Chiralpak AD (25% propan-2-ol in hexane, flow 1.0 mL min^{-1}), 20.2 min (minor), 22.4 min (major); $[\alpha]_D^{24} = +96.2^\circ$ ($c = 1.083$ in CHCl_3).

anti-1,3-Di(p-bromophenyl)-3-hydroxy-2-methyl-1-propanone (19d): ^1H NMR (CDCl_3): δ = 1.05 (d, 3H, $J = 7.5 \text{ Hz}$), 2.92 (d, 1H, $J = 4.4 \text{ Hz}$), 3.70 (quin, 1H, $J = 7.5 \text{ Hz}$), 4.95 (dd, 1H, $J = 4.4, 7.5 \text{ Hz}$), 7.29 (d, 2H, $J = 8.7 \text{ Hz}$), 7.50 (d, 2H, $J = 8.7 \text{ Hz}$), 7.62 (d, 2H, $J = 8.7 \text{ Hz}$), 7.83 (d, 2H, $J = 8.7 \text{ Hz}$); ^{13}C NMR (CDCl_3): δ = 15.6, 47.9, 76.1, 121.8, 128.3, 128.6, 129.8, 131.5, 131.9, 135.1, 140.9, 203.3; IR (KBr): $\bar{\nu}$ = 3494, 2978, 1661, 1581, 1396, 1244, 1069, 1009, 964, 822, 742 cm^{-1} ; m.p. 114.2–114.9 $^{\circ}\text{C}$; HRMS: m/z : calcd for $\text{C}_{16}\text{H}_{14}\text{Br}_2\text{O}_2$: 395.9362; found: 395.9390 [M^+]. HPLC: Daicel Chiralpak AD-H (10% propan-2-ol in hexane, flow 1.0 mL min^{-1}), 22.5 min (minor), 24.9 min (major); $[\alpha]_D^{24} = +97.8^\circ$ ($c = 1.038$ in CHCl_3).

anti-1,3-Di(p-methoxyphenyl)-3-hydroxy-2-methyl-1-propanone (19e): ^1H NMR (CDCl_3): δ = 1.06 (d, 3H, $J = 7.5 \text{ Hz}$), 2.98 (d, 1H, $J = 4.4 \text{ Hz}$), 3.75 (quin, 1H, $J = 7.5 \text{ Hz}$), 3.81 (s, 3H), 3.88 (s, 3H), 4.94 (dd, 1H, $J = 4.4, 7.5 \text{ Hz}$), 6.89 (d, 2H, $J = 8.9 \text{ Hz}$), 6.94 (d, 2H, $J = 8.9 \text{ Hz}$), 7.34 (d, 2H, $J = 8.9 \text{ Hz}$), 7.97 (d, 2H, $J = 8.9 \text{ Hz}$); ^{13}C NMR (CDCl_3): δ = 16.0, 47.6, 55.3, 55.5, 76.4, 113.71, 113.73, 127.7, 129.6, 130.7, 134.4, 159.0, 163.5, 203.2; IR (KBr): $\bar{\nu}$ = 3366, 2977, 2934, 1664, 1599, 1516, 1252, 1174, 1032, 973, 825, 576 cm^{-1} ; elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{20}\text{O}_4$: C 71.98, H 6.71; found: C 71.86, H 6.72; m.p. 80.8–81.7 $^{\circ}\text{C}$. HPLC: Daicel Chiralcel OD-H (10% propan-2-ol in hexane, flow 1.0 mL min^{-1}), 21.3 min (major), 26.4 min (minor); $[\alpha]_D^{24} = +124.8^\circ$ ($c = 1.079$ in CHCl_3).

anti-1,3-Diphenyl-2-ethyl-3-hydroxy-1-propanone (19f):^[72, 73] ^1H NMR (CDCl_3): δ = 0.82 (t, 3H, $J = 7.3 \text{ Hz}$), 1.48–1.61 (m, 1H), 1.66–1.80 (m, 1H), 3.07 (d, 1H, $J = 6.4 \text{ Hz}$), 3.78 (q, 1H, $J = 6.4 \text{ Hz}$), 5.03 (t, 1H, $J = 6.4 \text{ Hz}$), 7.22–7.49 (m, 7H), 7.51–7.58 (m, 1H), 7.88–7.95 (m, 2H); ^{13}C NMR (CDCl_3): δ = 11.8, 23.8, 54.3, 75.7, 126.3, 127.7, 128.2, 128.4, 128.5, 133.1, 138.1, 142.6, 205.4; IR (KBr): $\bar{\nu}$ = 3411, 3061, 2958, 2877, 1671, 1447, 1269, 1207, 1001, 768, 703 cm^{-1} ; m.p. 63.0–63.8 $^{\circ}\text{C}$; elemental analysis calcd (%) for $\text{C}_{17}\text{H}_{18}\text{O}_2$: C 80.28, H 7.13; found: C 80.24, H 7.28. HPLC: Daicel Chiralcak AD (1.5% propan-2-ol in hexane, flow 1.0 mL min^{-1}), 59.1 min (major), 67.5 min (minor); $[\alpha]_D^{24} = +90.7^\circ$ ($c = 1.046$ in CHCl_3).

anti-2-Allyl-1,3-diphenyl-3-hydroxy-1-propanone (19g): ^1H NMR (CDCl_3): δ = 2.24–2.35 (m, 1H), 2.37–2.50 (m, 1H), 3.17 (d, 1H, $J = 5.4 \text{ Hz}$), 3.90 (q, 1H, $J = 6.8 \text{ Hz}$), 4.88–5.06 (m, 3H), 5.55–5.69 (m, 1H), 7.23–7.47 (m, 7H), 7.51–7.58 (m, 1H), 7.85–7.91 (m, 2H); ^{13}C NMR (CDCl_3): δ = 34.8, 52.6, 75.5, 117.5, 126.3, 127.8, 128.2, 128.4, 128.5, 133.1, 134.2, 137.7, 142.2, 204.5; IR (KBr): $\bar{\nu}$ = 3374, 3073, 1671, 1448, 1241, 1209, 1012, 916, 767, 704, 607 cm^{-1} ; m.p. 79.3–80.2 $^{\circ}\text{C}$; elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{18}\text{O}_2$: C 81.17, H 6.81; found: C 81.07, H 6.78. HPLC: Daicel Chiralcel OD-H (3% propan-2-ol in hexane, flow 1.0 mL min^{-1}), 17.7 min (minor), 19.1 min (major); $[\alpha]_D^{24} = +74.7^\circ$ ($c = 1.053$ in CHCl_3).

anti-2-Benzyl-1,3-diphenyl-3-hydroxy-1-propanone (19h):^[73] ^1H NMR (CDCl_3): δ = 2.91 (dd, 1H, $J = 7.0, 13.3 \text{ Hz}$), 3.05 (dd, 1H, $J = 7.0, 13.3 \text{ Hz}$), 3.45 (d, 1H, $J = 7.0 \text{ Hz}$), 4.09 (q, 1H, $J = 7.0 \text{ Hz}$), 4.97 (t, 1H, $J = 7.0 \text{ Hz}$), 7.07–7.37 (m, 12H), 7.42–7.48 (m, 1H), 7.63–7.68 (m, 2H); ^{13}C NMR (CDCl_3): δ = 36.7, 54.7, 75.4, 126.0, 126.3, 127.6, 128.0, 128.2, 128.3, 128.4, 128.9, 133.0, 137.8, 138.4, 142.5, 205.3; IR (KBr): $\bar{\nu}$ = 3434, 3062, 3035, 1674, 1456, 1206, 1047, 1010, 751, 703 cm^{-1} ; m.p. 115.6–116.5 $^{\circ}\text{C}$; HRMS: m/z : calcd for $\text{C}_{22}\text{H}_{20}\text{O}_2$: 316.1463; found: 316.1481 [M^+]. HPLC: Daicel Chiralcel OD-H (5% propan-2-ol in hexane, flow 1.0 mL min^{-1}), 15.4 min (major), 17.3 min (minor); $[\alpha]_D^{24} = -8.7^\circ$ ($c = 1.024$ in CHCl_3).

anti-1,3-Diphenyl-3-hydroxy-2-isopropyl-1-propanone (19i): ^1H NMR (CDCl_3): δ = 0.87 (d, 3H, $J = 6.8 \text{ Hz}$), 1.15 (d, 3H, $J = 6.8 \text{ Hz}$), 2.24–2.35 (m, 1H), 3.59 (dd, 1H, $J = 4.4, 8.3 \text{ Hz}$), 4.04 (d, 1H, $J = 8.1 \text{ Hz}$), 5.17 (dd, 1H, $J = 4.4, 8.1 \text{ Hz}$), 7.08–7.14 (m, 1H), 7.18–7.35 (m, 6H), 7.42–7.48 (m, 1H), 7.60–7.66 (m, 2H); ^{13}C NMR (CDCl_3): δ = 21.1, 21.3, 29.6, 58.7, 73.5, 125.5, 127.1, 127.9, 128.2, 128.3, 133.0, 138.6, 143.0, 207.1; IR (KBr): $\bar{\nu}$ = 3435, 2952, 1666, 1447, 1271, 1207, 1010, 768, 700, 570 cm^{-1} ; m.p. 84.0–85.2 $^{\circ}\text{C}$; HRMS: m/z : calcd for $\text{C}_{18}\text{H}_{18}\text{O}_2$: 268.1463; found: 268.1502 [M^+]. HPLC: Daicel Chiralcak AD-H (15% propan-2-ol in hexane, flow 1.0 mL min^{-1}), 8.3 min (minor), 11.2 min (major); $[\alpha]_D^{24} = +40.1^\circ$ ($c = 0.261$ in CHCl_3).

Chemoselective reduction of 2-undecanone and 2-acetonaphthone in the presence of β -ketoiminato cobalt complex catalyst (Scheme 6): To the CHCl_3 solution (20 mL) of 2-undecanone **20a** (85.2 mg, 0.5 mmol),

2-acetonaphthone **20b** (85.1 mg, 0.5 mmol), and catalyst **22** (18.6 mg, 0.05 mmol) was added the solution of the premodified borohydride (3.2 mL, 0.4 mmol) under a dry nitrogen atmosphere at -20°C . After stirring for 12 h at -20°C , the reaction was quenched by a precooled aqueous THF solution at -20°C and pH 7 buffer solution; then the crude products were extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation, the residue was purified by silica gel column chromatography (hexane/AcOEt) to give undecan-2-ol **21a** (4.0 mg, 5%) and 1-(2-naphthyl)-1-ethanol **21b** (38.3 mg, 45%).

Preparation of 1,2-dialkyl-3-aryl-1,3-diketones: The 1-alkyl-3-aryl-1,3-diketones ($\text{RC(O)CH}_2\text{C(O)Ar}$) were prepared by conventional Claisen condensation of the corresponding RCOMe and ArCO₂Et, and then their sodium enolates were treated with the corresponding RX to obtain the 1,2-dialkyl-3-aryl-1,3-propanediones (RC(O)CH(R')C(O)Ar).

2,4-Dimethyl-1-phenyl-1,3-pentanedione (23a):^[74] ^1H NMR (CDCl_3): δ = 1.03 (d, 3H, $J = 6.9 \text{ Hz}$), 1.10 (d, 3H, $J = 6.9 \text{ Hz}$), 1.45 (d, 3H, $J = 7.0 \text{ Hz}$), 2.77 (sept, 1H, $J = 6.9 \text{ Hz}$), 4.64 (q, 1H, $J = 7.0 \text{ Hz}$), 7.46–7.53 (m, 2H), 7.56–7.64 (m, 1H), 7.93–8.00 (m, 2H); ^{13}C NMR (CDCl_3): δ = 13.8, 18.6, 19.2, 39.5, 54.4, 128.5, 128.8, 133.5, 135.9, 197.5, 210.8; HRMS: m/z : calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$: 204.1150; found: 204.1131 [M^+].

2-Ethyl-4-methyl-1-phenyl-1,3-pentanedione (23b):^[75] ^1H NMR (CDCl_3): δ = 0.95 (t, 3H, $J = 7.3 \text{ Hz}$), 0.99 (d, 3H, $J = 6.8 \text{ Hz}$), 1.06 (d, 3H, $J = 6.8 \text{ Hz}$), 2.02 (double quint, 2H, $J = 7.3, 14.6 \text{ Hz}$), 2.75 (sept, 1H, $J = 6.8 \text{ Hz}$), 4.49 (t, 1H, $J = 7.3 \text{ Hz}$), 7.46–7.53 (m, 2H), 7.57–7.63 (m, 1H), 7.94–8.01 (m, 2H); IR (neat): $\bar{\nu}$ = 2971, 1721 ($\nu_{\text{C=O}}$), 1674 ($\nu_{\text{C=O}}$), 1448, 1273, 1209, 694 cm^{-1} ; HRMS: m/z : calcd for $\text{C}_{14}\text{H}_{18}\text{O}_2$: 218.1307; found: 218.1281 [M^+].

2-Allyl-4-methyl-1-phenyl-1,3-pentanedione (23c): ^1H NMR (CDCl_3): δ = 1.01 (d, 3H, $J = 6.8 \text{ Hz}$), 1.10 (d, 3H, $J = 6.9 \text{ Hz}$), 1.45 (d, 3H, $J = 7.0 \text{ Hz}$), 2.77 (sept, 1H, $J = 6.9 \text{ Hz}$), 4.64 (q, 1H, $J = 7.0 \text{ Hz}$), 7.46–7.53 (m, 2H), 7.56–7.64 (m, 1H), 7.93–8.00 (m, 2H); ^{13}C NMR (CDCl_3): δ = 13.8, 18.6, 19.2, 39.5, 54.4, 128.5, 128.8, 133.5, 135.9, 197.5, 210.8; HRMS: m/z : calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$: 204.1150; found: 204.1131 [M^+].

2,4,4-Trimethyl-1-phenyl-1,3-pentanedione (23d): ^1H NMR (CDCl_3): δ = 1.01 (d, 3H, $J = 6.8 \text{ Hz}$), 1.06 (d, 3H, $J = 6.8 \text{ Hz}$), 2.64–2.81 (m, 3H), 4.68 (t, 1H, $J = 7.1 \text{ Hz}$), 5.02 (d, 1H, $J = 10.3 \text{ Hz}$), 5.08 (d, 1H, $J = 17.1 \text{ Hz}$), 5.69–5.82 (m, 1H), 7.46–7.54 (m, 2H), 7.58–7.64 (m, 1H), 7.95–8.01 (m, 2H); ^{13}C NMR (CDCl_3): δ = 18.4, 19.0, 33.1, 39.8, 60.4, 117.2, 128.5, 128.8, 133.6, 134.7, 136.4, 195.8, 208.9; IR (neat): $\bar{\nu}$ = 2974, 1722 ($\nu_{\text{C=O}}$), 1675 ($\nu_{\text{C=O}}$), 1448, 1000, 919, 693 cm^{-1} ; HRMS: m/z : calcd for $\text{C}_{15}\text{H}_{18}\text{O}_2$: 230.1307; found: 230.1300 [M^+].

2,4,4-Trimethyl-1-phenyl-1,3-pentanedione (23e):^[76] ^1H NMR (CDCl_3): δ = 1.01 (d, 3H, $J = 7.1 \text{ Hz}$), 1.12–1.33 (m, 12H), 1.45 (d, 3H, $J = 7.1 \text{ Hz}$), 1.47–1.57 (m, 2H), 2.38 (dt, 1H, $J = 7.3, 17.6 \text{ Hz}$), 2.51 (dt, 1H, $J = 7.3, 17.6 \text{ Hz}$), 4.49 (q, 1H, $J = 7.1 \text{ Hz}$), 7.46–7.52 (m, 2H), 7.57–7.62 (m, 1H), 7.95–8.00 (m, 2H); **2,5-Dimethyl-1-phenyl-1,3-hexanedione (23f):** ^1H NMR (CDCl_3): δ = 0.80 (d, 3H, $J = 6.8 \text{ Hz}$), 0.86 (d, 3H, $J = 6.8 \text{ Hz}$), 1.44 (d, 3H, $J = 7.0 \text{ Hz}$), 2.13 (nonet, 1H, $J = 6.8 \text{ Hz}$), 2.27 (dd, 1H, $J = 6.8, 17.1 \text{ Hz}$), 2.39 (dd, 1H, $J = 6.8, 17.1 \text{ Hz}$), 4.47 (q, 1H, $J = 7.0 \text{ Hz}$), 7.45–7.53 (m, 2H), 7.56–7.63 (m, 1H), 7.93–8.00 (m, 2H); ^{13}C NMR (CDCl_3): δ = 13.6, 22.4, 24.0, 49.4, 56.8, 128.6, 128.8, 133.5, 136.0, 197.1, 206.5; IR (neat): $\bar{\nu}$ = 2958, 1717 ($\nu_{\text{C=O}}$), 1677 ($\nu_{\text{C=O}}$), 1449, 1226, 969, 689 cm^{-1} ; HRMS: m/z : calcd for $\text{C}_{14}\text{H}_{18}\text{O}_2$: 218.1307; found: 218.1307 [M^+].

2-Methyl-1,4-diphenyl-1,3-butanedione (23g): ^1H NMR (CDCl_3): δ = 1.44 (d, 3H, $J = 7.1 \text{ Hz}$), 3.71 (d, 1H, $J = 15.9 \text{ Hz}$), 3.82 (d, 1H, $J = 15.9 \text{ Hz}$), 4.57 (q, 1H, $J = 7.1 \text{ Hz}$), 7.09–7.16 (m, 2H), 7.18–7.31 (m, 3H), 7.39–7.46 (m, 2H), 7.53–7.60 (m, 1H), 7.77–7.85 (m, 2H); ^{13}C NMR (CDCl_3): δ = 13.8, 48.2, 54.6, 127.1, 128.4, 128.6, 128.7, 129.6, 133.4, 133.5, 135.7, 197.4, 204.4; IR (neat): $\bar{\nu}$ = 1718 ($\nu_{\text{C=O}}$), 1675 ($\nu_{\text{C=O}}$), 1449, 1330, 1215, 970, 702 cm^{-1} ; HRMS: m/z : calcd for $\text{C}_{17}\text{H}_{16}\text{O}_2$: 252.1113; found: 252.1113 [M^+].

Chemo-, diastereo-, and enantioselective reduction of 2,4-dimethyl-1-phenyl-1,3-pentanedione (Scheme 7): Under a dry nitrogen atmosphere in a precooled vessel at -20°C were placed the (R,R)-catalyst **3b** (7.2 mg, 0.0125 mmol), 2,4-dimethyl-1-phenyl-1,3-pentanedione (51.0 mg, 0.25 mmol), and CHCl_3 (12.0 mL). The five portions of the 0.1 equiv of the premodified borohydride (0.2 mL, 0.025 mmol) were successively added at 1 h intervals to the reaction mixture, and stirred for 24 h at -20°C . The reaction was quenched by a precooled aqueous THF solution

at -20°C and pH 7 buffer solution; then the crude products were extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation, the residue was purified by silica gel column chromatography (hexane/AcOEt) to give the corresponding 2-substituted-3-hydroxyketone (22.2 mg, 43%). The chemo-selectivity and diastereoselectivity were determined by ^1H NMR analysis to be 97% aryl/alcohol selectivity and 99% *anti*-selectivity. The enantiomeric excess of the *anti*-form was determined by HPLC analysis to be 94%.

Analysis of the *ee* values of the remaining 2,4-dimethyl-1-phenyl-1,3-pentanedione after kinetic resolution: The above-mentioned reaction mixture, before the reaction was quenched by a precooled aqueous THF solution, was directly injected into HPLC chiral column (Daicel Chiralpak AD, 5% propan-2-ol in hexane, 1 mL min^{-1}) to determine the *ee* of 2,4-dimethyl-1-phenyl-1,3-pentanedione to be 99% *ee* (7.1 min (minor), 7.6 min (major)). Since racemization of 2-substituted-1,3-diketones gradually proceeded at room temperature, the substrate isolated by silica gel column chromatography was of low *ee*.

Optimized procedure of highly chemo-, diastereo-, and enantioselective reduction, example for the reaction of 2,4,4-trimethyl-1-phenyl-1,3-pentanedione: Under a dry nitrogen atmosphere in a precooled vessel at -20°C were placed the (*R,R*)-catalyst **3b** (7.2 mg, 0.0125 mmol), 2,4,4-trimethyl-1-phenyl-1,3-pentanedione **23d** (54.7 mg, 0.25 mmol), and CHCl_3 (12.0 mL). The four portions of the 0.1 equiv of the premodified borohydride (0.2 mL, 0.025 mmol) were successively added at 2 h intervals to the reaction mixture, and stirred for 12 h at -20°C . The reaction was quenched by a precooled aqueous THF solution at -20°C and pH 7 buffer solution; then the crude products were extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation, the residue was purified by silica gel column chromatography (hexane/AcOEt) to give the corresponding 2-substituted-3-hydroxyketone **24d** (26.6 mg, 48%). The chemo- and diastereoselectivity were determined by ^1H NMR analysis to be 99% aryl/alcohol selectivity and 99% *anti*-selectivity. The enantiomeric excess of the *anti*-form was determined by HPLC analysis to be 97%.

anti-1-Hydroxy-2,4-dimethyl-1-phenyl-3-pentanone (24a): ^1H NMR (CDCl_3): $\delta = 0.97$ (d, 3H, $J = 7.3, 3.4\text{ Hz}$), 0.98 (d, 3H, $J = 6.9\text{ Hz}$), 1.07 (d, 3H, $J = 6.9\text{ Hz}$), 2.64 (sept, 1H, $J = 6.9\text{ Hz}$), 3.07 (quin, 1H, $J = 7.3\text{ Hz}$), 4.75 (dd, 1H, $J = 3.4, 7.3\text{ Hz}$), 7.25–7.36 (m, 5H); ^{13}C NMR (CDCl_3): $\delta = 15.0, 17.70, 17.73, 41.3, 51.0, 76.7, 126.3, 127.7, 128.3, 142.3, 219.2$; IR (neat): $\tilde{\nu} = 3456, 2972, 2933, 1707$ ($\nu_{\text{C=O}}$), 1456, 1375, 1099, 756, 702 cm^{-1} ; HRMS: m/z : calcd for $\text{C}_{13}\text{H}_{18}\text{O}_2$: 206.1307; found: 206.1309 [M^+]. HPLC: Daicel Chiralcel OD-H, 3.0% propan-2-ol in hexane, 1 mL min^{-1} , 9.0 min (minor), 12.7 min (major), Daicel chiralpak AD-H, 2% propan-2-ol, 1 mL min^{-1} , 17.2 min (major), 20.0 min (minor); $[\alpha]_D^{25} = +97.1^\circ$ ($c = 1.04$ in CHCl_3).

anti-2-Ethyl-1-Hydroxy-4-methyl-1-phenyl-3-pentanone (24b): ^1H NMR (CDCl_3): $\delta = 0.85$ (d, 3H, $J = 6.8\text{ Hz}$), 0.89 (d, 3H, $J = 7.6\text{ Hz}$), 1.01 (d, 3H, $J = 6.8\text{ Hz}$), 1.44–1.55 (m, 1H), 1.57–1.68 (m, 1H), 2.46 (sept, 1H, $J = 6.8\text{ Hz}$), 2.98 (dt, 1H, $J = 6.1, 7.6\text{ Hz}$), 3.22 (d, 1H, $J = 6.1\text{ Hz}$), 4.82 (t, 1H, $J = 6.1\text{ Hz}$), 7.24–7.36 (m, 5H); ^{13}C NMR (CDCl_3): $\delta = 12.0, 17.2, 17.3, 23.1, 42.4, 58.1, 75.2, 126.0, 127.6, 128.3, 142.9, 219.7$; IR (neat): $\tilde{\nu} = 3464, 2968, 1705$ ($\nu_{\text{C=O}}$), 1456, 1031, 701 cm^{-1} ; HRMS: m/z : calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2$: 220.1463; found: 220.1465 [M^+]. HPLC: Daicel Chiralcel OD-H, 2.0% propan-2-ol in hexane, 1 mL min^{-1} , 18.1 min (major), 22.4 min (minor), Daicel chiralpak AD-H, 2% propan-2-ol, 1 mL min^{-1} , 9.1 min (minor), 13.7 min (major); $[\alpha]_D^{25} = +86.2^\circ$ ($c = 0.77$ in CHCl_3).

anti-2-Allyl-1-Hydroxy-4-methyl-1-phenyl-3-pentanone (24c): ^1H NMR (CDCl_3): $\delta = 0.83$ (d, 3H, $J = 6.9\text{ Hz}$), 0.97 (d, 3H, $J = 6.9\text{ Hz}$), 2.18–2.35 (m, 2H), 2.42 (sept, 1H, $J = 6.9\text{ Hz}$), 3.11 (dt, 1H, $J = 6.3, 8.3\text{ Hz}$), 3.33 (d, 1H, $J = 6.3\text{ Hz}$), 4.81 (t, 1H, $J = 6.3\text{ Hz}$), 5.02 (d, 1H, $J = 9.5\text{ Hz}$), 5.03 (d, 1H, $J = 17.1\text{ Hz}$), 5.68 (ddt, 1H, $J = 7.3, 9.5, 17.1\text{ Hz}$), 7.25–7.36 (m, 5H); ^{13}C NMR (CDCl_3): $\delta = 17.0, 17.2, 34.5, 42.5, 56.4, 75.1, 117.6, 126.0, 127.6, 128.3, 134.6, 142.6, 218.9$; IR (neat): $\tilde{\nu} = 3465, 2974, 2932, 1707$ ($\nu_{\text{C=O}}$), 1445, 1042, 701 cm^{-1} ; HRMS: m/z : calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2$: 232.1463; found: 232.1482 [M^+]. HPLC: Daicel Chiralcel OD-H, 1.0% propan-2-ol in hexane, 1 mL min^{-1} , 18.1 min (minor), 28.0 min (major). Daicel chiralpak AD-H, 1% propan-2-ol, 1 mL min^{-1} , 13.5 min (minor), 20.6 min (major); $[\alpha]_D^{25} = +39.6^\circ$ ($c = 1.26$ in CHCl_3).

anti-1-Hydroxy-2,4,4-trimethyl-1-phenyl-3-pentanone (24d): ^1H NMR (CDCl_3): $\delta = 1.03$ –1.04 (m, 12H), 3.17 (d, 1H, $J = 6.2\text{ Hz}$), 3.32 (quin,

1H, $J = 6.2\text{ Hz}$), 4.77 (t, 1H, $J = 6.2\text{ Hz}$), 7.25–7.36 (m, 5H); ^{13}C NMR (CDCl_3): $\delta = 16.7, 26.0, 45.0, 46.7, 77.4, 126.3, 127.7, 128.3, 142.9, 220.9$; IR (KBr): $\tilde{\nu} = 3506, 2976, 1699$ ($\nu_{\text{C=O}}$), 987, 700 cm^{-1} ; m.p. 66.4–68.0 $^{\circ}\text{C}$; HRMS: m/z : calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2$: 220.1463; found: 220.1491 [M^+]. HPLC: Daicel Chiralcel OD-H, 3.0% propan-2-ol in hexane, 1 mL min^{-1} , 6.8 min (minor), 15.8 min (major). Daicel chiralpak AD-H, 5% propan-2-ol, 1 mL min^{-1} , 8.3 min (major), 9.5 min (minor); $[\alpha]_D^{25} = +99.4^\circ$ ($c = 0.54$ in CHCl_3).

anti-1-Hydroxy-2-methyl-1-phenyl-3-dodecanone (24e): ^1H NMR (CDCl_3): $\delta = 0.88$ (t, 3H, $J = 6.8\text{ Hz}$), 0.94 (d, 3H, $J = 7.5\text{ Hz}$), 1.20–1.32 (m, 12H), 1.50–1.57 (m, 2H), 2.41 (dt, 1H, $J = 7.2, 17.3\text{ Hz}$), 2.50 (dt, 1H, $J = 7.6, 17.3\text{ Hz}$), 2.92 (quin, 1H, $J = 7.5\text{ Hz}$), 2.94 (s, 1H), 4.75 (d, 1H, $J = 7.5\text{ Hz}$), 7.27–7.37 (m, 5H); ^{13}C NMR ([D_6]DMSO): $\delta = 13.6, 14.0, 22.1, 22.8, 28.6, 28.7, 28.9, 29.0, 31.3, 42.3, 52.8, 75.6, 126.7, 127.2, 127.9, 143.6, 213.0$; IR (KBr): 3364, 3302, 2954, 2928, 2850, 1706 ($\nu_{\text{C=O}}$), 1467, 1009, 699 cm^{-1} ; m.p. 41.6–43.8 $^{\circ}\text{C}$; HRMS: m/z : calcd for $\text{C}_{19}\text{H}_{30}\text{O}_2$: 290.2246; found: 290.2948 [M^+]. HPLC: Daicel Chiralcel OD-H, 3.0% propan-2-ol in hexane, 1 mL min^{-1} , 14.4 min (major), 16.0 min (minor). Daicel chiralpak AD-H, 1% propan-2-ol, 1 mL min^{-1} , 15.7 min (minor), 19.7 min (major); $[\alpha]_D^{25} = +52.2^\circ$ ($c = 0.86$ in CHCl_3).

anti-1-Hydroxy-2,5-dimethyl-1-phenyl-3-hexanone (24f): ^1H NMR (CDCl_3): $\delta = 0.887$ (d, 1H, $J = 6.8\text{ Hz}$), 0.893 (d, 1H, $J = 6.3\text{ Hz}$), 0.93 (d, 1H, $J = 7.6\text{ Hz}$), 2.10–2.20 (m, 1H), 2.32 (dd, 1H, $J = 6.1, 16.5\text{ Hz}$), 2.38 (dd, 1H, $J = 7.3, 16.5\text{ Hz}$), 2.90 (quin, 1H, $J = 7.6\text{ Hz}$), 2.95 (d, 1H, $J = 3.1\text{ Hz}$), 4.75 (dd, 1H, $J = 3.1, 7.6\text{ Hz}$), 7.27–7.37 (m, 5H); ^{13}C NMR (CDCl_3): $\delta = 14.3, 22.5, 22.6, 24.0, 52.2, 53.1, 76.5, 126.5, 127.8, 128.4, 142.1, 215.1$; IR (neat): $\tilde{\nu} = 3452, 2958, 2933, 2871, 1707$ ($\nu_{\text{C=O}}$), 1456, 1356, 702 cm^{-1} ; HRMS: m/z : calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2$: 220.1463; found: 220.1449 [M^+]. HPLC: Daicel chiralpak AD-H, 5.0% propan-2-ol, 1 mL min^{-1} , 9.1 min (major), 10.6 min (minor); $[\alpha]_D^{25} = +72.1^\circ$ ($c = 0.64$ in CHCl_3).

anti-4-Hydroxy-3-methyl-1,4-diphenyl-2-pentanone (24g): ^1H NMR (CDCl_3): $\delta = 0.84$ (d, 3H, $J = 7.6\text{ Hz}$), 2.79 (br, 1H), 2.98 (quin, 1H, $J = 7.6\text{ Hz}$), 3.68 (s, 2H), 4.66 (d, 1H, $J = 7.6\text{ Hz}$), 7.06 (d, 2H, $J = 7.3\text{ Hz}$), 7.16–7.28 (m, 8H); ^{13}C NMR (CDCl_3): $\delta = 14.6, 50.6, 52.0, 76.8, 126.4, 126.9, 127.8, 128.4, 128.5, 129.5, 133.5, 142.0, 212.5$; IR (neat): $\tilde{\nu} = 3448, 3030, 1711$ ($\nu_{\text{C=O}}$), 1454, 702 cm^{-1} ; HRMS: m/z : calcd for $\text{C}_{17}\text{H}_{18}\text{O}_2$: 254.1307; found: 254.1325 [M^+]. HPLC: Daicel chiralpak AD-H, 3.0% propan-2-ol, 1 mL min^{-1} , 34.2 min (major), 39.0 min (minor); $[\alpha]_D^{25} = +101.8^\circ$ ($c = 0.63$ in CHCl_3).

Preparation of the 2-alkyl-3-ketoesters: The 2-alkyl-3-ketoesters were prepared by the conventional Claisen condensation and alkylation, or by the reported methods.

2-Methyl-3-(2-naphthyl)-3-oxopropionic acid ethyl ester (25a):^[77] ^1H NMR (CDCl_3): $\delta = 1.17$ (t, 3H, $J = 7.1\text{ Hz}$), 1.56 (d, 3H, $J = 7.0\text{ Hz}$), 4.09–4.21 (m, 2H), 4.55 (q, 1H, $J = 7.0\text{ Hz}$), 7.53–7.65 (m, 2H), 7.86–7.93 (m, 2H), 7.95–8.00 (m, 1H), 8.01–8.06 (m, 1H), 8.52 (s, 1H).

2-Methyl-3-phenyl-3-oxopropionic acid ethyl ester (25b):^[71] ^1H NMR (CDCl_3): $\delta = 1.17$ (t, 3H, $J = 7.1\text{ Hz}$), 1.50 (d, 3H, $J = 7.1\text{ Hz}$), 4.15 (q, 2H, $J = 7.1\text{ Hz}$), 4.38 (q, 1H, $J = 7.1\text{ Hz}$), 7.45–7.52 (m, 2H), 7.56–7.62 (m, 1H), 7.95–8.01 (m, 2H); ^{13}C NMR (CDCl_3): $\delta = 13.8, 14.0, 48.4, 61.3, 128.5, 128.6, 133.3, 135.7, 170.7, 195.7$.

2-Methyl-3-(*p*-methylphenyl)-3-oxopropionic acid ethyl ester (25c): ^1H NMR (CDCl_3): $\delta = 1.18$ (t, 3H, $J = 7.1\text{ Hz}$), 4.49 (d, 3H, $J = 7.0\text{ Hz}$), 2.42 (s, 3H), 4.15 (q, 2H, $J = 7.1\text{ Hz}$), 4.36 (q, 1H, $J = 7.0\text{ Hz}$), 7.28 (d, 2H, $J = 8.1\text{ Hz}$), 7.89 (d, 2H, $J = 8.1\text{ Hz}$); ^{13}C NMR (CDCl_3): $\delta = 13.9, 14.1, 21.7, 48.3, 61.3, 128.7, 129.3, 133.2, 144.3, 170.9, 195.3$; IR (neat): $\tilde{\nu} = 2984, 1739$ ($\nu_{\text{C=O}}$), 1684 ($\nu_{\text{C=O}}$), 1607, 1186, 969, 833, 746 cm^{-1} ; HRMS: m/z calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3$: 220.1099; found: 220.1121 [M^+].

2-Methyl-3-(*p*-methoxyphenyl)-3-oxopropionic acid ethyl ester (25d): ^1H NMR (CDCl_3): $\delta = 1.18$ (t, 3H, $J = 7.0\text{ Hz}$), 1.48 (d, 3H, $J = 7.1\text{ Hz}$), 3.88 (s, 3H), 4.15 (q, 2H, $J = 7.0\text{ Hz}$), 4.34 (q, 1H, $J = 7.1\text{ Hz}$), 6.95 (d, 2H, $J = 9.3\text{ Hz}$), 7.98 (d, 2H, $J = 9.3\text{ Hz}$); ^{13}C NMR (CDCl_3): $\delta = 13.9, 14.1, 48.1, 55.5, 61.3, 113.8, 128.7, 130.9, 163.6, 171.0, 194.2$; IR (neat): $\tilde{\nu} = 2983, 1736$ ($\nu_{\text{C=O}}$), 1677 ($\nu_{\text{C=O}}$), 1602, 1263, 1172, 1030, 971, 845 cm^{-1} ; HRMS: m/z : calcd for $\text{C}_{13}\text{H}_{16}\text{O}_4$: 236.1049; found: 236.1065 [M^+].

3-(*p*-Bromophenyl)-2-methyl-3-oxopropionic acid ethyl ester (25e): ^1H NMR (CDCl_3): $\delta = 1.18$ (t, 3H, $J = 7.1\text{ Hz}$), 1.49 (d, 3H, $J = 7.0\text{ Hz}$), 4.15 (q, 2H, $J = 7.1\text{ Hz}$), 4.31 (q, 1H, $J = 7.0\text{ Hz}$), 7.63 (d, 2H, $J = 8.5\text{ Hz}$), 7.85 (d, 2H, $J = 8.5\text{ Hz}$); ^{13}C NMR (CDCl_3): $\delta = 13.7, 14.0, 48.4, 61.5, 128.7, 130.0, 132.0, 134.5, 170.4, 194.6$; IR (neat): $\tilde{\nu} = 2984, 1739$ ($\nu_{\text{C=O}}$), 1689

($\nu_{C=O}$), 1585, 1397, 1071, 842 cm⁻¹; HRMS: m/z : calcd for C₁₂H₁₃BrO₃: 284.0049; found: 284.0028 [M⁺].

2-Ethyl-3-phenyl-3-oxopropionic acid ethyl ester (25f):^[78] ¹H NMR (CDCl₃): δ = 1.00 (t, 3H, J = 7.3 Hz), 1.18 (t, 3H, J = 7.1 Hz), 2.05 (quintet, 2H, J = 7.3 Hz), 4.15 (q, 2H, J = 7.1 Hz), 4.22 (t, 1H, J = 7.3 Hz), 7.45–7.52 (m, 2H), 7.56–7.62 (m, 1H), 7.97–8.03 (m, 2H); ¹³C NMR (CDCl₃): δ = 12.2, 14.1, 22.4, 55.9, 61.3, 128.5, 128.6, 133.3, 136.3, 169.9, 195.1; IR (neat): $\tilde{\nu}$ = 2974, 1738 ($\nu_{C=O}$), 1687 ($\nu_{C=O}$), 1448, 1217, 1025, 691 cm⁻¹.

2-Allyl-3-phenyl-3-oxopropionic acid ethyl ester (25g):^[78b] ¹H NMR (CDCl₃): δ = 1.17 (t, 3H, J = 7.1 Hz), 2.69–2.82 (m, 2H), 4.10–4.19 (m, 2H), 4.40 (t, 1H, J = 7.1 Hz), 5.05 (dd, 1H, J = 1.2, 10.3 Hz), 5.12 (dd, 1H, J = 1.2, 17.1 Hz), 5.76–5.88 (m, 1H), 7.45–7.52 (m, 2H), 7.56–7.62 (m, 1H), 7.97–8.03 (m, 2H); IR (neat): $\tilde{\nu}$ = 2982, 1738 ($\nu_{C=O}$), 1687 ($\nu_{C=O}$), 1449, 1237, 1001, 921, 670 cm⁻¹; HRMS: m/z : calcd for C₁₄H₁₆O₃: 232.1099; found: 232.1092 [M⁺].

Diastereo- and enantioselective reduction of the 2-alkyl-3-ketoester: Under a dry nitrogen atmosphere in a precooled vessel at –10°C were placed the (R,R)-cobalt catalyst **3b** (5.7 mg, 0.01 mmol), sodium methoxide (13.5 mg, 0.25 mmol), the 2-alkyl-3-ketoester (0.25 mmol), and CHCl₃ (12.0 mL). The premodified NaBH₄ (2.4 mL, 0.30 mmol) was added to the reaction mixture, and stirred for 15 h at –10°C. The reaction was quenched by a precooled aqueous THF solution at –10°C and pH 7 buffer solution, then the crude products were extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation, the residue was purified by silica gel column chromatography (hexane/AcOEt) to give the corresponding 2-alkyl-3-hydroxyester. The anti-selectivity was determined by ¹H NMR analysis. The enantiomer excess was determined by HPLC analysis.

anti-3-Hydroxy-2-methyl-3-(2-naphthyl)propionic acid ethyl ester (26a): ¹H NMR (CDCl₃): δ = 1.05 (d, 3H, J = 7.6 Hz), 1.26 (t, 3H, J = 7.1 Hz), 2.92 (quin, 1H, J = 7.6 Hz), 3.14 (d, 1H, J = 4.4 Hz), 4.20 (q, 2H, J = 7.1 Hz), 4.93 (dd, 1H, J = 4.4, 7.6 Hz), 7.45–7.53 (m, 3H), 7.77–7.88 (m, 4H); ¹³C NMR (CDCl₃): δ = 14.2, 14.7, 47.0, 60.8, 76.5, 124.2, 125.9, 126.0, 126.1, 127.6, 127.9, 128.3, 133.0, 133.1, 138.9, 175.7; IR (neat): $\tilde{\nu}$ = 3461, 2979, 1732 ($\nu_{C=O}$), 1376, 1182, 1034, 822, 749, 479 cm⁻¹; HRMS: m/z : calcd for C₁₆H₁₈O₃: 258.1256; found: 258.1236 [M⁺]. HPLC: Daicel Chiralpak AD-H (5.0% propan-2-ol in hexane, flow 1.0 mL min⁻¹), 24.9 min (minor), 27.3 (major); $[\alpha]_D^{21}$ = +33.9° (c = 0.45 in CHCl₃).

anti-3-Hydroxy-2-methyl-3-phenylpropionic acid ethyl ester (26b):^[79] ¹H NMR (CDCl₃): δ = 1.02 (d, 3H, J = 7.3 Hz), 1.26 (t, 3H, J = 7.0 Hz), 2.80 (quin, 1H, J = 7.3 Hz), 3.02 (d, 1H, J = 4.2 Hz), 4.19 (q, 2H, J = 7.0 Hz), 4.75 (dd, 1H, J = 4.2, 7.3 Hz), 7.23–7.43 (m, 5H); IR (neat): $\tilde{\nu}$ = 3461, 2980, 1733 ($\nu_{C=O}$), 1455, 1376, 1181, 1025, 767, 703 cm⁻¹. HPLC: Daicel Chiralpak AD-H (2.0% propan-2-ol in hexane, flow 1.0 mL min⁻¹), 27.5 min (major), 30.7 (minor); $[\alpha]_D^{21}$ = +48.7° (c = 0.63 in CHCl₃).

anti-3-Hydroxy-2-methyl-3-(*p*-methoxyphenyl)propionic acid ethyl ester (26c): ¹H NMR (CDCl₃): δ = 1.01 (d, 3H, J = 7.5 Hz), 1.27 (t, 3H, J = 7.0 Hz), 2.35 (s, 3H), 2.79 (quin, 1H, J = 7.5 Hz), 2.89 (d, 1H, J = 4.4 Hz), 4.19 (q, 2H, J = 7.0 Hz), 4.72 (dd, 1H, J = 4.4, 7.5 Hz), 7.16 (d, 2H, J = 7.1 Hz), 7.23 (d, 2H, J = 7.1 Hz); ¹³C NMR (CDCl₃): δ = 14.2, 14.6, 21.2, 47.2, 60.7, 76.2, 126.5, 129.1, 137.6, 138.5, 175.8; IR (neat): $\tilde{\nu}$ = 3471, 2980, 1734 ($\nu_{C=O}$), 1458, 1376, 1249, 1179, 1035, 819, 539 cm⁻¹; HRMS: m/z : calcd for C₁₃H₁₈O₃: 222.1256; found: 222.1286 [M⁺]. HPLC: Daicel Chiralcel OB-H (0.7% propan-2-ol in hexane, flow 1.0 mL min⁻¹), 20.8 min (minor), 32.0 (major); $[\alpha]_D^{21}$ = +43.2° (c = 0.46 in CHCl₃).

anti-3-Hydroxy-2-methyl-3-(*p*-methoxyphenyl)propionic acid ethyl ester (26d):^[79] ¹H NMR (CDCl₃): δ = 0.99 (d, 3H, J = 7.7 Hz), 1.28 (t, 3H, J = 7.2 Hz), 2.77 (quin, 1H, J = 7.7 Hz), 2.89 (d, 1H, J = 3.9 Hz), 3.81 (s, 3H), 4.20 (q, 2H, J = 7.2 Hz), 4.71 (dd, 1H, J = 3.9, 7.7 Hz), 6.89 (d, 2H, J = 8.3 Hz), 7.27 (d, 2H, J = 8.3 Hz); ¹³C NMR (CDCl₃): δ = 14.2, 14.6, 47.2, 55.3, 60.8, 76.0, 113.8, 127.8, 133.6, 159.2, 175.8; m.p. 66.5–67.5 °C. HPLC: Daicel Chiralcel OB-H (3% propan-2-ol in hexane, flow 1.0 mL min⁻¹), 18.7 min (minor), 26.1 (major); $[\alpha]_D^{21}$ = +42.1° (c = 0.51 in CHCl₃).

anti-3-(*p*-Bromophenyl)-3-hydroxy-2-methylpropionic acid ethyl ester (26e): ¹H NMR (CDCl₃): δ = 1.04 (d, 3H, J = 7.4 Hz), 1.26 (t, 3H, J = 7.2 Hz), 2.75 (quin, 1H, J = 7.4 Hz), 3.15 (d, 1H, J = 4.6 Hz), 4.18 (q, 2H, J = 7.2 Hz), 4.72 (dd, 1H, J = 4.6, 7.4 Hz), 7.23 (d, 2H, J = 8.3 Hz), 7.49 (d, 2H, J = 8.3 Hz); ¹³C NMR (CDCl₃): δ = 14.2, 14.5, 46.9, 60.9, 75.6, 121.7, 128.2, 131.5, 140.5, 175.5; IR (neat): $\tilde{\nu}$ = 3453, 2980, 1732 ($\nu_{C=O}$), 1377, 1181, 1011, 823, 542 cm⁻¹; HRMS: m/z : calcd for C₁₂H₁₅BrO₃: 286.0205; found:

286.0203 [M⁺]. HPLC: Daicel Chiralpak AD-H (5.0% propan-2-ol in hexane, flow 1.0 mL min⁻¹), 16.8 min (minor), 18.5 (major); $[\alpha]_D^{21}$ = +36.0° (c = 0.44 in CHCl₃).

anti-2-Ethyl-3-hydroxy-3-phenylpropionic acid ethyl ester (26f):^[79, 80] ¹H NMR (CDCl₃): δ = 0.87 (t, 3H, J = 7.6 Hz), 1.23 (t, 3H, J = 7.1 Hz), 1.33–1.45 (m, 1H), 1.53–1.66 (m, 1H), 2.63–2.72 (m, 1H), 2.89 (d, 1H, J = 5.5 Hz), 4.10–4.24 (m, 2H), 4.80 (dd, 1H, J = 5.5, 7.6 Hz), 7.25–7.40 (m, 5H). HPLC: Converted to acyl-form with Ac₂O, py, and DMAP. Daicel Chiralpak AD-H (0.7% propan-2-ol in hexane, flow 1.0 mL min⁻¹), 19.9 min (major), 31.1 (minor); $[\alpha]_D^{21}$ = +39.0° (c = 0.17 in CHCl₃).

anti-2-Allyl-3-hydroxy-3-phenylpropionic acid ethyl ester (26g):^[81] ¹H NMR (CDCl₃): δ = 1.20 (t, 3H, J = 7.1 Hz), 2.13–2.22 (m, 1H), 2.24–2.35 (m, 1H), 2.80–2.88 (m, 1H), 2.99 (d, 1H, J = 5.9 Hz), 4.08–7.21 (m, 2H), 4.83 (dd, 1H, J = 5.9, 7.3 Hz), 5.01 (d, 1H, J = 9.8 Hz), 5.04 (d, 1H, J = 17.1 Hz), 5.64–5.76 (m, 1H), 7.27–7.39 (m, 5H). HPLC: Daicel Chiralpak AD-H (1.2% propan-2-ol in hexane, flow 1.0 mL min⁻¹), 48.6 min (major), 52.4 (minor); $[\alpha]_D^{21}$ = +32.1° (c = 0.46 in CHCl₃).

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