Homogeneous Catalysis

DOI: 10.1002/anie.201102114

La/Ag Heterobimetallic Cooperative Catalysis: A Catalytic Asymmetric Conia-Ene Reaction**

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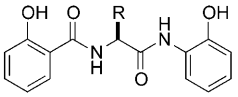
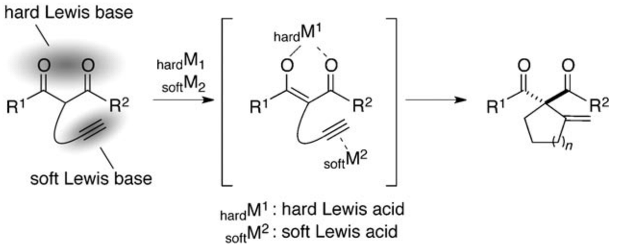
Cooperative catalysis continues to attract growing interest as a particularly effective strategy to promote specific bond formation under mild reaction conditions.[1] This intriguing approach allows for the activation of not only a single functionality through multiple coordination, but also chemically distinct multiple functionalities in a simultaneous manner. The latter option, under an asymmetric environment, is particularly powerful to assemble the multiple functionalities with a high degree of stereocontrol. A carbonyl group and an alkyne group represent hard and soft Lewis basic functionalities, respectively, and their simultaneous activation by hard and soft Lewis acid cooperative catalysis can be best manifested by a Conia-ene reaction.[2–5] Pioneering work on the catalytic asymmetric Conia-ene reaction of β-keto esters and 1,3-diketones with a hard Lewis acid (Yb(OTf)$_3$)/chiral soft Lewis acid (DTBM-Segphos/Pd^{II}) bimetallic catalytic system was reported by Corkey and Toste.[6] Subsequently, Dixon and co-workers reported a distinct approach with chiral amine base/soft Lewis acid (CuOTf) cooperative catalysis.[7] Meanwhile, our research group developed a La(NO$_3$)$_3$/amide-based ligand **1a**/amine ternary catalyst that promotes the catalytic asymmetric amination of malonamates to azodicarboxylates. In this reaction a La/**1a**/amine ternary complex formed under equilibrium acts as a chiral Lewis acid (Scheme 1).[8,9] We envisioned that endowing a soft Lewis acid function to the La/**1a** catalytic system would produce a hard Lewis acid/soft Lewis acid heterobimetallic cooperative catalyst.[1] In this catalyst system, the enolate is generated through activation of a carbonyl group by a hard Lewis acid, which subsequently couples with an electrophilically activated alkyne by a soft–soft interaction under an asymmetric environment (Scheme 2). Herein, we report that a chiral La/Ag heterobimetallic cooperative catalyst on a chiral amide-based ligand promotes an enantioselective Conia-ene reaction of alkyne-tethered malonamates and β-keto esters. This approach furnishes enatioenriched cyclopentane derivatives bearing exocyclic olefin and two distinct α-carbonyl groups at a quaternary stereogenic center.[10]



1a: R = *i*Pr
1b: R = *t*Bu
1c: R = CH$_2$CH$_2$SMe

Scheme 1. The structure of amide-based ligand **1**.



Scheme 2. Conia-ene reaction through hard Lewis acid/soft Lewis acid heterobimetallic cooperative catalysis.

Initial attempts at the catalytic asymmetric Conia-ene reaction of alkyne-tethered malonamate **2a** were conducted using the La(NO$_3$)$_3$/**1a**/H-L-Val-O*t*Bu (1:1:3) ternary catalyst,[8a] which is effective for prochiral face selection of the enolate derived from **2a**. Combined use of various soft Lewis acids was evaluated and the results are summarized in Table 1. In the presence of 10 mol% of the La catalyst and [Ni(acac)$_2$], the Conia-ene reaction of **2a** slowly proceeded at 50 °C and gave the desired product **3a** in low yield with marginal enantioinduction (Table 1, entry 1). The soft Lewis acids [Pd(CH$_3$CN)$_4$](BF$_4$)$_2$ and [Rh(CH$_3$CN)$_2$(cod)]BF$_4$ were totally ineffective and no formation of **3a** was detected (Table 1, entries 2 and 3). Metal salts of Group 11 elements exhibited higher catalytic performance, and afforded **3a** in 21% with CuOTf, albeit with virtually no enantioinduction (Table 1, entry 4). Degradation of the catalyst, likely owing to the precipitation of silver salts, was circumvented in the presence of phosphine ligand **5**, and AgOAc outperformed AgOTf (Table 1, entries 5 and 6). Concomitant alkyne hydration was observed when AgOAc/**5** was used as a soft Lewis acid catalyst and gave ketone **4a** in 12% yield (Table 1, entry 6). This pathway became even more dominant in the reaction using [AuCl(PPh$_3$)]/AgSbF$_6$ (Table 1, entry 7).

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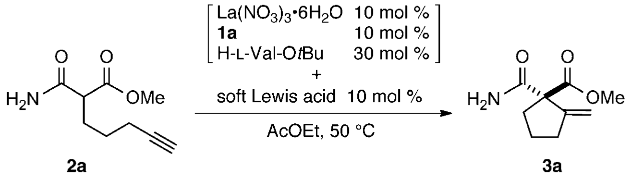
[**] This work was financially supported by Grant-in-Aid for Scientific Research (S) from the JSPS. T.M. thanks the JSPS for a predoctoral fellowship. Dr. M. Shiro is gratefully acknowledged for X-ray crystallographic analysis of **3a**.

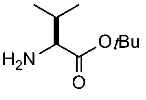
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201102114.

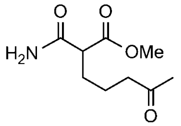
Table 1: Initial Screening of the catalyst.[d]



Entry	Soft Lewis acid	t [h]	Yield [%][a]		*ee* [%][b]
			3a	**4a**	
1	$[Ni(acac)_2 \cdot 2\,H_2O]$	70	7	–	−14
2	$[Rh(CH_3CN)_2(cod)]BF_4$	70	nd	–	–
3	$[Pd(CH_3CN)_4](BF_4)_2$	70	nd	–	–
4	$CuOTf \cdot {}^1/_2\,C_6H_6$	70	21	–	−2
5[c]	AgOTf/**5**	66	27	–	−3
6[c]	AgOAc/**5**	66	55	12	7
7	$[AuCl(PPh_3)]/AgSbF_6$	9	18	78	9

[a] Determined by ^1H NMR analysis. [b] Determined by HPLC on a chiral stationary phase. [c] Ag salt/**5** (1/1). [d] acac = acetylacetonate, cod = 1,5-cyclooctadiene, nd = not determined, Tf = trifluoromethanesulfonyl.


H-L-Val-OtBu


4a

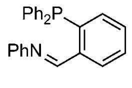

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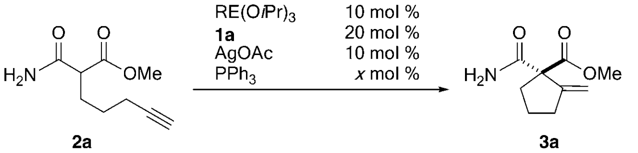
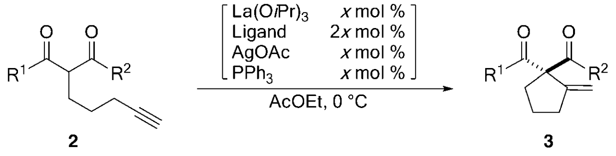
Table 2: Initial screening of the catalyst.



Entry	RE	x [mol %]	Solvent	T [°C]	t [h]	Yield [%][a]	*ee* [%][b]
1	Y	10	THF	50	21	58	−2
2	La	10	THF	50	21	92	37
3	Nd	10	THF	50	21	83	25
4	Gd	10	THF	50	21	55	0
5	Er	10	THF	50	21	64	−4
6[c]	La	10	THF	50	21	93	3
7	La	20	AcOEt	50	21	quant.	63
8	La	20	AcOEt	RT	21	96	82
9	La	20	AcOEt	0	48	63	90

[a] Determined by ^1H NMR analysis. [b] Determined by HPLC on a chiral stationary phase. [c] **5** was used instead of PPh_3. THF = tetrahydrofuran.

Table 3: Scope of catalytic asymmetric Conia-ene reaction promoted by $La(OiPr)_3$/**1a**/AgOAc/PPh_3 catalyst.[g]



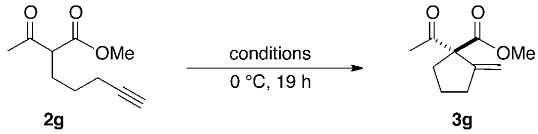
Entry	Substrate **2**	R¹	R²	Ligand	x [mol %]	t [h]	Prod.	Yield [%][a]	*ee* [%][b]
1[d]	**2a**	NH_2	OMe	**1a**	10	48	**3a**	63[c]	90
2	**2b**	Ph	OEt	**1a**	10	118	**3b**	quant.	91
3	**2c**	Ph	OBn	**1a**	10	64	**3c**	79	86
4	**2d**	2-naph	OEt	**1a**	10	64	**3d**	70	90
5	**2e**	p-FC_6H_4	OEt	**1a**	10	68	**3e**	82	91
6[b]	**2e**	p-FC_6H_4	OEt	**1a**	5	75	**3e**	92	87
7	**2f**	p-$MeOC_6H_4$	OEt	**1a**	10	120	**3f**	26	93
8[d,e]	**2g**	Me	OMe	**1a**	5	19	**3g**	89[c]	92
9[f]	**2g**	Me	OMe	**1a**	0.5	65	**3g**	quant.[c]	96
10	**2h**	Me	OEt	**1b**	5	14	**3h**	quant.[c]	84
11	**2h**	Me	OEt	**1b**	5	12	**3h**	quant.[c]	91
12	**2i**	Me	OBn	**1b**	5	12	**3i**	quant.	83
13	**2j**	Et	OMe	**1b**	5	15	**3j**	86[c]	90
14	**2j**	Et	OMe	**1b**	2.5	45	**3j**	96[c]	83
15	**2k**	Et	OEt	**1b**	5	24	**3k**	98[c]	87
16	**2l**	*n*Pr	OMe	**1a**	5	61	**3l**	92	83

[a] Yield of isolated product. [b] Determined by HPLC or GC on a chiral stationary phase. [c] Determined by ^1H NMR analysis. [d] Double the amount of PPh_3 was used. [e] The reaction was carried out in air. [f] Substrate was added over 24 h. [g] Bn = benzyl, naph = naphthyl.

Owing to the possibility of unavoidably deactivating the soft Lewis acid through coordination of the primary amino group of H-L-Val-O*t*Bu, the $RE(OiPr)_3$/**1a** (RE = rare-earth metal) catalytic system with a soft Lewis acid component AgOAc/PPh_3 was next examined (Table 2). Screening of rare-earth-metal alkoxides revealed that La was optimal as a hard Lewis acid with an amide-based ligand **1a**, in terms of both chemical yield and enantioselectivity (Table 2, entries 1–5). Of particular note was the absence of by-product **4a** in the $RE(OiPr)_3$/**1a**/AgOAc/PPh_3 catalytic system. Although the reaction using bidentate ligand **5** significantly decreased the enantioselectivity (Table 2, entries 2 vs. 6), employing AcOEt as the reaction solvent enhanced the enantioselectivity to 63 % *ee* (Table 2, entry 7). Further improvement of the enantioselectivity was observed at lower temperatures at the expense of chemical yield. Thus the reaction at 0 °C afforded **3a** with 90 % *ee* (Table 2, entry 9).

The scope of the Conia-ene reaction using the $La(OiPr)_3$/**1a**/AgOAc/PPh_3 heterobimetallic catalytic system is summarized in Table 3.[11,12] In addition to malonamate **2a** (Table 3, entry 1), the present hard Lewis acid/soft Lewis acid heterobimetallic system was also applicable to the Conia-ene reaction of β-keto esters. α-Benzoyl esters **2b** and **2c** were converted into the corresponding Conia-ene products with high enantioselectivity, irrespective of the ester group. The reaction using aromatic β-keto esters was dependent on the electronic nature of the substituent on the aromatic ring; the reaction proceeded smoothly with aromatic β-keto esters **2d** and **2e** with high enantioselectivity (Table 3, entries 4–6), whereas low conversion was observed with β-keto ester **2f** bearing an electron-donating methoxy substituent, even after an extended reaction time (Table 3, entry 7). Aliphatic β-keto esters exhibited higher reaction efficiency and the reaction of **2g** was achieved even with only 0.5 mol % catalyst loading (Table 3, entry 9). The present heterobimetallic catalyst system was robust and the reaction was performed in air with comparable yield and enantioselectivity (Table 3, entry 8). The ester group marginally impacted on the enantioselectivity and the use of amide-based ligand **1b** bearing a bulkier substituent derived from L-*tert*-butylglycine enhanced the enantioselectivity in the reaction of ethyl ester **2h** (Table 3, entries 10 and 11). Both reactivity and enantioselectivity diminished as the steric bulk around the ketone moiety increased (Table 3, entry 13–16). The enantioselectivity of the reaction with *n*-propyl ketone **2l** decreased to 83% *ee* (Table 3, entry 16).

The cooperative nature of the present catalyst system is suggested by results of the control experiments outlined in Scheme 3. When the reaction of **2g** was run without the AgOAc/PPh$_3$ component or La(O*i*Pr)$_3$ under otherwise identical conditions, no formation of the Conia-ene product **3g** was detected, thus indicating that simultaneous activation of the 1,3-dicarbonyl group by hard Lewis acidic La and the alkyne group by soft Lewis acidic Ag is crucial to promote the reaction.

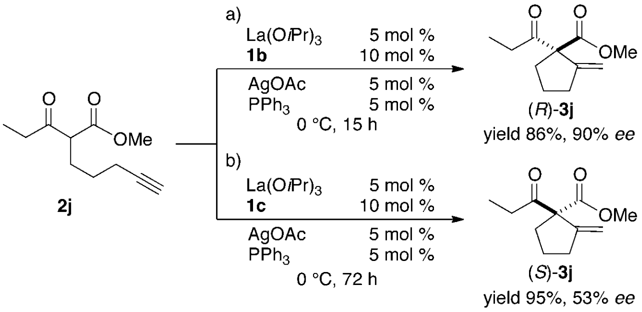


Optimal conditions: yield 89%, 92% *ee*
Conditions A: yield 0%
Conditions B: yield 0%

Scheme 3. Control experiment. Optimal conditions: La(O*i*Pr)$_3$ (5 mol%)/**1a**(10 mol%)/AgOAc(5 mol%)/PPh$_3$(5 mol%); conditions A: La(O*i*Pr)$_3$(5 mol%)/**1a**(10 mol%); conditions B: **1a**(10 mol%)/AgOAc(5 mol%)/PPh$_3$(5 mol%).

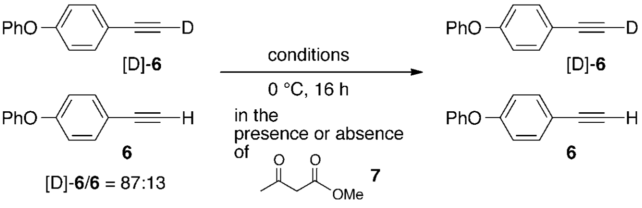
To gain insight into the actual active catalyst, ^{31}P and ^{1}H NMR analyses of La(O*i*Pr)$_3$/**1a**/AgOAc/PPh$_3$ (1:2:1:1) heterobimetallic catalyst were conducted. The ^{31}P NMR spectrum of the same heterobimetallic catalyst in CDCl$_3$ was nearly identical to that of AgOAc/PPh$_3$, thus suggesting that the La(O*i*Pr)$_3$/**1a** component did not form a stable complex with the Ag cation.[13] Broad signals were observed in the ^{1}H NMR spectrum of La(O*i*Pr)$_3$/**1a** (1:2) in CDCl$_3$, thus indicating that complexation of La(O*i*Pr)$_3$ and **1a** was in equilibrium as demonstrated in previous studies.[8b] These spectroscopic patterns remained unchanged upon the addition AgOAc/PPh$_3$, as expected from ^{31}P NMR analysis. Taken together, these findings suggest that the hard Lewis acid component La(O*i*Pr)$_3$/**1a** and the soft Lewis acid component AgOAc/PPh$_3$ were not inherently associative and thus associated on hard and soft Lewis basic substrate **2** to function together in the transition state.

An amide-based ligand **1c** bearing a soft Lewis basic sulfide substituent (Scheme 1), derived from L-methionine, likely interacts with the Ag cation as well as with the La cation to drastically change the stereochemical course of the reaction. Indeed, with **2j** the Conia-ene product (*S*)-**3j** was obtained in 53% *ee* with the catalyst prepared from **1c** (Scheme 4b). Thus opposite enantioselection was produced when **1b** was used (Scheme 4a). The ^{31}P NMR spectrum of La(O*i*Pr)$_3$/**1c**/AgOAc/PPh$_3$ (1:2:1:1) displayed an upfield shift compared to that of AgOAc/PPh$_3$ (1:1), and is thus indicative of the formation of the **1c**/AgOAc/PPh$_3$ complex, which would account for the opposite enantioselectivity.



Scheme 4. Opposite stereoselection using amide-based ligand **1c** bearing a soft Lewis basic sulfide substituent.

The coexistence of alkyne and Ag salts may produce an unreactive Ag acetylide species and halt the desired catalytic process. To probe this possibility, deuterated alkyne [D]-**6** (87% deuterated) was subjected to the La/Ag heterobimetallic catalyst system in the presence of the proton donor methyl acetoacetate (**7**), which is chemically analogous to the 1,3-dicarbonyl substrate **2**. Stirring at 0°C with **7** led to a significant H/D exchange of [D]-**6** (Scheme 5, conditions A). Comparable level of H/D exchange was detected in the absence of **7**, and was likely due to proton exchange with the amide-based ligand **1a** (Scheme 5, conditions B). No H/D exchange proceeded in the absence of the soft Lewis acid component AgOAc/PPh$_3$ (Scheme 5, conditions C). These findings can be ascribed to silver-assisted deprotonation of the acetylenic proton of **6** to form silver acetylide and reprotonation through proton exchange with **7**, which occured in equilibrium as a nonproductive pathway.[14]



Conditions A: [D]-**6**/**6** = 6:94
Conditions B: [D]-**6**/**6** = 18:82
Conditions C: [D]-**6**/**6** = 87:13

Scheme 5. H/D exchange of acetylenic proton by the La/Ag heterobimatallic catalyst system. Conditions A: La(O*i*Pr)$_3$(10 mol%)/**1a** (20 mol%)/AgOAc(10 mol%)/PPh$_3$(20 mol%), **7** (1 equiv); conditions B: La(O*i*Pr)$_3$(10 mol%)/**1a**(20 mol%)/AgOAc(10 mol%)/PPh$_3$(20 mol%); conditions C: La(O*i*Pr)$_3$(10 mol%)/**1a**(20 mol%); **7** (1 equiv).

In summary, we have developed La(O*i*Pr)$_3$/**1**/AgOAc/PPh$_3$, a heterobimetallic hard Lewis acid/soft Lewis acid cooperative catalyst system, to promote an asymmetric Conia-ene reaction of malonamates and β-keto esters. Cooperative activation of a 1,3-dicarbonyl and alkyne moieties induced by the La/Ag heterobimetallic catalyst promoted the desired reaction with as little as 0.5 mol% catalyst loading. Applications of this cooperative catalyst for the asymmetric assembly of substrates bearing hard and soft Lewis basic functionalities are underway.

Received: March 25, 2011
Published online: June 6, 2011

Keywords: cooperative catalysis · heterobimetallic complexes · homogeneous catalysis · lanthanum · silver

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[11] The absolute configuration of **3a** was determined by X-ray crystallographic analysis. CCDC 817622 **3a** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Summary of crystallographic analysis and the crystal structure was provided in the Supporting Information.

[12] **3g**,**h**,**j**,**k** are volatile compounds and as a result the yield of isolated material fluctuated.

[13] See the Supporting Information.

[14] On the basis of the independent nature of La(O*i*Pr)$_3$/**1a** and AgOAc/PPh$_3$ components, the present catalytic asymmetric Conia-ene reaction likely proceeded through a formal *trans* carbometalation via a 5-*exo-dig* cyclization mode. 5-*Endo-dig* cyclization proceeded with substrate **2m** bearing an internal alkyne under optimized reaction conditions (La(O*i*Pr)$_3$ (5 mol%)/**1b**(10 mol%)/AgOAc(5 mol%)/PPh$_3$(10 mol%), AcOEt, 40 h) at room temperature, and afforded endocyclic cyclopentene **3m** in 65% yield and 52% *ee*. Product **3m** is not accessible via a *cis* carbometalation pathway, and *trans* carbometalation would be more likely for substrates **2a–l**. However, the possibility that *trans* carbometalation proceeded only with **2m** via the 5-*endo-dig* cyclization mode cannot be ruled out. The determination of the absolute configuration of **3m** is detailed in the Supporting Information.