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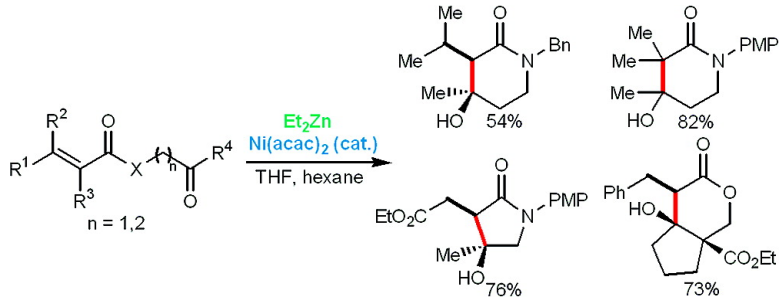
J. Am. Chem. Soc., **2008**, 130 (23), 7328-7338 • DOI: 10.1021/ja0775624 • Publication Date (Web): 16 May 2008



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Diastereoselective Nickel-Catalyzed Reductive Aldol Cyclizations Using Diethylzinc as the Stoichiometric Reductant: Scope and Mechanistic Insight

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Abstract: In the presence of diethylzinc as a stoichiometric reductant, $Ni(acac)_2$ functions as an efficient precatalyst for the reductive aldol cyclization of α,β-unsaturated carbonyl compounds tethered to a ketone electrophile through an amide or an ester linkage. The reactions are tolerant of a wide range of substitution at both α,β-unsaturated carbonyl and ketone components and proceed smoothly to furnish β-hydroxylactams and β-hydroxylactones with generally high diastereoselectivities. A series of experiments, including deuterium-labeling studies, was carried out in an attempt to gain some insight into the possible reaction mechanisms that might be operative.

Introduction

Nickel-catalyzed reductive coupling and cyclization reactions have recently emerged as powerful methods for accessing numerous polyfunctionalized products.[1,2] Typically operating under mild conditions, these reactions enable rapid increases in molecular complexity from relatively simple starting materials, with often high levels of diastereo- and enantiocontrol. Using reductants such as triethylborane, diethylzinc, and silanes, a variety of reactions have been developed that couple unsaturated species such as alkynes, 1,3-dienes, 1,3-enynes, and allenes with an array of electrophiles that includes aldehydes, ketones, imines, and epoxides.[2]

Another important class of reaction partners for nickel-catalyzed reductive coupling/cyclization reactions are α,β-unsaturated carbonyl compounds. With these substrates, the majority of examples described to date result in carbon−carbon bond formation at the β-position. For example, Montgomery and co-workers have described reductive cyclizations of electron-deficient alkenes with a range of tethered unsaturation where coupling at the β-position was the predominant pathway,[1t] and Tanaka and co-workers have reported similar carbocyclizations of enones onto vinyl sulfoxides.[1i] In addition, the Montgomery group has recently described intermolecular [3 + 2] reductive cycloadditions of enals with alkynes[1d] and intermolecular reductive couplings of enones with alkynes,[1b] where coupling also occurs at the β-carbon of the α,β-unsaturated carbonyl component.

In contrast, corresponding reactions where coupling occurs at the α-position of an α,β-unsaturated carbonyl compound have been rare;[3] although this deficiency has now been partially addressed by the recent report of nickel-catalyzed reductive aldol reactions between acrylate esters and aldehydes, where aryl halides were found to be essential reaction ingredients.[4] Given the wealth of literature that exists in the area of catalytic reductive aldol couplings and cyclizations of α,β-unsaturated carbonyl substrates mediated by other metals,[5] the relative dearth of corresponding nickel-catalyzed transformations is surprising. The development of such processes would considerably expand the repertoire of synthetic methods available to organonickel

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(1) For recent, representative examples, see: (a) Chaulagain, M. R.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 9568–9569. (b) Herath, A.; Thompson, B. B.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 8712–8713. (c) Yang, Y.; Zhu, S.-F.; Duan, H.-F.; Zhou, C.-Y.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 2248–2249. (d) Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 14030–14031. (e) Samih ElDouhaibi, A.; Lozanov, M.; Montgomery, J. *Tetrahedron* **2006**, *62*, 11460–11469. (f) Kimura, M.; Ezoe, A.; Mori, M.; Iwata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8559–8568. (g) Moslin, R. M.; Miller, K. M.; Jamison, T. F. *Tetrahedron* **2006**, *62*, 7598–7610. (h) Knapp-Reed, B.; Mahandru, G. M.; Montgomery, J. *J. Am. Chem. Soc.* **2005**, *127*, 13156–13157. (i) Maezaki, N.; Sawamoto, H.; Ishihara, H.; Tanaka, T. *Chem. Commun.* **2005**, 3992–3994. (j) Miller, K. M.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 3077–3080. (k) Luanphaisarnnont, T.; Ndubaku, C. O.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 2937–2940. (l) Kimura, M.; Miyachi, A.; Kojima, K.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2004**, *126*, 14360–14361. (m) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3941–3944. (n) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698–3699. (o) Sato, Y.; Saito, N.; Mori, M. *J. Org. Chem.* **2002**, *67*, 9310–9317. (p) Sato, Y.; Sawaki, R.; Saito, N.; Mori, M. *J. Org. Chem.* **2002**, *67*, 656–662. (q) Kimura, M.; Ezoe, A.; Tanaka, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 3600–3602. (r) Shibata, K.; Kimura, M.; Shimizu, M.; Tamaru, Y. *Org. Lett.* **2001**, *3*, 2181–2183. (s) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 397–400. (t) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911–4920.

(2) For a review, see: Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890–3908.

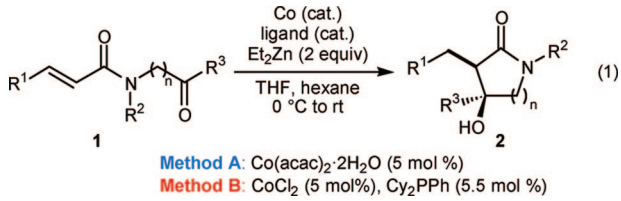
(3) The Zhou and Tamaru groups have reported isolated examples of both inter- and intramolecular reductive couplings of dienyl esters with aldehydes, where coupling occurred α to the ester carbonyl. However, it is the diene functionalities of these substrates that are essential for reaction to proceed, rather than the α,β-unsaturated ester. See refs 1c, 1f, and 1q.

(4) Chrovian, C. C.; Montgomery, J. *Org. Lett.* **2007**, *9*, 537–540.

10.1021/ja0775624 CCC: $40.75

chemistry and would provide complementary approaches for executing reductive aldol reactions.

With these considerations in mind, we recently initiated a program targeted at the development of new reductive aldol cyclizations and couplings catalyzed by nickel (among other metals), where emphasis was placed on less reactive substrate classes such as β-substituted α,β-unsaturated esters, β-substituted α,β-unsaturated amides, and ketones that might otherwise prove difficult to couple using existing catalytic methodologies.[5] As part of these studies, we recently disclosed that cobalt salts function as effective precatalysts in the diethylzinc-mediated reductive aldol cyclization of substrates of general structure **1**, containing an α,β-unsaturated carbonyl moiety tethered to a ketone through an amide (eq 1).[6,7] These reactions delivered β-hydroxylactams **2** in 47 to >99% yield, and with generally high levels of diastereoselection (8:1 to >19:1).



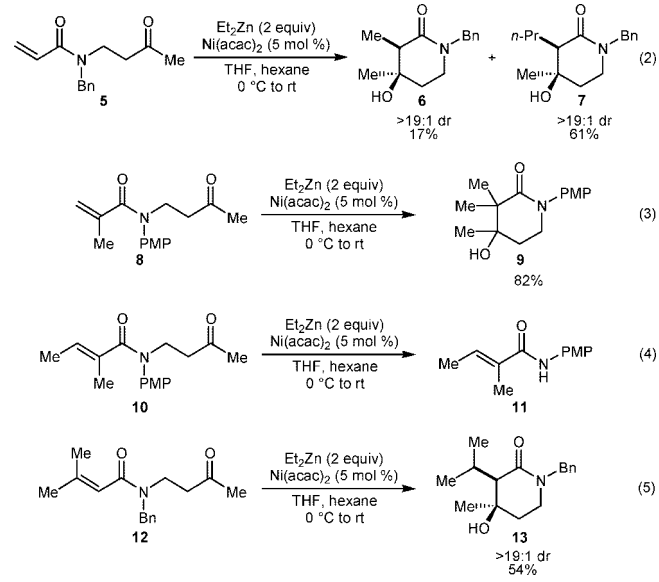
(1)

In this Article, we demonstrate that the combination of $Ni(acac)_2$ and diethylzinc not only functions in much the same capacity but also promotes the reactions of substrates that are either completely inert to the cobalt conditions[6] or react with much lower efficiencies and/or reproducibilities. This significantly expanded substrate scope includes cyclization precursors containing ester tethers, α-substituted α,β-unsaturated amides, β,β-disubstituted α,β-unsaturated amides, and β-ester-substituted α,β-unsaturated amides, allowing access to a correspondingly broader array of mono- and bicyclic products in diastereoselective fashion.

Results and Discussion

Reaction Scope. Our investigations into nickel-catalyzed reductive aldol cyclizations commenced with reactions that provided six-membered β-hydroxylactams as the products (Table 1). Using 5 mol % of $Ni(acac)_2$ and 2 equiv of Et_2Zn, a range of substrates **3a**−**3m** underwent smooth cyclization to furnish 4-hydroxypiperidin-2-ones **4a**−**4m**. A variety of substituents at the α,β-unsaturated amide component that encompassed linear and branched alkyl (entries 1−3, 8−10, and 12), aromatic (entries 4, 7, and 13), and heteroaromatic (entries 5, 6, and 13) groups was accommodated to provide cyclized products in good to excellent yields and with generally high diastereoselectivities (≥9:1 by ^1H NMR analysis of the unpurified reaction mixtures).[8] The reactions were also tolerant of variation of the ketone component, with alkyl (entries 1−7), cycloalkyl (entries 12 and 13), and phenyl (entries 8−11) ketones all participating successfully. Variation of the nitrogen protecting group from benzyl (entries 1−5 and 9−11) to *para*-methoxyphenyl (entries 6, 7, 12, and 13) or *ortho*-methoxyphenyl (entry 8) was also permitted, and a pre-existing stereocenter in substrates **3l** and **3m** led to high levels of internal asymmetric induction to provide bicyclic δ-lactams **4l** and **4m**, respectively (entries 12 and 13). Overall, the results presented in Table 1 are comparable to those reported previously using $Co(acac)_2\cdot 2H_2O$ as the precatalyst.[6]

Simple β-unsubstituted acrylamides are less competent substrates in these reactions, due to their propensity to undergo *alkylative* aldol cyclization[9] in preference to reductive cyclization. For example, acrylamide **5** provided the desired product **6** in only 17% yield, with the major product obtained being **7**, derived from ethyl conjugate addition and aldol cyclization (eq 2). This result contrasts with that obtained previously using $Co(acac)_2\cdot 2H_2O$ as the precatalyst in place of $Ni(acac)_2$, where the reductive cyclization product **6** was obtained in 88% yield and none of the alkylative product **7** was detected.[6] However, substitution at the α-position of the acrylamide re-established reductive cyclization as the dominant pathway, as illustrated by the cyclization of methacrylamide **8** to provide lactam **9** containing two contiguous quaternary centers in 82% yield (eq 3). Efforts to extend the scope of these reactions to more highly substituted α,β-unsaturated amides were partially successful; although tiglic amide **10** did not undergo cyclization (furnishing elimination product **11** instead) (eq 4), α,β-unsaturated amide **12** provided lactam **13** in 54% yield (eq 5). It should be noted that attempted cyclizations of substrates **8**, **10**, and **12** using $Co(acac)_2\cdot 2H_2O$[6] were completely unsuccessful.



Substrates **14a** and **14b** afforded bicyclic products **16a** and **16b**, respectively, as a result of the presumed tertiary zinc

(5) For a seminal reference, see: (a) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809–4812. For an extensive collection of reports of catalytic reductive aldol reactions, see references cited within: (b) Ngai, M.-Y.; Kong, J.-R.; Krische, M. J. *J. Org. Chem.* **2006**, *72*, 1063–1072. For relevant reviews, see: (c) Nishiyama, H.; Shiomi, T. *Top. Curr. Chem.* **2007**, *279*, 105–137. (d) Jang, H.-Y.; Krische, M. J. *Eur. J. Org. Chem.* **2004**, 3953–3958. (e) Jang, H.-Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653–661. (f) Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, 12–21. (g) Chiu, P. *Synthesis* **2004**, 2210–2215. (h) Motherwell, W. B. *Pure Appl. Chem.* **2002**, *74*, 135–142.

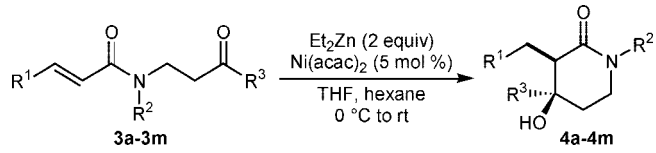
(6) Lam, H. W.; Joensuu, P. M.; Murray, G. J.; Fordyce, E. A. F.; Prieto, O.; Luebbers, T. *Org. Lett.* **2006**, *8*, 3729–3732.

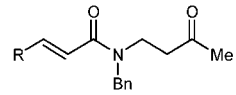
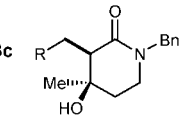
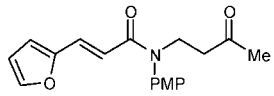
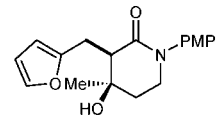
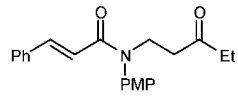
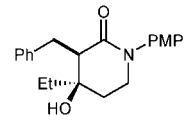
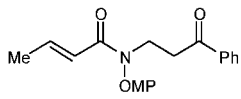
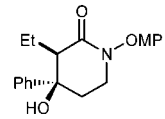
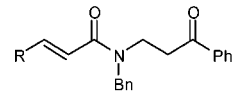
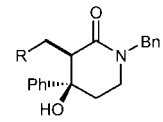
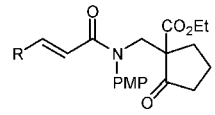
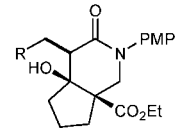
(7) For *inter*molecular variants of these reactions, see: Lumby, R. J. R.; Joensuu, P. M.; Lam, H. W. *Org. Lett.* **2007**, *9*, 4367–4370.

(8) The products **4a**, **4b**, **4d**, **4e**, **4g**, **4i**, **4j**, **4l**, and **4m** have been described previously (see ref 6). Product **4h** has been described previously: Lam, H. W.; Murray, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743–5746. The relative stereochemistries of the remaining products in Table 1 were assigned by analogy

(9) For examples of alkylative aldol cyclizations (sequential 1,4-conjugate addition−intramolecular aldol reactions), see: (a) Caube, D. F.; Gipson, J. D.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 1110–1111. (b) Bocknack, B. M.; Wang, L.-C.; Krische, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5421–5424. (c) Agapiou, K.; Cauble, D. F.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4528–4529.

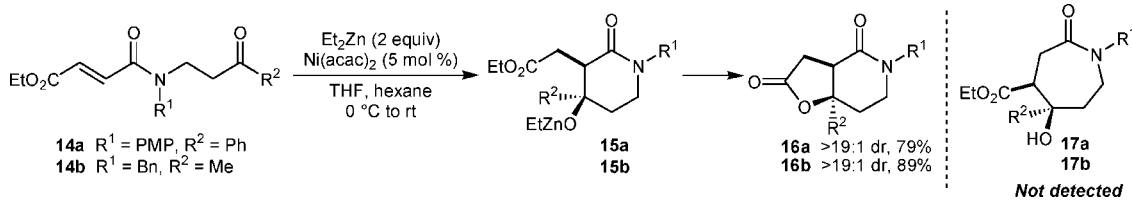
Table 1. Nickel-Catalyzed Reductive Aldol Cyclization Furnishing 4-Hydroxypiperidinones[a]



entry	substrate		product		dr[b]	yield (%)[c]
1		R = Me **3a**		**4a**	>19:1	97
2		R = *i*-Pr **3b**		**4b**	>19:1	98
3		R = CH_2CH_2Ph **3c**		**4c**	>19:1	95
4		R = Ph **3d**		**4d**	>19:1	97
5		R = 2-furyl **3e**		**4e**	>19:1	>99
6		**3f**		**4f**	>19:1	75
7		**3g**		**4g**	9:1	82
8		**3h**		**4h**	>19:1	62
9		R = Me **3i**		**4i**	9:1	84
10		R = *i*-Bu **3j**		**4j**	12:1	84
11		R = 2-furyl **3k**		**4k**	>19:1	79
12		R = Me **3l**		**4l**	>19:1[d]	62
13		R = Ph **3m**		**4m**	>19:1[d]	50

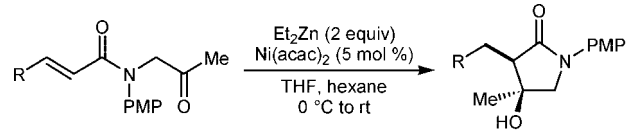
[a] Reactions were conducted using 0.20 mmol of substrate in THF (1.5 mL) and hexane (0.4 mL). [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c] Isolated yield of major diastereomer. [d] Here dr = (major isomer):(Σ other isomers). PMP = *para*-methoxyphenyl. OMP = *ortho*-methoxyphenyl.

Scheme 1. Sequential Reductive Cyclization−Lactonization



alkoxides **15a** and **15b** produced on initial reductive cyclization undergoing lactonization onto the pendant ester (Scheme 1). Notably, none of the possible alternative regiosomeric products **17a** and **17b**, resulting from cyclization α to the ester rather than the amide, were detected in the product mixtures. These examples highlight the high chemoselectivity of these transformations. Again, it should be noted that attempted cyclizations of **14a** and **14b** using $Co(acac)_2 \cdot 2H_2O$[6] in place of $Ni(acac)_2$ were unsuccessful.

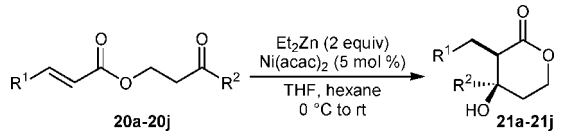
These reactions are also applicable to the synthesis of five-membered lactams, as illustrated by eqs 6–9. These results once again demonstrate the tolerance of these reactions to variation of the substituent at the *β*-position of the α,*β*-unsaturated carbonyl component, with substrates containing alkyl (eqs 6 and 7), aromatic (eq 8), and ester groups (eq 9) successfully undergoing the reaction. In the case of substrate **18d**, <10% of lactonization was observed (compare with Scheme 1).



18a R = Me — **19a** 5:1 dr, 42% (6)
18b R = *i*-Pr — **19b** 5:1 dr, 70% (7)
18c R = 2-MeOPh — **19c** >19:1 dr, 58% (8)
18d R = CO_2Et — **19d** >19:1 dr, 76% (9)

The cyclizations of oxygen-linked precursors were studied next (Table 2). In contrast to the use of $Co(acac)_2 \cdot 2H_2O$ as the

Table 2. Nickel-Catalyzed Reductive Aldol Cyclization Furnishing β-Hydroxylactones[a]

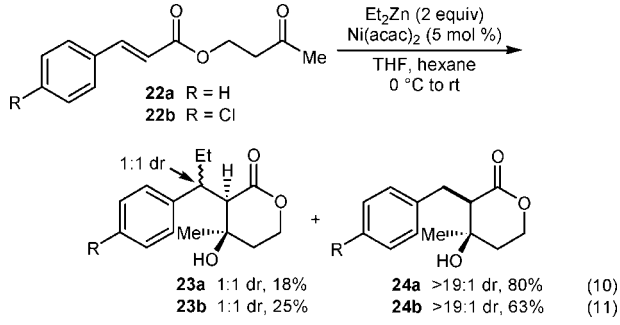


entry	substrate		product		dr[b]	yield (%)[c]
1		R = *i*-Bu **20a**		**21a**	>19:1	77
2		R = CH_2CH_2Ph **20b**		**21b**	>19:1	85
3		R = 4-MeOPh **20c**		**21c**	>19:1	76
4		R = 2-furyl **20d**		**21d**	>19:1	81
5		R = *i*-Bu **20e**		**21e**	5.5:1	84[d]
6		R = CH_2CH_2Ph **20f**		**21f**	≥10:1	76[e]
7		R = 2-furyl **20g**		**21g**	n.d[f]	75[f]
8		R = Me **20h**		**21h**	>19:1[g]	88
9		R = *i*-Pr **20i**		**21i**	>19:1[g]	74
10		R = Ph **20j**		**21j**	>19:1[g]	73

[a] Reactions were conducted using 0.20 mmol of substrate in THF (1.5 mL) and hexane (0.4 mL). [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c] Isolated yield of major diastereomer. [d] Isolated as an inseparable 5.5:1 mixture of diastereomers. [e] Accompanied by <5% of alkylative cyclization product as an inseparable impurity. Cited yield of **21f** has been adjusted to reflect this impurity. [f] Accompanied by ca. 10% of alkylative cyclization product as an inseparable impurity, making determination of the diastereomeric ratio of **21g** difficult. Cited yield of **21g** has been adjusted to reflect this impurity. [g] Here dr = (major isomer):(Σ other isomers).

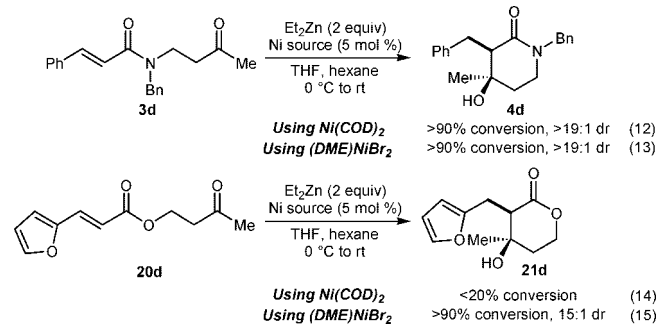
precatalyst, which generally provides negligible (<5%) conversions with ester-tethered substrates, the $Ni(acac)_2/Et_2Zn$ combination was found to give productive cyclizations to afford a range of β-hydroxylactones **21a**−**21j** in good to excellent yields with high diastereoselectivities.[10,11] Furthermore, compared to their amide-tethered counterparts (Table 1), these reactions display similar tolerance of substitution at both the α,β-unsaturated carbonyl component and the ketone. With substrates **20f** and **20g**, small quantities of the corresponding alkylative aldol cyclization products were observed (entries 6 and 7). A pre-existing stereocenter in substrates **20h**−**20j** again led to high levels of internal asymmetric induction (entries 8−10).

An interesting electronic effect was observed with cinnamic substrates. While *p*-methoxy-substituted precursor **20c** gave only the reductive aldol product **21c** in 76% yield (Table 2, entry 3), less electron-rich substrates **22a** and **22b** provided significant quantities of alkylative aldol products **23a** and **23b**, respectively, as 1:1 inseparable mixtures of diastereomers (eqs 10 and 11).[9] It appears that, as the aromatic group becomes more electron-deficient, the degree of alkylative aldol cyclization becomes more significant.



(10)
(11)

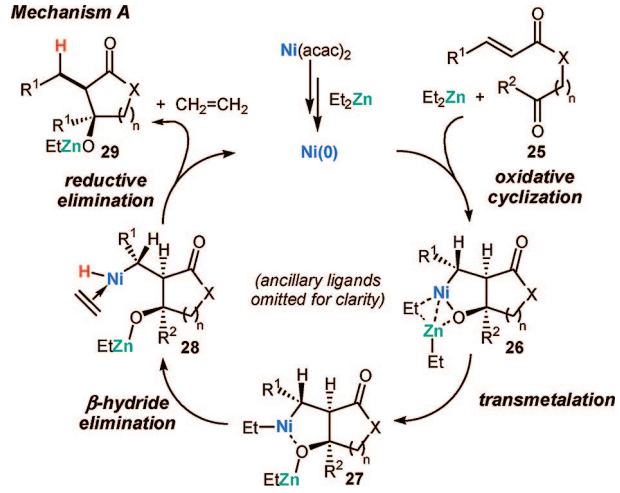
Mechanistic Considerations. Numerous mechanistic possibilities (often speculative) have been advanced to explain the outcome of nickel-catalyzed reductive couplings and cyclizations.[2] The generally accepted active oxidation state of nickel in these reactions is 0, and we assume that Ni(0), generated by the well-known reduction of $Ni(acac)_2$ with Et_2Zn,[2] is also responsible for catalysis of the reactions described herein. Nevertheless, with $Ni(acac)_2$ as a precatalyst, there exists the possibility that the active catalyst is actually a Ni(II) species. We therefore repeated two representative reactions using $Ni(COD)_2$ in place of $Ni(acac)_2$, with the expectation that, if Ni(0) is the true active species, cyclization would occur. In the event, cyclization was observed in both cases (eqs 12 and 14), thus supporting the notion that Ni(0) is the catalytically competent species. However, the efficiencies of these reactions were markedly different. In the reaction of cinnamic amide **3d**, $Ni(COD)_2$ was almost identical to $Ni(acac)_2$, providing lactam **4d** in high diastereoselectivity (>19:1) and high conversion (eq 12, compare with Table 1, entry 4). On the other hand, $Ni(COD)_2$ functioned poorly compared to $Ni(acac)_2$ with ester-tethered substrate **20d**, providing the product **21d** in <20% conversion (eq 14, compare with Table 2, entry 4). Although the catalytic efficiencies of $Ni(COD)_2$ and $Ni(acac)_2$ have sometimes proven to be essentially indistinguishable in other classes of reactions involving main group organometallics, such as the cross-coupling of cyclic anhydrides with organozinc reagents developed by the Rovis group,[12] the outcome of eq 14, along with the reductive aldol reactions developed by the Montgomery group,[4] demonstrates that this is not always the case. Given the increasing awareness that olefins, present either as ligands in precatalyst sources or as exogenous additives, do not always act as innocent bystanders in transition-metal-catalyzed reactions,[13] these results are not entirely surprising, and we suspect that the cyclooctadiene ligands present in $Ni(COD)_2$ are responsible for the different behavior of $Ni(acac)_2$ and $Ni(COD)_2$.



The cyclizations of substrates **3d** and **20d** using $(DME)NiBr_2$ as the precatalyst provided very similar outcomes to those obtained using $Ni(acac)_2$ (eqs 13 and 15, compare with Table 1, entry 4 and Table 2, entry 4, respectively). These results lend further support to the hypothesis that the inferiority of $Ni(COD)_2$ compared with $Ni(acac)_2$ for ester-tethered substrates is due to a negative effect of the cyclooctadiene ligands in $Ni(COD)_2$

(10) Compare with results obtained using copper bisphosphine catalysts in conjunction with siloxane reductants: Lam, H. W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225–4228.
(11) The products **21a**−**21d** have been described previously (see ref 10), and the relative stereochemistries of the remaining products in Table 2 were assigned by analogy.
(12) Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 247–254.
(13) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840–871.

Scheme 2. A Possible Reaction Mechanism Invoking Metallacycle Participation



rather than some beneficial role played by the acetylacetonate ligands or Zn-acac byproducts resulting from the use of $Ni(acac)_2$. Having established that Ni(0) is the likely active oxidation state in the reactions described herein, our attention turned to consideration of the possible reaction mechanism. Of the reactive pathways available to organonickel chemistry that could explain these reactions,[2] two in particular seemed to be plausible.

A significant number of nickel-catalyzed reductive coupling and cyclizations are consistent with the intervention of metallacyclic intermediates, formed by the oxidative cyclization of Ni(0) with two π-components.[2] Further support for the involvement of metallacycles in these reactions comes in the form of oxidative cyclization products that have been isolated and characterized by X-ray crystallography.[14,15] Although the present reactions are formally reductive aldol processes, it is conceivable that they actually occur through metallacycle participation rather than via discrete enolates, and a possible catalytic cycle for such a pathway is depicted in Scheme 2 (mechanism A). Oxidative cyclization of Ni(0) with the alkene and the ketone of the substrate **25** would result in oxanickellacycle **26**. By analogy with a detailed study conducted by Schlegel, Montgomery, and co-workers,[15a] we suggest that diethylzinc would facilitate oxidative cyclization by (i) Lewis acid activation of the ketone through binding with zinc, and (ii) Lewis basic activation of Ni(0) through a three-center two-electron bridging interaction of a zinc−ethyl bond. The rate-accelerating effect of Lewis acids on nickel-promoted oxidative cyclizations has also been demonstrated by Ogoshi, Kurosawa, and coworkers.[14c,d] Cleavage of the oxanickellacycle **26** by transmetalation would provide nickel−ethyl species **27**, which can then undergo β-hydride elimination to generate nickel hydride **28**. Finally, reductive elimination of **28** would provide zinc alkoxide **29** (which would be protonated upon workup to give the product), ethylene, and Ni(0), which would re-enter the catalytic cycle. Within this mechanistic framework, the relative stereochemistries of the major diastereomers obtained in these reactions may be explained by the preference for formation of the bicyclic metallacycle **26** containing a cis-ring junction, as opposed to a likely higher energy trans-ring junction.

A second, alternative catalytic cycle that does invoke the intervention of discrete enolate intermediates is illustrated in Scheme 3 (mechanism B). Interaction of Ni(0) with Et_2Zn may lead to intermediate **30**, containing a three-center two-electron bridging interaction.[15a] Coordination of **30** to the substrate **25** would then provide **31**, which can undergo β-hydride elimination to provide nickel hydride **32**. Reorganization of **32** can then occur to provide zinc enolate **33**,[16] which would undergo aldol cyclization to **29**, and Ni(0), which can re-enter the catalytic cycle. Here, the observed stereochemical outcome of the reactions may be explained by preferential formation of the (*Z*)-zinc enolate **33**, along with a chelated Zimmerman−Traxler-type transition state **34**.[17]

If mechanism B is operative, the formation of alkylative aldol cyclization products in varying quantities from precursors **5** (eq 2), **20f** and **20 g** (Table 2, entries 6 and 7), and **22a** and **22b** (eqs 10 and 11) might be accounted for by the particular steric and/or electronic properties of these particular substrates enabling conjugate addition from **31** to compete with β-hydride elimination to **32**. Alternatively, the formation of **7** from substrate **5** (eq 2) can be explained using mechanism A if reductive elimination from **27** competes effectively with β-hydride elimination to **28**. However, the isolation of alkylative cyclization products **23a** and **23b** (eqs 10 and 11) as 1:1 mixtures of diastereomers might be more difficult to rationalize by a metallacycle pathway, assuming all steps in mechanism A are stereospecific (vide infra).

Our efforts to shed light on these two mechanistic possibilities began with an experiment to establish whether mechanism B (Scheme 3) is possible, by subjecting α,β-unsaturated amide **35** lacking the pendant ketone electrophile to our standard reaction conditions (Scheme 4). In principle, mechanism B does not require the participation of the ketone until the zinc enolate **33** is formed, whereas in mechanism A (Scheme 2), the ketone is an essential component for oxidative cyclization to occur to provide oxanickellacycle **26**. Therefore, if mechanism B is operative, we might expect to observe the simple conjugate reduction product **38**.[18,19] In the event, exposure of **35** to our standard conditions provided only a complex mixture that appeared to be composed of oligomeric products, with none of the amide **38** being observed (Scheme 4). The failure to detect **38** does not rule out mechanism B since the zinc enolate **36** that would be formed from conjugate reduction of **35** could react

(14) (a) Ogoshi, S.; Ikeda, H.; Kurosawa, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4930–4932. (b) Ogoshi, S.; Tonomori, K.; Oka, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 7077–7086. (c) Ogoshi, S.; Ueta, M.; Arai, T.; Kurosawa, H. *J. Am. Chem. Soc.* **2005**, *127*, 12810–12811. (d) Ogoshi, S.; Oka, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2004**, *126*, 11802–11803.

(15) (a) Hratchian, H. P.; Chowdhury, S. K.; Gutiérrez-García, V. M.; Amarasinghe, K. K. D.; Heeg, M. J.; Schlegel, H. B.; Montgomery, J. *Organometallics* **2004**, *23*, 4636–4646. (b) Amarsinghe, K. K. D.; Chowdhury, S. K.; Heeg, M. J.; Montgomery, J. *Organometallics* **2001**, *20*, 370–372.

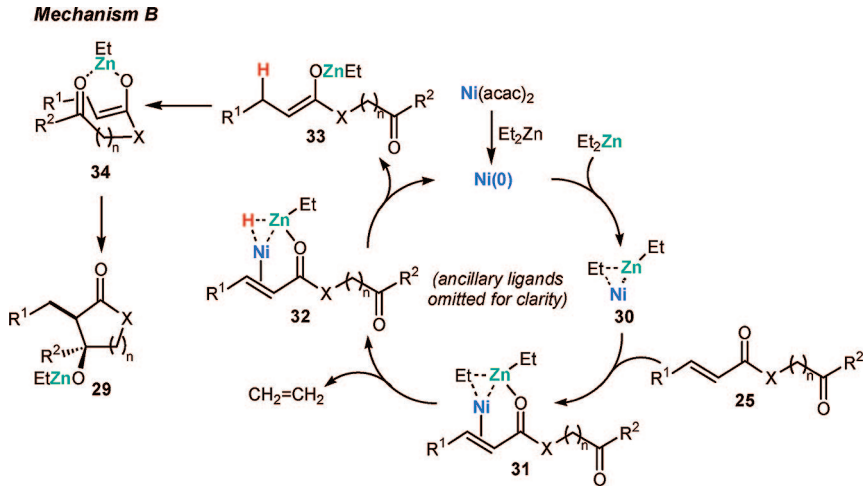
(16) A more detailed discussion of the putative conversion of intermediates of general structure **31** into zinc enolates is provided in the discussion of reaction mechanism (see Scheme 12).

(17) Zimmerman, H. E.; Traxler, M.; D, *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

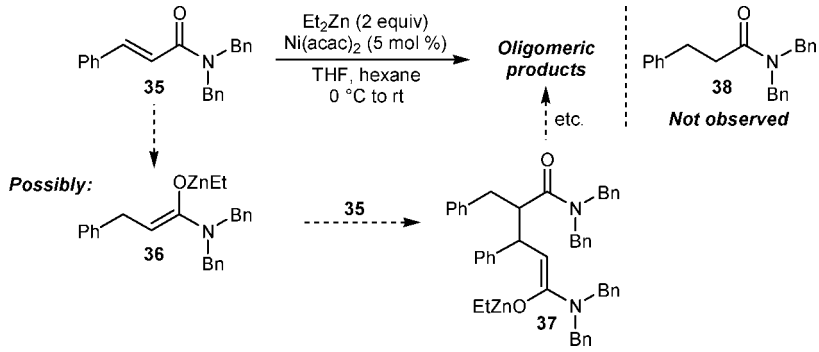
(18) Conjugate reductions of sterically hindered di- and trisubstituted enones in low yields have been observed previously in attempted conjugate addition reactions using $Ni(acac)_2/Et_2Zn$. See: (a) Chaloner, P. A.; Hitchcock, P. B.; Langadianou, E.; Readney, M. J. *Tetrahedron Lett.* **1991**, *32*, 6037–6038. (b) Bolm, C.; Ewald, M.; Felder, M. *Chem. Ber.* **1992**, *125*, 1205–1215.

(19) For $Co(acac)_2/Et_2Zn$-mediated conjugate reduction of chalcone, see: de Vries, A. H. M.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 1377–1378, See also ref 6 for $Co(acac)_2/Et_2Zn$-mediated conjugate reductions of α,β-unsaturated amides.

Scheme 3. A Possible Reaction Mechanism Invoking Zinc Enolate Formation



Scheme 4. Attempted Conjugate Reduction of **35**

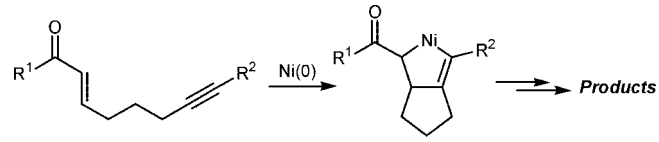


with additional starting material **35** in a Michael addition to provide a second zinc enolate **37** that could then lead to further oligomeric products. This type of behavior is known for poorly chemoselective 1,4-addition reactions of organometallic reagents.[20] This result differs from that obtained previously using $Co(acac)_2 \cdot 2H_2O$ in place of $Ni(acac)_2$, where amide **38** was formed in 73% yield.[6]

Since this experiment did not provide concrete evidence for or against mechanism B, a different approach was adopted in the hope of gaining more useful insight, which involved analysis of products obtained through variation of the connectivity of the substrates. As mentioned previously, most of the nickel-catalyzed reductive cyclizations reported to date involving α,β-unsaturated carbonyl substrates result in products where carbon−carbon bond formation has occurred at the β-position. The principal reason for this preference lies in the fact that the second reactive functional group in these substrates is tethered to the α,β-unsaturated carbonyl through the β-carbon. Consequently, as a result of geometrical constraints imposed by this mode of tethering, the metallacyclic mechanisms often invoked for these reactions must lead to an overwhelming preference for cyclization at the β-position, placing nickel α to the carbonyl carbon (e.g., Scheme 5, showing cyclization of an alkynyl enone/enal[1t,15]).

Because all of the substrates we have described thus far have the ketone tethered to the α,β-unsaturated carbonyl via

Scheme 5. Nickellacycle Formation for β-Tethered Substrates Such as Alkynyl Enones/Enals

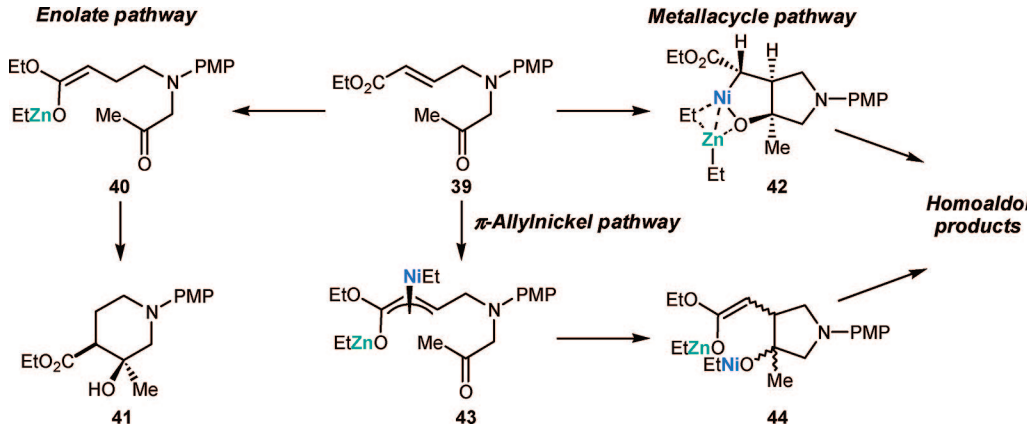


an amide or an ester linkage, it stood to reason that the cyclization of substrates where the ketone is tethered to the α,β-unsaturated carbonyl through the β-carbon might provide valuable information. Accordingly, substrate **39** was prepared for study (Scheme 6).

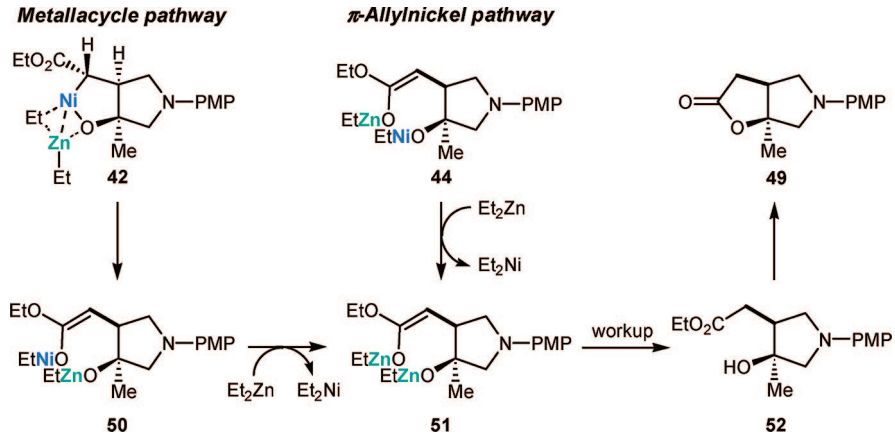
If reductive aldol product **41** was obtained in the cyclization of **39**, a mechanism analogous to that shown in Scheme 3, involving a discrete zinc enolate intermediate **40**, would most likely be operative, as a metallacyclic pathway (analogous to mechanism A, Scheme 2) would be precluded on the basis of geometric constraints. Although this outcome would not provide rigorous proof, it would then be tempting to suggest mechanism B (Scheme 3) as the most likely explanation for the cyclization of the amide- and ester-tethered substrates. However, if products resulting from cyclization at the β-position were formed, a mechanism (akin to that shown in Scheme 2) involving oxanickellacycle **42** could be responsible. A third option that is relevant in this case, but which could not explain the cyclization of the amide- and ester-tethered substrates, involves Et_2Zn-assisted oxidative addition of Ni(0) to the α,β-unsaturated ester to form π-allylnickel complex **43**, followed by migratory

(20) (a) Fraser, P.; Woodward, S. *Chem.—Eur. J.* **2003**, *9*, 776–783. (b) Blake, A. J.; Shannon, J.; Stephens, J. C.; Woodward, S. *Chem.—Eur. J.* **2007**, *13*, 2462–2472.

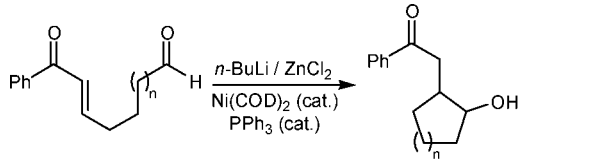
Scheme 6. Possible Cyclization Outcomes for Substrate **39**



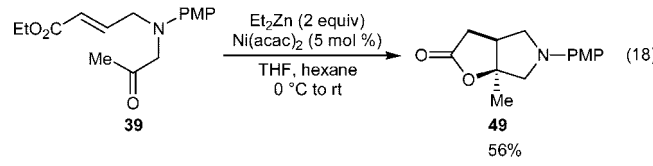
Scheme 7. Possible Mechanisms for the Formation of **49** from **42** or **44**



insertion of the ketone to give **44**.[2] Therefore, it can be seen that the cyclization of substrate **39** allows a clearer distinction between alternative mechanisms than the substrates we have described thus far. Of course, delineation of the probable mechanism for the cyclization of **39** would not necessarily mean that the same mechanism is also at work for the amide- and ester-tethered substrates. Nevertheless, the reaction of **39** still represented an important experiment, as the result would at least demonstrate whether enolate formation or metallacycle participation is possible for substrates containing both α,β-unsaturated carbonyl and ketone functional groups using $Ni(acac)_2/Et_2Zn$ and would add to the overall weight of evidence. In this context, it is important to note relevant precedent from the Montgomery group involving nickel-catalyzed cyclization of enone−aldehydes **45** and **46** under somewhat different conditions, which provided formal reductive homoaldol products **47** and **48**, respectively, rather than aldol products (eqs 16 and 17).[1t]

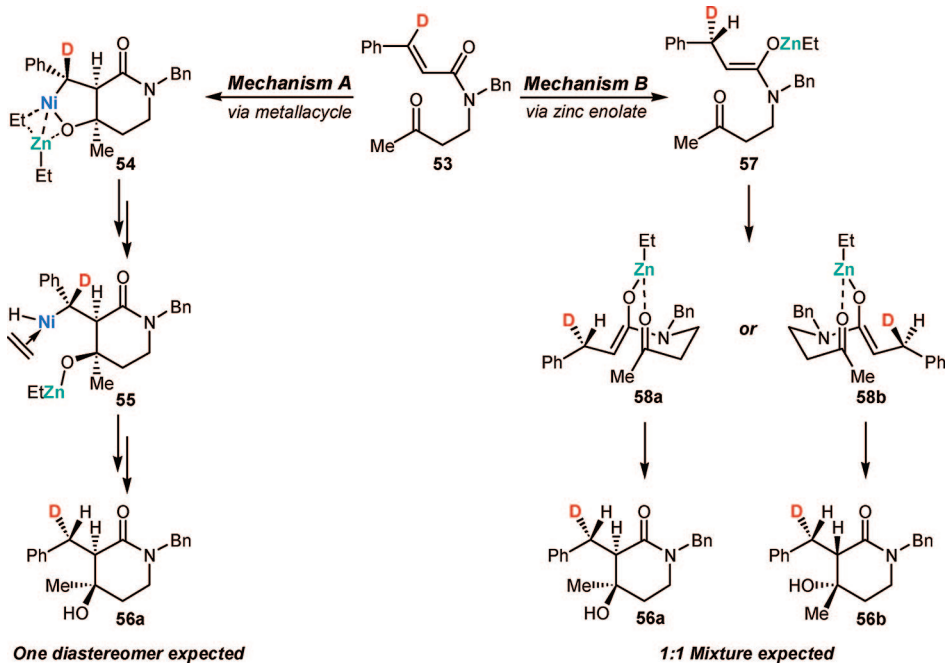


In the event, the reaction of **39** under standard conditions provided bicyclic lactone **49**, where carbon−carbon formation has occurred at the β-carbon, in 56% yield (eq 18), with no evidence of reductive aldol product **41**. Therefore, an enolate mechanism can be ruled out for the cyclization of **39**, leaving metallacycle or π-allylnickel pathways as viable options (see Scheme 6).



Scheme 7 illustrates possible pathways for the formation of bicyclic lactone **49** from oxanickellacycle **42** or migratory insertion product **44**. If a metallacycle pathway is operative, transmetalation of **42** to provide nickel enolate **50**, followed by further transmetalation with Et_2Zn, would provide zinc enolate **51**, which upon workup would result in γ-hydroxyester **52**, which in turn would then undergo spontaneous lactonization to **49**. In this case, it is important to note that a β-hydrogen-containing organometallic reagent is not required for this formal reductive homoaldol cyclization−lactonization sequence.[21] Alternatively, if a π-allylnickel pathway is operative, the same zinc enolate intermediate **51** could arise via transmetalation of **44** with Et_2Zn. As mentioned previously, the result of eq 18 is certainly informative insofar that it complements the results of Montgomery and co-workers[1t] (eqs 16 and 17) and demonstrates

Scheme 8. Expected Stereochemical Outcomes of Reductive Cyclization of Deuterium-Labeled Substrate **53** under Mechanisms A and B



metallacycle formation using α,β-unsaturated ester and ketone reaction partners as a possibility. However, this result in no way constitutes rigorous proof that a metallacyclic pathway is operative for the cyclizations of the amide- and ester-tethered precursors, nor does it allows us to confidently exclude an enolate mechanism for these substrates.

Our next attempt to discriminate between mechanisms A and B involved analysis of the stereochemical outcome of cyclization of deuterium-labeled substrate **53**, which was prepared in straightforward fashion.[22] If metallacycle-based mechanism A (Scheme 2) is operative, the concerted nature of the oxidative cyclization would be expected to provide metallacycle **54** with the relative stereochemistry shown (Scheme 8). An eventual reductive elimination of a nickel hydride **55** that proceeds with retention of configuration would be expected to provide only one diastereomer **56a** of the cyclized product. However, if the alternative mechanism B invoking the intervention of a zinc enolate **57** is operative, we should in principle expect a 1:1 mixture of two product diastereomers **56a** and **56b** to be formed since diastereomeric Zimmerman−Traxler-type transition states[17] **58a** and **58b** differ only with respect to the deuterium label and would therefore be expected to possess virtually identical energies.

In the event, the nickel-catalyzed reductive cyclization of **53** provided a 1:1.3 inseparable mixture of diastereomeric products **56a** and **56b** (relative stereochemistries of major and minor diastereomers not assigned) as determined by ^{1}H NMR analysis of the unpurified reaction mixture (Scheme 9, spectrum b, and eq 19). That a nonequimolar ratio of diastereomers was obtained was confirmed after removal of trace impurities by column chromatography,[23] and this result proved to be repeatable. This outcome, which is intermediate between the two limiting cases outlined in Scheme 8, suggests that mechanisms A and B are probably oversimplified descriptions, and the true mechanism is appreciably more complex.

Although at first glance the mixture of diastereomers obtained in eq 19 would appear to provide strong evidence against mechanism A, a possible scenario that was not discussed earlier, but which could potentially complicate the analysis of this deuterium-labeling study, is that the alkene of the α,β-unsaturated carbonyl moiety undergoes *E*/*Z* equilibration during these reactions (Scheme 10). Although less thermodynamically stable (*Z*)-**53** is likely to be present as only a minor component in an *E*/*Z* equilibrium mixture, its influence could nonetheless be important if *E*/*Z* interconversion is rapid, and it displays comparable or higher reactivity compared with that of (*E*)-**53** (Curtin−Hammett-type kinetics[24]). This scenario means the diastereomeric ratio obtained in eq 19 could still result from mechanism A (Scheme 10). In addition, *E*/*Z* isomerization within a metallacyclic manifold could provide an explanation for the isolation of alkylative cyclization products **23a** and **23b** (eqs 10 and 11) as 1:1 mixtures of diastereomers (vide supra).

To determine whether attainment of *E*/*Z* equilibrium is possible, we prepared (*Z*)-cinnamic amide (*Z*)-**60**[25] and ran the cyclization of this compound to partial completion by using only 0.5 equiv of Et_2Zn, as opposed to the 2 equiv used under our standard conditions (eq 21). Examination of the ^{1}H NMR spectrum of the unpurified reaction mixture revealed the presence of lactam **61** in addition to uncyclized material *which*

(21) The cyclization of **39** using Me_3Al (2 equiv) in place of Et_2Zn also resulted in the formation of **49** in ca. 80% conversion. Montgomery and co-workers have shown that bisenone substrates tethered through their β-carbons undergo nickel-catalyzed reductive cyclizations in the presence of organozincs lacking β-hydrogens. See ref 1t.

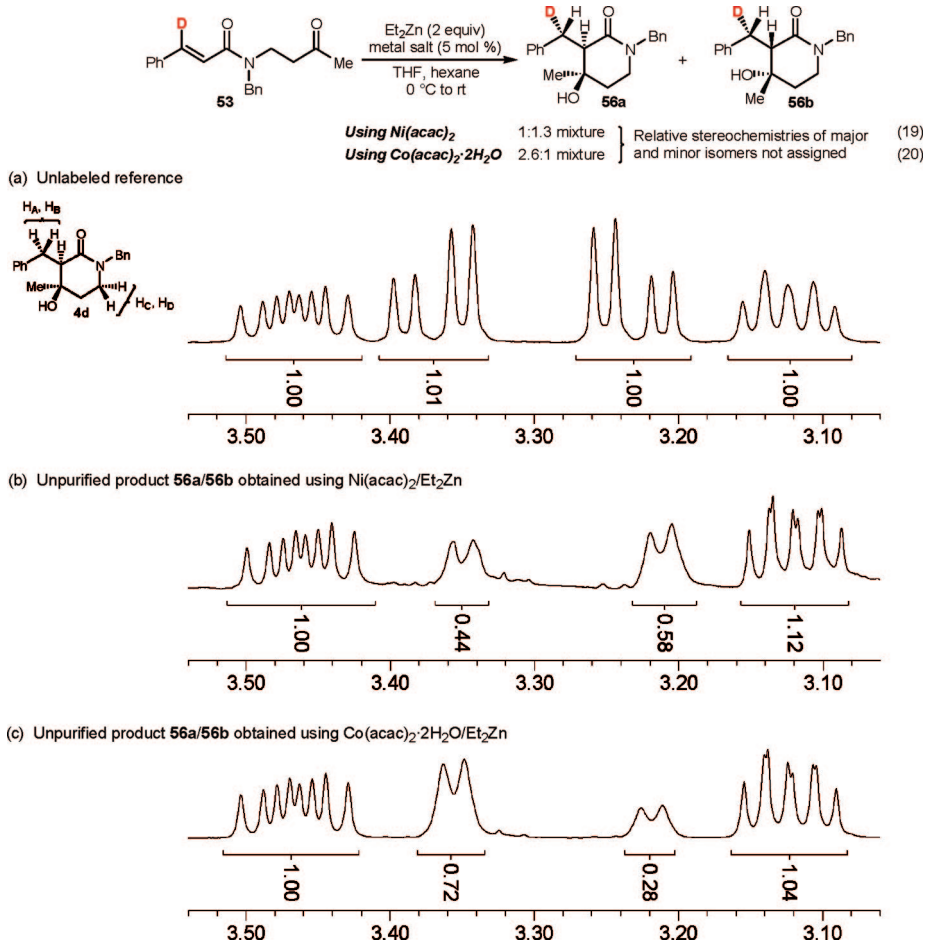
(22) See the Supporting Information for details.

(23) Purification of the product of the reaction depicted in eq 19 by column chromatography gave **56a**/**56b** in a 1:1.5 ratio (relative stereochemistries of major and minor isomers not assigned).

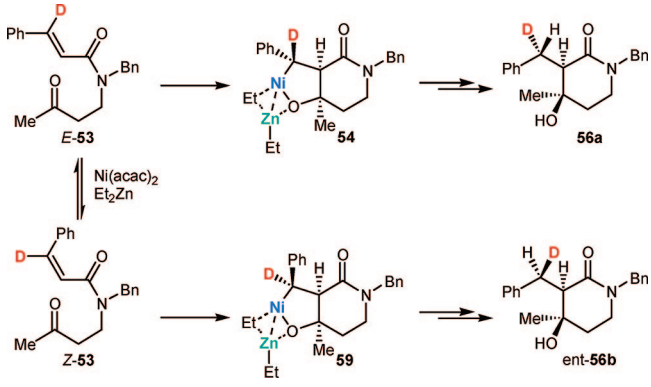
(24) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83–134.

(25) Substrate (*Z*)-**60** containing an aromatic N-substituent was chosen to simplify analysis because acyclic *N*-aryl tertiary amides exist predominantly in one rotameric form, leading to less complex ^{1}H NMR spectra. See: (a) Pederson, B. F.; Pederson, B. *Tetrahedron Lett.* **1965**, *6*, 2995–3001. (b) Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett.* **1989**, *30*, 6177–6180. (c) Curran, D. P.; Hale, G. R.; Geib, S. J.; Balog, A.; Cass, Q. B.; Degani, A. L. G.; Hernandes, M. Z.; Freitas, L. C. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3955–3975.

Scheme 9. Reductive Cyclization of Deuterium-Labeled Substrate **53** and ^{1}H NMR Spectra of Unlabeled Reference and Diastereomeric Products Obtained

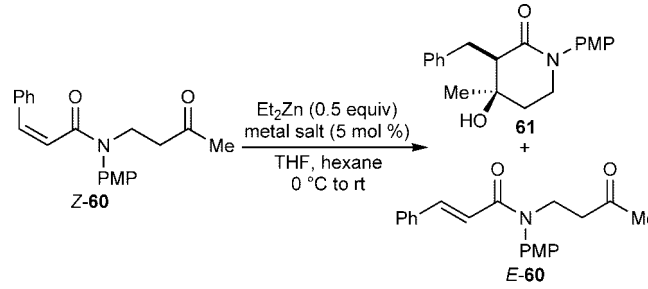


Scheme 10. *E*- to *Z*-Alkene Isomerization Could Allow a Mixture of **56a** and **56b** to be Obtained via a Metallacycle Mechanism



had undergone virtually complete isomerization (E/Z >19:1) to the more thermodynamically stable E-isomer, (*E*)-**60**. Therefore, mechanism A cannot be excluded on the basis of the results of eq 19.

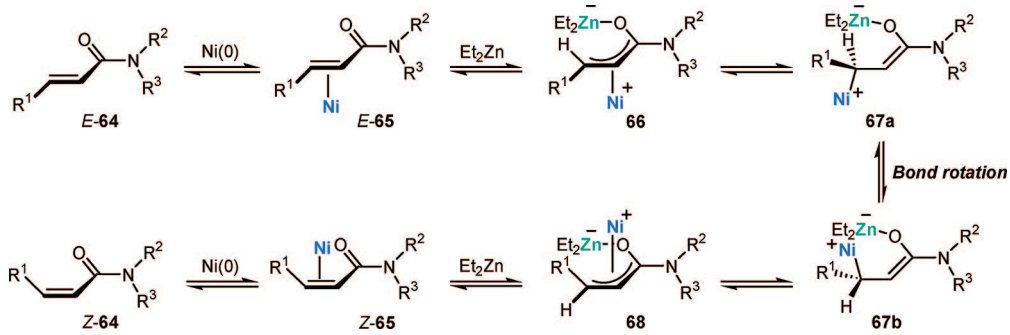
We suggest that alkene isomerization occurs via the formation of π-allylnickel species. The generation of π-allylmetal complexes by the oxidative addition of low-valent transition metals to α,β-unsaturated carbonyl compounds in the presence of Lewis acids is well precedented.[26,27] A particularly relevant example comes in the form of pioneering studies by MacKenzie and co-workers, who demonstrated that Ni(0) undergoes oxidative addition to α,β-unsaturated aldehydes **62** in the presence of trialkylsilyl chlorides to provide isolable π-allylnickel complexes **63** (eq 23).[26] In addition, Ogoshi, Kurosawa, and co-workers have isolated the products of oxidative addition of Pd(0) to enones in the presence of a range of Lewis acids.[27] π-Allylmetal species of this type have also been invoked as intermediates in several classes of transition-metal-catalyzed reactions[2,27,28] (see also Scheme 6).



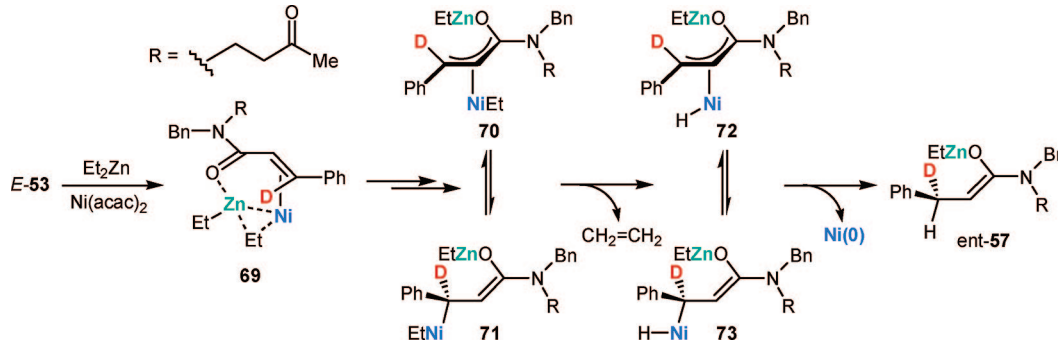
	Relative ratios			
	Z-**60**	**61**	*E*-**60**	
Using Ni(acac)$_2$	trace	1	1.6	(21)
Using Co(acac)$_2$·2H$_2$O	6.9	1	1.4	(22)

On the basis of this precedent, *E*/*Z* equilibration is therefore likely initiated by coordination of Ni(0) to α,β-unsaturated amide (*E*)-**64** to provide η^2-coordinated complex (*E*)-**65**, followed by Et_2Zn-assisted oxidative addition to provide π-allylnickel complex **66** (Scheme 11). A hapticity change from η^3 to η^1 to

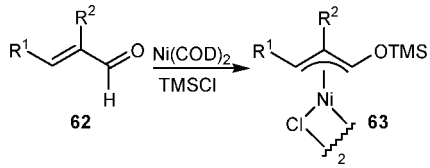
Scheme 11. Establishment of *E*/*Z* Alkene Equilibrium via $\eta^3-\eta^1-\eta^3$ Isomerization



Scheme 12. Zinc Enolate Formation via π-Allylnickel Species



give **67a** would then allow bond rotation to occur to provide **67b**. Re-establishment of η^3 hapticity to give π-allylnickel complex **68**, followed by reductive elimination to (*Z*)-**65** and decomplexation, would then furnish the isomerized α,β-unsaturated amide (*Z*)-**64**. The entire process is of course reversible, and this type of $\eta^3-\eta^1-\eta^3$ (also known as $\pi-\sigma-\pi$) isomerization has good precedence in the area of transition-metal-catalyzed allylic alkylations.[29] It should be stated that, for the purposes of simplicity, no three-center two-electron bridging interaction[15a] of the type depicted in structure **31** (see Scheme 3) and in structure **69** (Scheme 12, vide infra) between nickel, zinc, and an ethyl ligand has been shown for structures **65**−**68** in Scheme 11. However, an associative interaction of this type seems highly likely,[15a] which would also have important implications for mechanism B (see below).



(23)

Having determined that mechanism A (Scheme 8, left) remains a possibility, the question of whether mechanism B (Scheme 8, right) could also give rise to the observed ratio of **56a** and **56b** from the cyclization of **53** must be addressed. In this regard, and in light of the above discussion, a more detailed representation of the mechanism of zinc enolate formation from **53**, involving η^3 and η^1 intermediates, is depicted in Scheme 12. A tacit assumption in the simplified representation of mechanism B shown in Scheme 8 is that coordination of the pendant ketone in Zimmerman−Traxler-type transition states **58a** and **58b** only occurs *after* zinc enolate **57** has formed, which should then provide a 1:1 mixture of **56a** and **56b**. However, this assumption is not necessarily valid, as association of the Lewis basic ketone to the nickel and/or zinc center in any of the intermediates **70**−**73** (Scheme 12) is certainly possible, which would place the ketone on one particular diastereotopic face. If the degree of this association remains significant until formation of the zinc enolate (*ent*-**57** in the case of Scheme 12), and aldol cyclization is able to occur before the ketone has the opportunity to fully establish equilibrium in interchanging between the two diastereotopic enolate faces, a nonequimolar distribution of diastereomers could certainly result. Other factors which could complicate the situation further include the *E*/*Z* isomerization discussed above (Scheme 12 only shows the reaction of (*E*)-**53**), the nature/hapticity of the zinc enolate itself (oxa-π-allyl species, C-bound versus O-bound enolates), and changes in this hapticity during the course of the reaction. Therefore, mechanism B remains a strong possibility.

To summarize, these mechanistic investigations have (a) provided compelling evidence that Ni(0), generated in situ by the reduction of $Ni(acac)_2$ with Et_2Zn, is the catalytically competent species in these reactions; (b) shown $Ni(acac)_2$ to be a superior nickel source to the other commonly used precatalyst for nickel-catalyzed reductive couplings and cyclizations, namely, $Ni(COD)_2$; (c) demonstrated that a substrate

(26) (a) Johnson, J. R.; Tully, P. S.; MacKenzie, P. B.; Sabat, M. *J. Am. Chem. Soc.* **1991**, *113*, 6172–6177. (b) Grisso, B. A.; Johnson, J. R.; MacKenzie, P. B. *J. Am. Chem. Soc.* **1992**, *114*, 5160–5165.
(27) (a) Ogoshi, S.; Yoshida, T.; Nishida, T.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 1944–1950. (b) Ogoshi, S.; Tomiyasu, S.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2002**, *124*, 11598–11599.
(28) For relevant examples involving Ni(0)-catalyzed reactions, see: (a) Hirano, K. Yorimitsu, H. Oshima, K. *Org. Lett.* **2007**, *9*, 5031–5033. (b) Hirano, K. Yorimitsu, H. Oshima, K. *Org. Lett.* **2007**, *9*, 1541–1544. (c) Seiber, J. D. Liu, S. Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 2214–2215. (d) Ikeda, S.-i. Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975–5976. See also ref 2.
(29) See for example: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422. (b) Ogasawara, M.; Takizawa, K.-i.; Hayashi, T. *Organometallics* **2002**, *21*, 4853–4861.

39 containing a ketone connected to an α,β-unsaturated carbonyl through the β-carbon provides a reductive homoaldol product **49** rather than a reductive aldol product **41**, thus suggesting metallacycle or π-allylnickel mechanisms as possible pathways; and (d) uncovered that *E*/*Z* isomerization of the α,β-unsaturated carbonyl component can occur under these conditions. The implications of the latter phenomenon have meant that, unfortunately, a deuterium-labeling study designed specifically to distinguish between alternative metallacyclic (Scheme 8, left) and enolate (Scheme 8, right) pathways does not allow us to exclude either of these mechanisms. Although certain mechanistic issues remain unresolved, we believe the insights gained through these studies will be of benefit to other researchers engaged in the design, development, and understanding of related nickel-catalyzed reactions.

For comparison purposes, we also repeated the experiments of these mechanistic investigations using $Co(acac)_2 \cdot 2H_2O$ as the precatalyst[6] in place of $Ni(acac)_2$. For the cyclization of substrate **39**, $Co(acac_2) \cdot 2H_2O$ was found to be inferior to $Ni(acac)_2$. Although appreciable quantities of bicyclic lactone **49** were formed on occasions, with none of the reductive aldol product **41** detected (thus suggesting the ability of cobalt to participate in metallacycle or π-allylmetal pathways), the reproducibility of this reaction was variable. The cyclization of deuterium-labeled substrate **53** using $Co(acac)_2 \cdot 2H_2O$ again resulted in a nonequimolar ratio of diastereomeric products **56a** and **56b** (eq 20), but compared to the result obtained using $Ni(acac)_2$ (eq 19), the magnitude of diastereoselection was increased, and most importantly, *the sense of diastereoselection was reversed* (2.6:1 diastereomeric mixture, see Scheme 9, spectrum c). While the differences between the $Ni(acac)_2/Et_2Zn$ and $Co(acac)_2 \cdot 2H_2O/Et_2Zn$ reagent combinations are highlighted by the generally broader substrate scope of the nickel system, and their divergent behavior with simple β-unsubstituted acrylamides such as **5** and with substrates such as **35** lacking a pendant ketone (vide supra), the results of this isotopic labeling study also point to differences in their mechanisms. Finally, the cyclization of (*Z*)-**60** was conducted using $Co(acac)_2 \cdot 2H_2O$ and 0.5 equiv of Et_2Zn, which resulted in a mixture of recovered (*Z*)-**60**, the cyclized product **61**, and (*E*)-**60** (eq 22). Although this reaction proceeded to lower conversion than the analogous experiment using $Ni(acac)_2$ (eq 21), the presence of (*E*)-**60** in the unpurified mixture demonstrates that *E*/*Z* interconversion is also possible using the $Co(acac)_2 \cdot 2H_2O/Et_2Zn$ combination.

Conclusions

We have shown that, in the presence of diethylzinc, $Ni(acac)_2$ serves as a highly effective precatalyst for the reductive aldol cyclization of substrates containing an α,β-unsaturated carbonyl moiety tethered to a ketone through either an amide or an ester. In these reactions, diethylzinc acts a stoichiometric reducing agent, formally delivering a hydride to the β-position of the α,β-unsaturated carbonyl component of the cyclization precursor, leading to the formation of β-hydroxylactams and β-hydroxylactones with good to high levels of diastereoselection. A notable feature of these reactions is the broad tolerance of variation of the ketone, the β-substituent of the α,β-unsaturated carbonyl component, and the nitrogen protecting group in the case of amide-linked precursors to give a range of five- and six-membered products. Possible mechanisms for these transformations have been discussed, and a deuterium-labeling study designed to probe the stereochemical outcome of cyclization within the context of these mechanisms has revealed the complex nature of these reactions. We anticipate the reactions described herein will stimulate the development of further nickel-catalyzed reductive coupling and cyclization reactions that will be of broad utility.

Acknowledgment. This research was supported by the University of Edinburgh, Hoffmann-La Roche, and the EPSRC. We thank AstraZeneca and Merck Sharp & Dohme for unrestricted research support, Stephen Dixon for assistance with the cyclization of substrate **14a**, Claire L. Oswald for assistance in the preparation of **39**, and the groups of Polly L. Arnold and Jason B. Love for the use of their glovebox. We thank Dr. Richard C. Hartley at the Department of Chemistry, University of Glasgow, for helpful discussions, and the reviewers of this Article for valuable suggestions regarding reaction mechanisms. We gratefully acknowledge the EPSRC National Mass Spectrometry Centre at the University of Wales, Swansea, for providing high-resolution mass spectra.

Supporting Information Available: Detailed experimental procedures, spectroscopic data for all new compounds, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0775624