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# Diastereoselective Cobalt-Catalyzed Reductive Aldol Cyclizations Using Diethylzinc as the Stoichiometric Reductant

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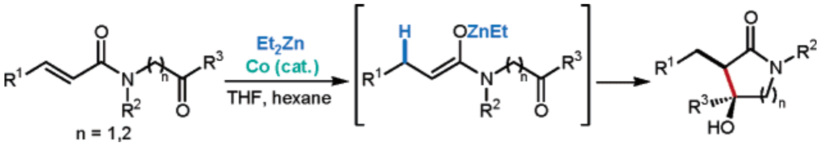
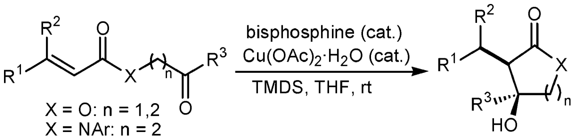
## ABSTRACT



**Cobalt catalysis enables a new method for the generation of zinc enolates using diethylzinc to reduce α,β-unsaturated amides. This method has been applied to a high-yielding diastereoselective reductive aldol cyclization.**

The trapping of aldehydes and ketones with enolates generated in situ via metal-catalyzed conjugate reduction of α,β-unsaturated carbonyl compounds has emerged as a powerful method for accessing aldol products.[1] Despite the tremendous progress that has been made in this area,[1] the continued development of new methods that exhibit high stereocontrol for an increased range of substrates remains an important goal. Recent contributions to this field from our laboratory have detailed copper(I)-bisphosphine-catalyzed reductive aldol cyclizations using TMDS (1,1,3,3-tetramethylhydrosiloxane) as the stoichiometric reductant that could be applied to the synthesis of β-hydroxylactones[2a] and β-hydroxylactams[2b] (eq 1).



(1)

Although the products were obtained with generally high levels of diastereoselectivity (and with moderate enantioselectivities[3] in the case of β-hydroxylactones when suitable chiral bisphosphines were employed[2a]), the process suffered from a number of limitations. First, the yields of these reactions were moderate at best (typically in the range 60−70%) due to competing side reactions.[2] Second, the attenuated electrophilicity of α,β-unsaturated amides compared with the corresponding esters meant that productive cyclizations were limited to those amide substrates where $R^1 = H$

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[1] 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) Jung, C.-K.; Garner, S. A.; Krische, M. J. *Org. Lett.* **2006**, *8*, 519−522. For relevant reviews, see: (c) Jang, H.-Y.; Krische, M. J. *Eur. J. Org. Chem.* **2004**, 3953−3958. (d) Jang, H.-Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653−661. (e) Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, 12−21. (f) Chiu, P. *Synthesis* **2004**, 2210−2215. (g) Motherwell, W. B. *Pure Appl. Chem.* **2002**, *74*, 135−142.

[2] (a) Lam, H. W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225−4228. (b) Lam, H. W.; Murray, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743−5746.

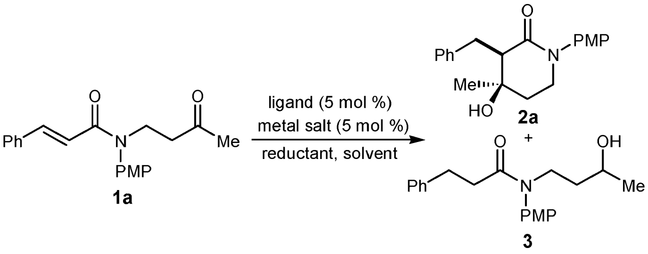
[3] For enantioselective copper-catalyzed intermolecular reductive aldol reactions with ketones, see: (a) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 1292−1597. (b) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *46*, 1403−1407.

10.1021/ol061329d CCC: $33.50

or Me (with $R^2 = H$).[2b] Therefore, a search for improved reaction conditions was initiated, and we describe herein a new cobalt-based catalyst system that exhibits broader scope for amide-tethered substrates and allows products to be isolated with higher yields.

Initial investigations began with the cyclization of cinnamic amide **1a** (Table 1). Application of our previously reported copper conditions[2] proved ineffective, providing the desired product **2a** but contaminated with significant quantities of the uncyclized side product **3** along with the starting material (entry 1). The formation of **3** may be attributed to conjugate reduction of the α,β-unsaturated amide being slow, allowing prior reduction of the ketone to become competitive. Replacement of DPPF with *rac*-BINAP led to a similar result (entry 2), whereas use of $PhSiH_3$ in place of TMDS led to minimal reaction (entry 3). Having obtained no success with copper-based catalyst systems, our attention turned to the use of other metals. In conjunction with an appropriate chiral ligand, the combination of $CoCl_2$ and $NaBH_4$ has proven useful for the asymmetric conjugate reduction of α,β-unsaturated amides.[4] Unsurprisingly, conditions employing $NaBH_4$ led to rapid reduction of the ketone of **1a**. Conditions employing cobalt salts that were developed for intermolecular reductive aldol reactions[5a] and later extended to aldol cyclizations[5b,c] also proved ineffective, providing complex mixtures (entries 4 and 5). In light of recent reports of organometallic reagents with β-hydrogen-containing alkyl groups being utilized as stoichiometric reductants for a variety of transition-metal-catalyzed reductive couplings,[6] we examined $Et_3B$[6b−e] and $Et_2Zn$[6a,b] in our reaction. In the presence of 5 mol % of $Co(acac)_2$ hydrate (degree of hydration ~ 2), $Et_3B$ resulted in no reaction (entry 6), but we were delighted to observe that the more reactive $Et_2Zn$ led to the formation of **2a** in 89% yield with none of the side product **3** being observed (entry 7). No reaction occurs in the absence of $Co(acac)_2{\cdot}2H_2O$.

**Table 1.** Survey of Reaction Conditions



| entry | reagents | solvent | temp (°C) | conv (%)[a] | **2a/3**[a] |
|---|---|---|---|---|---|
| 1 | $Cu(OAc)_2{\cdot}H_2O$, DPPF, TMDS (1 equiv) | THF | rt | 77 | 34:66 |
| 2 | $Cu(OAc)_2{\cdot}H_2O$, *rac*-BINAP, TMDS (1 equiv) | THF | rt | 87 | 39:61 |
| 3 | $Cu(OAc)_2{\cdot}H_2O$, DPPF, $PhSiH_3$ (1 equiv) | THF | rt | <5 | na |
| 4 | $Co(dpm)_2$, $PhSiH_3$ (1 equiv) | $CH_2Cl_2$ | rt | ca. 90 | na[b] |
| 5 | $Co(dpm)_2$, $PhSiH_3$ (1 equiv) | DCE | rt to 50 | ca. 80 | na[b] |
| 6 | $Co(acac)_2{\cdot}2H_2O$, $Et_3B$ (2 equiv) | THF/hexane | 0 to rt | <5 | na |
| 7 | $Co(acac)_2{\cdot}2H_2O$, $Et_2Zn$ (2 equiv) | THF/hexane | 0 to rt | >95 | >95:5[c] |

[a] Determined by $^1H$ NMR analysis of the unpurified reaction mixture. [b] A complex mixture containing unidentified side products was obtained, with only a trace (<10%) of **2a** present. [c] Product **2a** was isolated in 89% yield. PMP = *para*-methoxyphenyl, DPPF = 1,1′-bis(diphenylphosphino)ferrocene, TMDS = 1,1,3,3-tetramethylhydrosiloxane, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, dpm = dipivaloylmethane, acac = acetonylacetonate.

With effective conditions identified, the scope of the process was next explored (Table 2). Substrates containing a wide range of substitution at both the α,β-unsaturated amide and the ketone[7] underwent cyclization to give 4-hydroxypiperidin-2-one products in generally excellent yields and high diastereoselectivities[8] (entries 1−12). It should be noted that the copper conditions (as in Table 1, entry 1) proved ineffective in the majority of these examples. In a number of reactions, incomplete conversions were observed using $Co(acac)_2{\cdot}2H_2O$ (method A), but the combination of $CoCl_2$ and the electron-rich phosphine $Cy_2PPh$ (method B) was found to provide good results in these cases (entries 10−12). The reaction could also be applied to the formation of pyrrolidin-2-ones (entries 13−15), though with somewhat lower yields and diastereoselectivities. Although 5 mol % of the cobalt source was employed for convenience in these experiments, the reaction is tolerant of lower catalyst loadings. For example, on a 5 mmol scale, substrate **1a** underwent cyclization using 0.5 mol % of $Co(acac)_2{\cdot}2H_2O$ to provide **2a** in 79% yield (entry 2).

Difficulties were encountered when substrates **4a**,**b** containing phenyl ketones were employed; in contrast to methyl ketones **1l−n** (Table 2, entries 13−15), the desired pyrrolidin-2-ones were obtained in <20% yield along with numerous other side products. However, replacement of $Et_2$-

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(4) (a) v. Matt, P.; Pfaltz, A. *Tetrahedron: Asymmetry* **1991**, *2*, 691−700. (b) Gieger, C.; Kreitmeier, P.; Reiser, O. *Adv. Synth. Catal.* **2005**, *347*, 249−254. (c) Yamada, T.; Ohtsuka, Y.; Ikeno, T. *Chem. Lett.* **1998**, 1129−1130. (d) Ohtsuka, Y.; Ikeno, T.; Yamada, T. *Tetrahedron: Asymmetry* **2003**, *14*, 967−970.

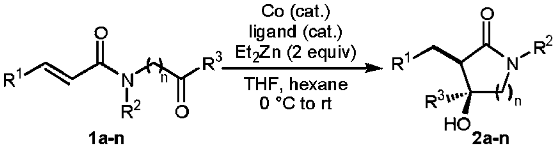
(5) (a) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 2005−2008. (b) Baik, T.-G.; Luis, A.-L. Wang, L.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112−5113. (c) Wang, L.-C.; Jang, H.-Y.; Roh, Y.; Lynch, V.; Schultz, A. J.; Wang, X.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 9448−9453.

(6) For selected examples, see: (a) Kimura, M.; Miyachi, A.; Kojima, K.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2004**, *126*, 14360−14361. (b) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033−4034. (c) Molinaro, C.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2004**, *44*, 129−132. (d) Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076−8077. (e) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442−3443. For a review, see: (f) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890−3908.

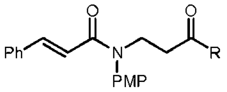
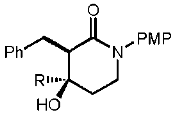
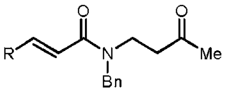
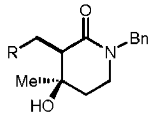
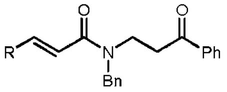
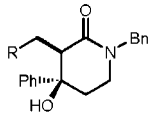
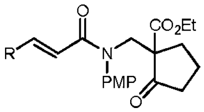
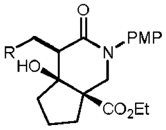
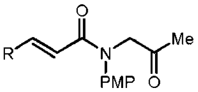
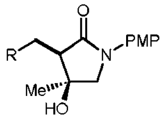
(7) Aldehydes do not serve as competent electrophiles under these conditions, as they undergo reduction and ethylation instead.

(8) The relative stereochemistries of **2f**, **2i**, and **2m** were confirmed by X-ray crystallography and matched those of products obtained previously using copper catalysis (see ref 2). The stereochemistries of the remaining products were assigned by analogy. See Supporting Information for further details.

**Table 2.** Cobalt-Catalyzed Reductive Aldol Cyclizations[a]

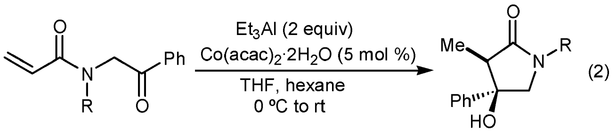


**Method A**: $Co(acac)_2 \cdot 2H_2O$ (5 mol %)
**Method B**: $CoCl_2$ (5 mol %), $Cy_2PPh$ (5.5 mol %)

| entry | substrate | | method | product | | dr[b] | yield (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 |  | R = Me **1a** | A |  | **2a** | 12:1 | 89 |
| 2 | | R = Me **1a** | –[d] | | **2a** | 12:1 | 79 |
| 3 | | R = Et **1b** | A | | **2b** | 9:1 | 88 |
| 4 |  | R = H **1c** | A |  | **2c** | 9:1 | 88 |
| 5 | | R = *i*-Pr **1d** | A | | **2d** | >19:1 | >99 |
| 6 | | R = Ph **1e** | A | | **2e** | >19:1 | 97 |
| 7 | | R = 2-furyl **1f** | A | | **2f** | >19:1 | >99 |
| 8 |  | R = Me **1g** | A |  | **2g** | >19:1 | 94 |
| 9 | | R = *i*-Bu **1h** | A | | **2h** | >19:1 | 94 |
| 10 |  | R = H **1i** | B |  | **2i** | 9:1[e] | 56 |
| 11 | | R = Me **1j** | B | | **2j** | >19:1[e] | 80 |
| 12 | | R = Ph **1k** | B | | **2k** | >19:1[e] | 88 |
| 13 |  | R = H **1l** | A |  | **2l** | 9:1 | 47 |
| 14 | | R = Ph **1m** | A | | **2m** | 8:1 | 56 |
| 15 | | R = OMP **1n** | B | | **2n** | 14:1 | 74 |

[a] Unless otherwise stated, reactions were conducted using 0.2 mmol of substrate in THF (1.5 mL) and hexane (0.4 mL) for 1−24 h. [b] Determined by $^1H$ NMR analysis of the unpurified reaction mixtures. [c] Isolated yield of the major diastereomer. [d] Reaction conducted using 5 mmol of **1a** using 0.5 mol % of $Co(acac)_2 \cdot 2H_2O$ in THF (10 mL) and hexane (10 mL). [e] Here, dr = (major isomer):(Σ other isomers). OMP = *ortho*-methoxyphenyl.

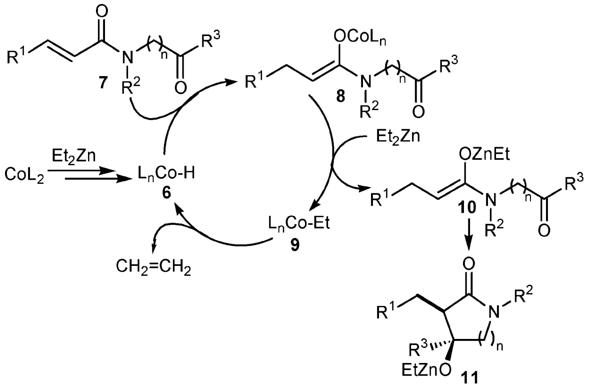
Zn with $Et_3Al$ allowed isolation of **5a**,**b** in modest yield (eq 2).[9] Analogues of **4a**,**b** containing substituted α,β-unsaturated



**4a** R = PMP
**4b** R = PMB
**5a** (57% yield, >19:1 dr)
**5b** (53% yield, 8:1 dr)

amides did not cyclize under any conditions examined.

**Scheme 1.** Plausible Catalytic Cycle



In the absence of detailed studies, discussion of the mechanism of the reaction can only be speculative at this stage. We believe that a zinc enolate is the species that undergoes aldol cyclization, but the precise details leading to the formation of this enolate are not known. One possible catalytic cycle is presented in Scheme 1. Treatment of $Co(acac)_2 \cdot 2H_2O$ (or $CoCl_2$) with $Et_2Zn$ results in the formation of a cobalt hydride species **6**,[10] presumably via a transmetalation/β-hydride elimination sequence. Hydrometalation of the substrate **7** with **6** generates a cobalt enolate **8**[11] that reacts with $Et_2Zn$ to give an ethylzinc enolate **10**[11,12] and an ethylcobalt species **9**. Enolate **10** then undergoes cyclization to give the zinc alkoxide **11**, whereas the ethylcobalt species **9** undergoes β-hydride elimination to regenerate **6** along with ethylene. This mechanism bears similarities to those proposed for catalytic variants of the Reformatsky reaction employing

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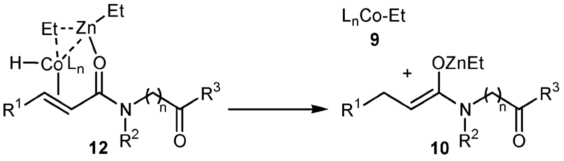
(9) Pyrrolidin-2-ones **5a**,**b** were accompanied by ca. 15% of the corresponding products resulting from conjugate addition of an ethyl group from $Et_3Al$ followed by aldol cyclization.

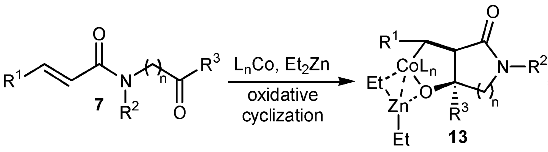
α-bromocarbonyl compounds and dialkylzinc reagents mediated by rhodium[13a] and nickel.[13b,c]

Another scenario that we do not rule out involves the participation of $Et_2Zn$ at an earlier stage of the mechanism. Binding of $Et_2Zn$ to the α,β-unsaturated carbonyl in Lewis acidic fashion, along with Lewis basic interaction with the cobalt hydride via three-center, two-electron bridging of a zinc−ethyl bond (as in **12**, eq 3), would lead to zinc enolate **10** without the intermediacy of a cobalt enolate. Although to our knowledge this type of bridging interaction has not been invoked for a cobalt-catalyzed reaction, it has been proposed for a number of related Ni(0)-catalyzed alkylative couplings to explain the accelerating effect of organozinc reagents.[14a,b] Furthermore, it has been observed crystallographically for cobalt[14c] and nickel[14d,e] complexes involving Grignard[14c,d] and organoaluminum[14e] reagents.



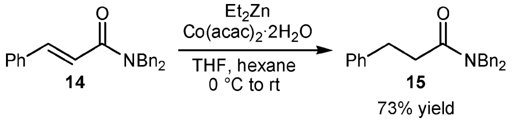
(3)

Yet another possibility that was initially considered involves the $Et_2Zn$-assisted oxidative cyclization[14a] of a low-valent cobalt species with substrate **7** to form the cobaltacycle **13** (eq 4).



(4)

Metallacycles have been implicated as intermediates in a number of cobalt-[15] and nickel-catalyzed[6f] reductive couplings; in the present case, the final product would be formed from **13** by a sequence involving transmetalation, β-hydride elimination, and reductive elimination. However, a number of observations led us to conclude that this pathway is not operative. First, reaction in the presence of catalytic quantities of a variety of chiral ligands[16] led to racemic products in all cases, providing circumstantial evidence that cobalt is not involved in the stereochemical-determining step. Second, the simple α,β-unsaturated amide **14** underwent conjugate reduction to give **15** in 73% yield under these conditions (eq 5), demonstrating that a second electrophilic π-component is not required for the reaction to proceed.



(5)

In conclusion, we have developed an efficient and highly diastereoselective cobalt-catalyzed reductive aldol cyclization that utilizes $Et_2Zn$ as the stoichiometric reductant. This study has highlighted two important features: (i) conjugate reduction of α,β-unsaturated amides using $Et_2Zn$, which to our knowledge has not been developed as a general synthetic method,[17] and (ii) a mild new approach to access zinc enolates that does not require the prior formation of an alkali metal enolate (for transmetalation with a zinc halide) or the use of α-halocarbonyl compounds (which can be difficult to prepare for complex substrates). We anticipate this method of zinc enolate generation will find application in a range of other reactions. Further studies in this area will be reported in due course.

**Acknowledgment.** This work was supported by the EPSRC (EP/C51243X/01), the University of Edinburgh, and Hoffmann-La Roche (studentship support to E.A.F.F). AstraZeneca and Merck Sharp & Dohme are gratefully acknowledged for unrestricted research support. We thank the EPSRC Mass Spectrometry Service at the University of Wales, Swansea, for their assistance.

**Supporting Information Available:** Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The oxidation state of cobalt species **8** is not known, though we assume a reduction occurs to generate a low-valent cobalt hydride. For the presumed generation of cobalt hydride by treatment of $Co(acac)_3$ with $Et_2AlCl$, see: Takacs, J. M.; Mehrman, S. J. *Tetrahedron Lett.* **1996**, *37*, 2749−2752.

(11) Although we have arbitrarily depicted enolates as being O-bound, high C-bound character is possible.

(12) For a discussion of the preparation, characterization, and reactivity of an ethylzinc enolate, see: Hansen, M. M.; Bartlett, P. A.; Heathcock, C. H. *Organometallics* **1987**, *6*, 2069−2074.

(13) (a) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549−2551. (b) Adrian, J. C., Jr.; Snapper, M. L. *J. Org. Chem.* **2003**, *68*, 2143−2150. (c) Cozzi, P. G.; Rivalta, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3600−3603.

(14) (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) Subbaraj, K.; Montgomery, J. *J. Am. Chem. Soc.* **2003**, *125*, 11210−11211. (c) Jonas, K.; Koepe, G.; Krueger, C. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 923−925. (d) Kaschube, W.; Pörschke, K.-R.; Angermund, K.; Krüger, C.; Wilke, G. *Chem. Ber.* **1988**, *121*, 1921−1929. (e) Ogoshi, S.; Ueta, M.; Arai, T.; Kurosawa, H. *J. Am. Chem. Soc.* **2005**, *127*, 12810−12811.

(15) (a) Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 9696−9697. (b) Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *Tetrahedron Lett.* **2004**, *45*, 6203−6206.

(16) Ligands screened included chiral diols, bisoxazolines, bis(oxazolinyl)pyridines, semicorrins, and bisphosphines.

(17) For an isolated example of conjugate reduction of a sterically hindered enone using $Et_2Zn$ under nickel catalysis, see: Bolm, C.; Ewald, M.; Felder, M. *Chem. Ber.* **1992**, *125*, 1205−1215.