Published in final edited form as:

Org Lett. 2015 August 21; 17(16): 3978–3981. doi:10.1021/acs.orglett.5b01836.

Rh(II)-catalyzed Reactions of Diazoesters with Organozinc Reagents

Robert Panish[‡], Ramajeyam Selvaraj[‡], and Joseph M. Fox^{*}

Brown Laboratories, Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716, United States

Abstract

Rh(II)-catalyzed reactions of diazoesters with organozinc reagents are described. Diorganozinc reagents participate in reactions with diazo compounds by two distinct, catalyst-dependent mechanisms. With bulky diisopropylethylacetate ligands, the reaction mechanism is proposed to involve initial formation of a Rh-carbene and subsequent carbozincation to give a zinc enolate. With $\text{Rh}_2(\text{OAc})_4$, it is proposed that initial formation of an azine precedes 1,2-addition by an organozinc reagent. This straightforward route to the hydrazone products provides a useful method for preparing chiral quaternary α -aminoesters or pyrazoles via the Paul-Knorr condensation with 1,3-diketones. Crossover and deuterium labeling experiments provide evidence for the mechanisms proposed.

Rhodium (II) catalyzed reactions of diazo compounds play an important role across a variety of selective synthetic transformations involving Rh-carbene intermediates,¹ which subsequently participate in a number of bond-activating reactions. Selected examples include X-H insertion reactions (where X = C, N, O, Si or S),^{2–9} ylide forming reactions,^{10,11} and cyclopropanation or cyclopropene reactions of alkenes and alkynes, respectively.^{11–14} While the scope of catalytic reactions of diazo compounds is extensive, there are relatively few methods for combining diazo compounds with organometallic reagents. The reactivity of carbon-boron compounds with diazocompounds has been studied.¹⁵ Wang has described the Pd(0)-catalyzed as well as metal-free methods for the carboboration of diazo compounds.^{16–21} Schaus has described three-component Mannich-type reaction involving arylboron reagents, diazo compounds, and alkylidene carbamates.^{22,23} Recently, Rh(I) catalyzed arylation of α -diazoesters with arylboronic acids

^{*}Corresponding Author. jmfox@udel.edu.

[‡]R. A. P. and R. S. contributed equally.

ASSOCIATED CONTENT

Supporting Information

Full experimental details, characterization, ¹H and ¹³C NMR spectra are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.

has been described by Anbarasan,²⁴ and Rh(I) catalyzed arylation of α -diazoesters with arylsiloxanes and arylstannanes have been described by Wang.²⁵ However, we were unaware of reports where transition row organometallic compounds have been used as substrates in Rh-catalyzed reactions of diazocompounds.

Organozinc reagents have been employed in a variety of transition-metal catalyzed coupling reactions, and have been shown to display a wide range of functional group tolerance.^{26–31} We considered that organozinc reagents may participate in catalytic reactions with diazo compounds (**1**) by one of two mechanisms (Scheme 1). The diazo compound could initially form carbene **A** by a Rh-catalyzed process, and carbozincation of this carbene would lead to the enolate **C**.³² The organozinc **C** may combine with electrophiles, including a second equivalent of diazo compound **1** to give rise to hydrazone **2**. Alternatively, Rh-carboxylates could catalyze the formation of the azine **B**,³³ which is able to participate subsequently in a 1,2-addition reaction with an organozinc reagent. This straightforward route to the hydrazone products **2** was expected to provide a useful method for preparing chiral quaternary α -aminoesters or pyrazoles via the Paul-Knorr condensation with 1,3-diketones.

To investigate carbozincation of diazoesters, the coupling of Et₂Zn and methyl α -phenyl- α -diazoacetate **1a** was chosen for initial study. A number of Rh(II) catalysts were explored in an effort to optimize the yield of **2a**. As shown in Scheme 2, simple Rh₂(OAc)₄ gave **2a** in the highest yield. Thus, diazo **1a** with catalytic Rh₂(OAc)₄ (5 mol %) and Et₂Zn (2 equiv) gave **2a** in 92% yield with only traces of methyl α -phenylbutyrate **3a**.

With suitable conditions for hydrazone product formation identified, the substrate scope for the reaction was explored. As shown in Scheme 3, the reaction was also found to proceed efficiently with Me₂Zn. Thus, Rh₂(OAc)₄ (5 mol %) catalyzes the reaction of Me₂Zn with a variety of α -aryl- α -diazoacetate derivatives in 65–100% yield. As shown in Scheme 3, our exploration revealed that *ortho*-substituents are tolerated under the reaction conditions. Additionally, the reaction conditions are compatible with various functional groups including halide, cyano, ester, methoxy, and dioxolane groups. Diethylzinc as well as *in situ* generated dihexylzinc and dibenzylzinc also add smoothly to α -aryl- α -diazoesters in 83 – 92% yields.³⁴

Several synthetic applications of the hydrazone products were investigated. The α -quaternary aminoesters **4a** and **4k** could be formed upon hydrogenation in good yields. Additionally, Paul-Knorr conditions provide access to pyrazole products. Thus, treatment of hydrazone **2a** with pentane-2,4-dione under acidic conditions afforded pyrazole **5a** in 81% yield.

In contrast to the Rh₂(OAc)₄ catalyzed reactions which lead to hydrazone products, Rh(II)-carboxylates with sterically demanding ligands displayed a complete reversal of selectivity. In this regard, the most effective catalyst was Rh₂(DIEA)₄, a Rh-complex with bulky carboxylate ligands first described by our laboratory.³⁵ The Rh₂(DIEA)₄ (1 mol %) catalyzed reaction of **1a** with Et₂Zn provided the carbozincation product **3a** in 89% yield (Scheme 2). Likewise, Et₂Zn and *tert*-butyl α -diazohydrocinnamate **6** could be combined under Rh-catalyzed conditions to give the protonated product **7** (Scheme 5). This

transformation was achieved with $\text{Rh}_2(\text{OPiv})_4$ (1 mol %) as a catalyst in 78% yield. $\text{Rh}_2(\text{DIEA})_4$ gave only 50% yield for this substrate, giving β -hydride migration and azine formation as significant byproducts. Unfortunately, our attempts to create fully substituted carbon centers by capturing these putative zinc enolates with a variety of electrophiles³⁶ were unsuccessful. Cook and coworkers have investigated conjugate addition/enolate capture sequences of diorganozinc reagents with cyclic ketones, and were only able to capture the zinc enolate intermediates efficiently using reactive allyl halide electrophiles after extensively screening reaction conditions.³⁷ As the zinc enolates generated in this manner are fully substituted and would lead to quaternary centers upon functionalization, it is not surprising that they are less reactive.

Several mechanistic studies were performed to support the hypothesis that $\text{Rh}_2(\text{OAc})_4$ catalyzed reactions proceed through an azine intermediate (**B**), whereas the $\text{Rh}_2(\text{DIEA})_4$ and $\text{Rh}_2(\text{OPiv})_4$ catalyzed reactions proceed via a zinc enolate intermediate (see Scheme 1). As additional evidence for the formation of **8** from **1a**, two mass spectrometry experiments were performed by quenching the intermediate zinc enolate with D_2O . In the first experiment, the reaction was quenched with D_2O to form the deuterated product **3ad** (Scheme 6). GC/MS analysis of the deuterium quenched product showed a parent peak (m/z 179) corresponding to the deuterated product **3ad** (see Supporting Information). A second MS experiment was performed to confirm that **3ad** was formed by quenching the zinc enolate **8**, and not by deuterium exchange. In this experiment, the product of the reaction was initially quenched with H_2O (10 equiv) and then with D_2O (280 equiv). GC/MS analysis showed a major parent peak of m/z 178 (see Supporting Information), for the product **3a**. These experiments are consistent with the formation of **3a** via protonation of zinc enolate **8**.

We also considered that a zinc enolate may be an intermediate in the mechanism for hydrazone formation. As depicted in Scheme 1, a rhodium carboxylate would catalyze the transformation of diazoester **1** to zinc enolate **C**, which in a catalyst dependent manner may combine with another equivalent of **1** to form the hydrazone product **2**. To test this hypothesis, a 'crossover' experiment was performed in which Et_2Zn was combined with diazoester **1a** in the presence of 1 mol % $\text{Rh}_2(\text{DIEA})_4$ —conditions shown above to catalyze the formation of zinc enolate **8**. To this enolate was added $\text{Rh}_2(\text{OAc})_4$ (which catalyzes hydrazone formation) and a different diazo compound **1i** (Scheme 7).

If a zinc enolate were an intermediate, then the formation of unsymmetrical hydrazone **2o** would be expected. In the event, **2o** was not formed. Instead proton quenched product **3a** was formed, and the hydrazone **2p** derived from two equivalents of **1i** was obtained in 70% yield (based on **1i**) as depicted in Scheme 7. This experiment suggests that enolate **8** is unlikely to be an intermediate in hydrazone formation.

An alternate hypothesis for hydrazone formation is that $\text{Rh}_2(\text{OAc})_4$ catalyzes the conversion of the diazoester to form an azine intermediate initially, which upon subsequent reaction with Et_2Zn provides the hydrazone product. To provide support for this hypothesis, diazoester **1a** was allowed to react with catalytic amounts of $\text{Rh}_2(\text{OAc})_4$ (5 mol %). The azine **9** was isolated in 78% yield. In a separate reaction with Et_2Zn (4.0 equiv) in toluene,

hydrazone **2a** was formed and isolated in 72% yield (Scheme 7). These experiments support the hypothesis that azine formation precedes the addition of the organozinc reagent.

In conclusion, the first Rh(II)-catalyzed reactions of diazoesters with organozinc reagents are described. Diorganozinc reagents participate in reactions with diazo compounds by two distinct, catalyst-dependent mechanisms. With the bulky Rh₂(DIEA)₄, the reaction mechanism is proposed to involve initial formation of a Rh-carbene and subsequent carbozincation to give a zinc enolate. With Rh₂(OAc)₄, initial formation of an azine precedes a 1,2-addition reaction with an organozinc reagent. This straightforward route to the hydrazone products provides a useful method for preparing chiral quaternary α-aminoesters or pyrazoles via the Paul-Knorr condensation with 1,3-diketones. Crossover and deuterium labeling experiments provide evidence for the mechanisms proposed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

For financial support we thank NSF CHE 1300329. R. A. P. thanks NIH for support through a CBI training grant: 5T32GM008550. For instrumentation support we thank NIH S10RR026962, NIH S10OD016267, NIH P30GM110758, NIH P20GM104316, and NSF CHE-1229234.

REFERENCES

1. Doyle MP. J. Org. Chem. 2006; 71:9253. [PubMed: 17137350]
2. Aller E, Buck RT, Drysdale MJ, Ferris L, Haigh D, Moody CJ, Pearson ND, Sanghera JB. J. Chem. Soc. Perkin Trans. 1. 1996:2879.
3. Bulugahapitiya P, Landais Y, Parra-Rapado L, Planchenault D, Weber V. J. Org. Chem. 1997; 62:1630.
4. Davies HML, Beckwith REJ. Chem. Rev. 2003; 103:2861. [PubMed: 12914484]
5. Zhang X, Ma M, Wang J. ARKIVOC. 2003; 2003:84.
6. Doyle MP, Duffy R, Ratnikov M, Zhou L. Chem. Rev. 2010; 110:704. [PubMed: 19785457]
7. Gillingham D, Fei N. Chem. Soc. Rev. 2013; 42:4918. [PubMed: 23407887]
8. Forbes DC, Doyle MP. Chem. Rev. 1998; 98:911. [PubMed: 11848918]
9. DeAngelis A, Shurtleff VW, Dmitrenko O, Fox JM. J. Am. Chem. Soc. 2011; 133:1650. [PubMed: 21265565]
10. DeAngelis A, Panne P, Yap GPA, Fox JM. J. Org. Chem. 2008; 73:1435. [PubMed: 18189412]
11. DeAngelis A, Dmitrenko O, Yap GPA, Fox JM. J. Am. Chem. Soc. 2009; 131:7230. [PubMed: 19469571]
12. Lebel H, Marcoux JF, Molinaro C, Charette AB. Chem. Rev. 2003; 103:977. [PubMed: 12683775]
13. Panne P, Fox JM. J. Am. Chem. Soc. 2007; 129:22. [PubMed: 17199269]
14. Panish R, Chintala SR, Boruta DT, Fang Y, Taylor MT, Fox JM. J. Am. Chem. Soc. 2013; 135:9283. [PubMed: 23758288]
15. Hooz J, Bridson JN. J. Am. Chem. Soc. 1973; 95:602.
16. Peng C, Zhang W, Yan G, Wang J. Org. Lett. 2009; 11:1667. [PubMed: 19260704]
17. Peng C, Cheng J, Wang J. J. Am. Chem. Soc. 2007; 129:8708. [PubMed: 17589999]
18. Peng C, Wang Y, Wang J. J. Am. Chem. Soc. 2008; 130:1566. [PubMed: 18186640]
19. Peng C, Yan G, Wang Y, Jiang Y, Zhang Y, Wang J. Synthesis (Stuttg). 2010; 2010:4154.
20. Wu G, Deng Y, Wu C, Zhang Y, Wang J. Angew. Chem. Int. Ed. 2014; 53:10510.

21. Li H, Zhang Y, Wang J. *Synthesis*. 2013; 45:3090.
22. Luan Y, Schaus SE. *Org. Lett.* 2011; 13:2510. [PubMed: 21473584]
23. Luan Y, Yu J, Zhang X, Schaus SE, Wang G. *J. Org. Chem.* 2014; 79:4694. [PubMed: 24787904]
24. Ghorai J, Anbarasan P. *J. Org. Chem.* 2015; 80:3455. [PubMed: 25759939]
25. Liu Z, Xia Y, Feng S, Wang S, Qiu D, Zhang Y, Wang J. *Aust. J. Chem.* 2015; 68 accepted, DOI <http://dx.doi.org/10.1071/CH15218>.
26. Knochel P, Singer RD. *Chem. Rev.* 1993; 93:2117.
27. Boudet N, Sase S, Sinha P, Liu C-Y, Krasovskiy A, Knochel P. *J. Am. Chem. Soc.* 2007; 129:12358. [PubMed: 17887673]
28. Tarwade V, Selvaraj R, Fox JM. *J. Org. Chem.* 2012; 77:9900. [PubMed: 23035947]
29. Tarwade V, Liu X, Yan N, Fox JM. *J. Am. Chem. Soc.* 2009; 131:5382. [PubMed: 19323580]
30. Sidduri A, Tilley JW, Fotouhi N. *Synthesis*. 2014; 46:430.
31. Chemla, F.; Ferreira, F.; Jackowski, O.; Micouin, L.; Perez-Luna, A. Carbon-Carbon Bond Forming Reactions Mediated by Organozinc Reagents. In: de Meijere, A.; Bräse, S.; Oestreich, M., editors. *Metal-Catalyzed Cross-Coupling Reactions and More*. Weinheim, Germany: Wiley-VCH; 2014. p. 279-364.
32. For recent descriptions of oxidative umpolung coupling reactions of diorganozinc reagents with enolizable carbonyl compounds: Shneider OS, Pisarevsky E, Fristrup P, Szpilman AM. *Org. Lett.* 2015; 17:282. [PubMed: 25562460] Targel TA, Kumar JN, Schneider OS, Bar S, Fridman N, Maximenko S, Szpilman AM. *Org. Biomol. Chem.* 2015; 13:2546. [PubMed: 25600653]
33. For precedent for the formation of azines in Rh-catalyzed reactions of diazocompounds, see ref 10 and Petrukhina MA, Andreini KW, Walji AM, Davies HML. *J. Chem. Soc. Dalton Trans.* 2003:4221. Ohno M, Itoh M, Umeda M, Furuta R, Kondo K, Eguchi S. *J. Am. Chem. Soc.* 1996; 118:7075. Ace KW, Husain N, Lathbury DC, Morgan D. *Tetrahedron Lett.* 1995; 36:8141. Pomerantz M, Levanon M. *Tetrahedron Lett.* 1990; 31:4265. Doyle MP, Bagheri V, Wandless TJ, Harn NK, Brinker DA, Eagle CT, Loh K-L. *J. Am. Chem. Soc.* 1990; 112:1906. Taber DF, Hennessy MJ, Louey JP. *J. Org. Chem.* 1992; 57:436. Kornecki KP, Briones JF, Boyarskikh V, Fullilove F, Autschbach J, Schrote KE, Lancaster KM, Davies HML, Berry JF. *Science*. 2013; 342:351. [PubMed: 24030489] Panne P, DeAngelis A, Fox JM. *Org. Lett.* 2008; 10:2987. [PubMed: 18547051]
34. Diarylzinc reagents prepared *in situ* were also shown to combine with methyl α -diazophenylacetate to give hydrazones, but the product purity was <90% after purification. Diarylzincs generated included diphenylzinc and di(*o*-methoxyphenyl)zinc. Further, a diorganozinc with an ester functional group (bis(6-(benzyloxy)-6-oxohexyl)zinc) also provided hydrazones with an inseparable impurity.
35. DeAngelis A, Dmitrenko O, Fox JM. *J. Am. Chem. Soc.* 2012; 134:11035. [PubMed: 22676258]
36. Various electrophiles were evaluated with **1a** including TMSOTf, TMSCl (rt and 60 °C), NIS (60 °C), BzCl (60 °C), and allyl acetate with Pd(PPh₃)₄ (5 mol %, 60 °C). Unfortunately, none of these experiments were successful, and only provided **3a**, the product of protonation. Similarly, various electrophiles were evaluated with enolate from **6**, including PhCHO (with and without CuI at 60 °C), allylBr (with CuI, rt), TIPSOTf (60 °C), I₂ (r.t.), NIS (50 °C), TMSCl (rt), and allyl acetate with Pd(PPh₃)₄ (5 mol %), 60 °C). Unfortunately, none of these gave the anticipated product, but only provided the product of protonation.
37. Jarugumilli GK, Zhu C, Cook SP. *Eur. J. Org. Chem.* 2012; 2012:1712.

Scheme 1.
Hydrazones via Rh-mediated organozincation

[Rh]	2a	3a
$\text{Rh}_2(\text{OAc})_4$	92%	trace
$\text{Rh}_2(\text{DIEA})_4$	trace	89%
$\text{Rh}_2(\text{TPA})_4$	0%	53%
$\text{Rh}_2(\text{OPiv})_4$	6%	40%
$\text{Rh}_2(\text{OOct})_4$	60%	8%
No [Rh]	0%	0%

Scheme 2.
Optimization of Rh(II)-catalyst

Scheme 3.
Scope of hydrazone formation

Scheme 4.
Elaboration of hydrazone products

Scheme 5.
Organozinc addition to a Rh-carbene bearing β -hydrogens

Scheme 6.

Evidence for a Zn-enolate intermediate in $\text{Rh}_2(\text{DIEA})_4$ catalyzed reaction of diazoesters with Et_2Zn

Scheme 7.

Evidence for an azine intermediate in $\text{Rh}_2(\text{OAc})_4$ catalyzed reaction of diazoesters with Et_2Zn