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Catalytic Conversion of Diazocarbonyl Compounds to Imines: Applications to the Synthesis of Tetrahydropyrimidines and β-Lactams

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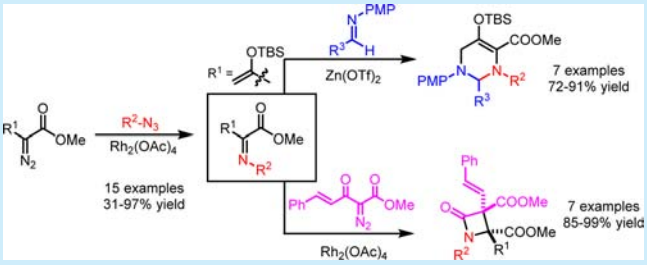
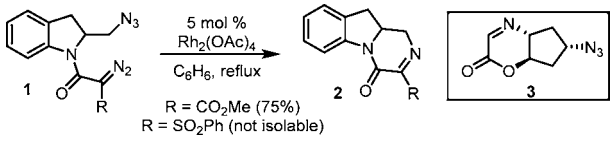
Supporting Information

ABSTRACT: The synthesis of α-carbonylimines by rhodium(II)-catalyzed reactions of α-diazoesters and organic azides has been developed and applied in hetero-Diels–Alder reactions to form highly functionalized tetrahydropyrimidines and in a one-pot, multicomponent transformation between aryldiazoacetates, *p*-anisyl azide, and an enonediazoacetate to produce β-lactams in high yields and diastereoselectivities.



The selective preparation of imines in organic compounds having multiple carbonyl functional groups is a daunting task in view of the common condensation methodology employed for imine synthesis.[1] Azides are well-known to form transition metal imido complexes ([ML_n]=NR) through coordination with the metal complexes[2] followed by dinitrogen extrusion. The mechanism of this transformation has been a subject of continuing interest.[3−5] Electrophilic metal complexes coordinate with the internal nitrogen of the azide to initiate the elimination of dinitrogen,[5] and this mechanistic pathway is operational in catalytic metal nitrene reactions.[6] However, there are few examples for this selective transformation with ketones or derivative functional groups, and all of them have been intramolecular reactions. Zakarian and Pelc have employed a Staudinger reduction of an azide with Me_3P for the synthesis of the α,γ-spirobicyclic ring system of pinnatoxins and pteriatoxins,[7] but reaction conditions (refluxing toluene) and the modest yield (51%) limit broader applicability. In their presentation of metal catalyzed intramolecular reactions of indoline diazoamides, Wee and Slobodian reported for the first time two examples of rhodium(II) acetate catalyzed conversion of a diazocarbonyl compound to an imine (**1**→**2**) from the reaction with an internal azide (Scheme 1).[8] With Wee's report as precedent, Micouin, Lecourt and co-workers employed the same transformation to prepare a surrogate of 2-deoxystreptamine **3**,[9] but these are the only reports for this transformation.

Scheme 1. Previous Examples of Rhodium Catalyzed Formation of Imines



With the limited number of examples of this potentially useful transformation available, we decided to investigate the scope of the reaction with a broad selection of diazocarbonyl compounds and azides, determine the optimum catalyst for this transformation, and provide examples of reaction processes that effectively utilize α-carbonylimines. The latter search has taken us to [4 + 2]- and [2 + 2]-cycloaddition processes that employ α-carbonylimines for the formation of tetrahydropyrimidines and β-lactams in high yield and with a high degree of selectivity.

Initial efforts were directed toward reactions of methyl diazoacetoacetate **4a** with a stoichiometric amount of *p*-anisyl azide **5a** catalyzed by rhodium acetate. Because diazoacetoacetates, as examples of acceptor/acceptor diazo compounds,[10] are relatively stable to reactions with Lewis acids and less selective than aryl- and vinyl-diazoacetates in metal carbene transformations, they are suitable substrates for examination of the feasibility of the transformation. Because the product formed in the transformation with azide is an α-ketoimine, its formation would demonstrate a unique advantage over traditional methods for imine formation. Reactions at room temperature were sluggish due to imine coordination with the moderately Lewis acidic $Rh_2(OAc)_4$, but in refluxing dichloromethane, imine **6a** was produced in moderate yield (Table 1, entry 1). Alternative uses of $CuPF_6$ and $Cu(OTf)_2$ were examined but, although dinitrogen loss from **4a** was observed, azide **5a** remained intact (entries 2−3). Lower yields of **6a** were obtained with the more soluble $Rh_2(oct)_4$ and with the less Lewis acidic $Rh_2(cap)_4$ (entries 4−5). A reaction performed at 80 °C in refluxing DCE provided **6a** in only 45% yield (entry 6). In all cases with stoichiometric **4a** and **5a**, a fraction of azide **5a** remained. By increasing the amount of **4a** to 1.2 and 1.5

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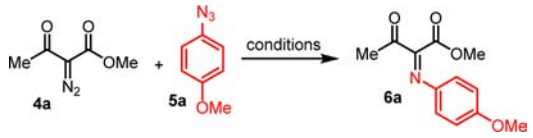
Table 1. Optimization of Imine Formation[a]



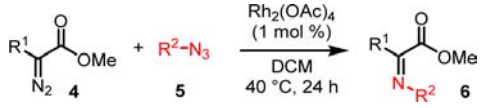
entry	catalyst (mol %)	temp (°C)	solvent	yield (%)[b]
1	$Rh_2(OAc)_4$ (1)	40	DCM	59
2	$CuPF_6$ (5)	40	DCM	NR
3	$Cu(OTf)_2$ (5)	40	DCM	NR
4	$Rh_2(oct)_4$ (1)	40	DCM	43
5	$Rh_2(cap)_4$ (1)	80	DCE	22
6	$Rh_2(OAc)_4$ (1)	80	DCE	45
7	$Rh_2(OAc)_4$ (1)	40	DCM	68[c]
8	$Rh_2(OAc)_4$ (1)	40	DCM	68[d]

[a]A solution of diazo compound (1.0 equiv) was added over 1 h via syringe pump to a solution containing azide (1.0 equiv) and catalyst and stirred for an additional 24 h under a nitrogen atmosphere. [b]Isolated yield after column chromatography. [c]1.2 equiv of diazo compound was used. [d]1.5 equiv of diazo compound was used.

equiv, relative to **5a**, the reaction yield improved to 68% (entries 7–8).

The generality of this process was evaluated under these optimized conditions with a selection of azides and diazo compounds (Table 2). Product yields were sequentially lower with phenyl azide and *p*-nitrophenyl azide (entries 2, 3) than with *p*-methoxyphenyl azide, suggesting the importance of azide nucleophilicity on the outcome of the reaction. The reaction with benzyl azide produced imine **6d** cleanly prior to workup; however, **6d** was prone to isomerization on silica that formed the corresponding benzylideneimine, and only a 53% yield of **6d** was obtained after chromatography (entry 4). With donor/acceptor carbene precursors,[10] such as phenyldiazoacetate **4b**, the reaction was complete within an hour and gave **6e** in 97% isolated yield (entry 5). With aryldiazoacetates **4** (R^1 = Ar) isolated yields were all above 81% (entries 5–12). When R^1 = COOMe, which is less electron-withdrawing than Ac, imine **6m** was obtained in 60% yield (entry 13). Diazoacetoacetate **4i** containing a remote ketone functional group gave an expected moderate yield of imine **6n** (entry 14). Enoldiazoacetate **4j**, whose metal carbene intermediate normally undergoes nucleophilic attack at the vinylogous carbon, reacted with the azide at the metal carbene carbon to give the corresponding azadiene **6o** in moderate yield (entry 15).

Table 2. Reaction Scope and Limitations[a]

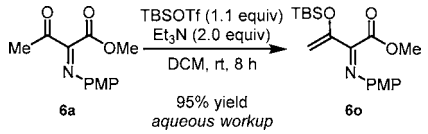


entry	R^1	R^2	6	yield (%)[b]
1	Ac (**4a**)	4-$MeOC_6H_4$	**6a**	68
2	Ac	Ph	**6b**	50
3	Ac	4-$NO_2C_6H_4$	**6c**	31
4	Ac	Bn	**6d**	53
5	Ph (**4b**)	4-$MeOC_6H_4$	**6e**	97
6	Ph	Ph	**6f**	90
7	Ph	4-$NO_2C_6H_4$	**6g**	81
8	 (**4c**)	4-$MeOC_6H_4$	**6h**	86
9	4-$MeOC_6H_4$ (**4d**)	4-$MeOC_6H_4$	**6i**	90
10	4-ClC_6H_4 (**4e**)	4-$MeOC_6H_4$	**6j**	95
11	4-$NO_2C_6H_4$ (**4f**)	4-$MeOC_6H_4$	**6k**	82
12	2-naphthyl (**4g**)	4-$MeOC_6H_4$	**6l**	96
13	COOMe (**4h**)	4-$MeOC_6H_4$	**6m**	60
14	 (**4i**)	4-$MeOC_6H_4$	**6n**	65
15	 (**4j**)	4-$MeOC_6H_4$	**6o**	40

[a]Reactions were performed as described in Table 1. [b]Isolated yield after column chromatography.

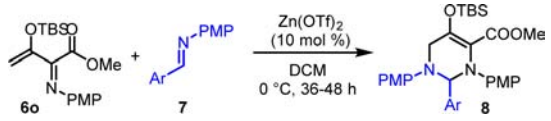
We envisioned that the highly functionalized 1-azadiene **6o** that can be accessed via the diazo-nitrene exchange methodology would be a good candidate for the aza-Diels–Alder reaction. However, since **6o** was only obtained in moderate yield from enoldiazoacetate **4j**, an alternative route involving treatment of imine **6a** with triethylamine and TBSOTf generated **6o** in 95% yield and only required aqueous workup (Scheme 2).

Scheme 2. Alternative Route to 1-Azadiene 6o



With functionalized 1-azadiene **6o** in hand we discovered that 1,2,3,4-tetrahydropyrimidines **8** were readily formed in high yield via a Lewis acid catalyzed [4 + 2]-cycloaddition reaction between **6o** and imines **7** (Table 3). Under optimized conditions (see Supporting Information), the reaction between **6o** and imine **7a** catalyzed by 10 mol % $Zn(OTf)_2$ provided tetrahydropyrimidine **8a** in 91% yield (Table 3, entry 1).

Table 3. Synthesis of Tetrahydropyrimidines[a]



entry	Ar	8	yield (%)[b]
1	C_6H_5	**8a**	91
2	4-BrC_6H_4	**8b**	88
3	4-$NO_2C_6H_4$	**8c**	90
4	2-naphthyl	**8d**	82
5	4-$CH_3C_6H_4$	**8e**	82
6	2-ClC_6H_4	**8f**	75
7	4-$MeOC_6H_4$	**8g**	72

[a]To a solution containing **6o** (0.20 mmol) and imine **7** (0.24 mmol, 1.2 equiv) in DCM (1 mL) under a N_2 atmosphere, at 0 °C, was added $Zn(OTf)_2$ (10 mol %), and the mixture was stirred for 36–48 h. [b]Isolated yield after column chromatography.

This transformation tolerated a broad selection of aryl imines **7**, including those with electron-donating, electron-withdrawing, halogen, and ortho substituents (Table 3, entries 1–7). To our knowledge, this is the first example of the aza-Diels–Alder reaction involving imines in both the diene and dienophile.[11] This methodology provides an efficient route to highly functionalized tetrahydropyrimidines, a class of molecules

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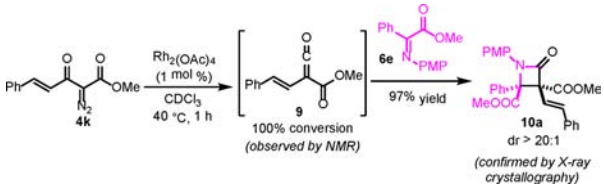
whose members have anti-inflammatory and antimicrobial properties.[12]

In our efforts to form the imine product when enonediazoacetate **4k** was reacted with azides we confirmed that this diazo compound undergoes a catalyst promoted Wolff rearrangement, first reported by Taylor and Davies,[13] to form ketene **9** and does not react with the azide (Scheme 3). Since **9**

Scheme 3. Wolff Rearrangement of 4k and [2 + 2] Cycloaddition to β-Lactam 10a



is moderately stable under these reaction conditions, we envisioned that subsequent treatment with imine **6e** would be possible, and, indeed, [2 + 2]-cycloaddition between **9** and **6e** yielded β-lactam **10a** as a single diastereomer. Structural assignment of **10a** was confirmed by single crystal X-ray analysis (see Supporting Information).

Other α-carbonylimines **6** formed from diazoesters were also reacted with **9** by this application of the Staudinger reaction,[14,15] and these results are reported in Table 4. The

Table 4. Synthesis of β-Lactams 10[a]

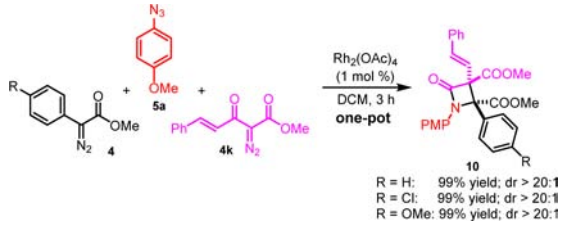
entry	R^1	R^2	**10**	yield (%)[b]	dr (*anti:syn*)[c]
1	Ph	4-$MeOC_6H_4$	**10a**	97	> 20:1
2	Ph	4-$NO_2C_6H_4$	**10b**	95	> 20:1
3	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**10c**	81	> 20:1
4	4-$NO_2C_6H_4$	4-$MeOC_6H_4$	**10d**	89	15:1
5	Ac	4-$MeOC_6H_4$	**10e**	93	1.4:1
6	OTBS	4-$MeOC_6H_4$	**10f**	85	> 20:1

[a]A solution containing **4k** (0.43 mmol, 1.2 equiv), imine **6** (0.36 mmol, 1.0 equiv), and $Rh_2(OAc)_4$ (1 mol %) in 2 mL of DCM was stirred for 1 h at 40 °C. [b]Isolated yield after column chromatography. [c]Diastereoselectivity was determined by ^1H NMR spectroscopic analysis of the unpurified reaction mixture.

reaction is general toward electron-donating and -withdrawing R^1 and R^2 substituents on imine **6**, providing high yields and diastereoselectivities (Table 4, entries 1−4). When R^1 = Ac, a high yield of β-lactam was obtained but with essentially no diastereoselectivity (entry 5). When R^1 = silylenol **6o**, **10f** was produced in 85% yield with dr >20:1, providing a highly functionalized β-lactam (entry 6) suitable for further elaboration.

To ascertain if the overall transformation could be performed as a one-pot reaction, phenyldiazoacetate **4b**, azide **5a**, enonediazoacetate **4k**, *p*-anisyl azide, and rhodium acetate were stirred at 40 °C for 2 h to give **10a** in remarkably high yield and diastereoselectivity (Scheme 4). This transformation

Scheme 4. One-Pot Multicomponent Synthesis of β-Lactam 10



requires highly selective and sequential dinitrogen extrusion from the diazo compounds with initial reaction with phenyldiazoacetate to form the imine intermediate followed by the Wolff rearrangement with **4k** and subsequent cycloaddition. Reaction with 4-methoxyphenyldiazoacetate **4d**, also conducted at 40 °C, cleanly provided **10c** in 99% yield, and 4-chlorophenyldiazoacetate **4e** gave **10g** in nearly quantitative yield from the reaction conducted at room temperature.

In conclusion, we have developed a mild and chemoselective process for the synthesis of imines via a formal nitrene replacement of dinitrogen by the combination of diazocarbonyl compounds and azides. The azadiene formed from enoldiazoacetate **4j** undergoes highly efficient hetero-Diels−Alder reactions with imines to form tetrahydropyrimidines. The ketene formed catalytically from enonediazoacetate **4k** undergoes a Staudinger reaction with α-carbonylimines to yield functionalized β-lactam derivatives. The efficiency and yield of β-lactams formed from aryldiazoacetates were nearly quantitative in multicomponent reactions with *p*-anisyl azide and enonediazoacetate **4k**, catalyzed by dirhodium(II) acetate.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures, the X-ray crystal structure of **10a**, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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