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Synthesis of 5-Substituted a,b-Unsaturated g-Lactams from *N*-Sulfinyl Azadienes by Iron-mediated Reaction Cascades and Palladium-catalyzed Cyclocarbonylation Strategies

Patrick Amrhein and Karola Rück-Braun*

Institut für Organische Chemie, Johannes Gutenberg-Universität,

Duesbergweg 10-14, 55099 Mainz, Germany

E-mail: krueck@mail.uni-mainz.de

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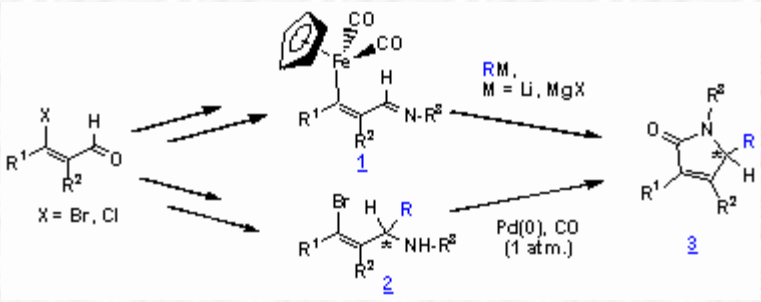
Introduction:

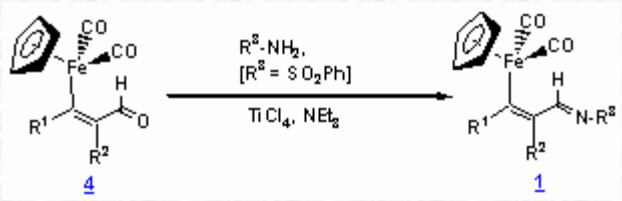
A new synthesis of 5-substituted a,b-unsaturated g-lactams is reported. b-[$Cp(CO)_2Fe$]-Substituted *N*-sulfonyl[1] and *N*-sulfinyl azadienes **1** react with Grignard reagents or organolithium compounds furnishing 5-substituted a,b-unsaturated g-lactams **3**.[2,3] These reaction cascades occur by initial attack of the organometallic reagent at the imine functionality followed by an intramolecular cyclocarbonylation step. In a number of cases non-*N*-protected lactams are obtained from *N*-sulfonyl azadienes besides the desired *N*-sulfonyl g -lactams **3**. Moreover, chiral b-[$Cp(CO)_2Fe$]-substituted *N*-sulfinyl azadienes **1** react with the organometallic reagents to furnish exclusively 5-substituted non-*N*-protected g -lactams **3**.[2,3]

In addition, the synthesis of 5-substituted a,b-unsaturated g-lactams **3** by palladium-catalyzed cyclocarbonylations of chiral bromo-substituted sulfinamides **2,** derived from the corresponding azadiene precursors and organometallic reagents, is described.[4]

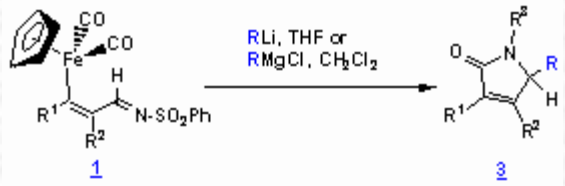


Reactions of b-[Cp(CO)$_2$Fe]-substituted *N*-Sulfonyl Azadienes with C-Nucleophiles:

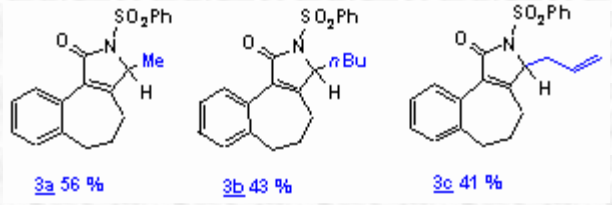
a,b-Unsaturated imines **1** are synthesized e.g. from b-[Cp(CO)$_2$Fe]-substituted (*Z*)-alkenals **4** and electron poor primary amino compounds in CH_2Cl_2 in the presence of $TiCl_4$ and NEt_3 in dichloromethane (66-100 %).[1,4]



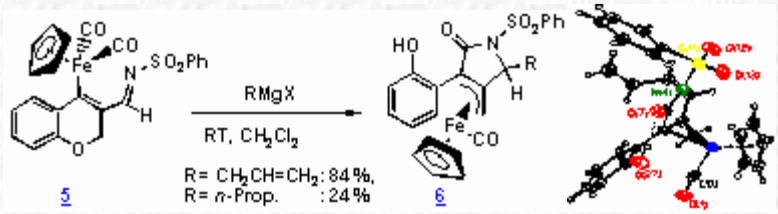
The g-lactams **3** are accessible by treatment of the a,b-unsaturated imines **1** with organolithiums in THF at -78°C or 0°C followed by prolonged stirring at room temperature (39-56 %). Reactions with Grignard-reagents carried out in dichloromethane at room temperature furnished the g-lactams **3** in 37-62 % yield.



Examples:

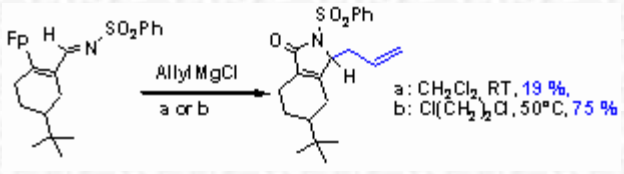


The reaction of imine **5** with Grignard reagents is found to furnish the allyliron complexes **6**. The structure of the allyl-substituted product was elucidated by X-ray analysis. Therefrom an anti-orientation of the metal fragment and the allyl residue at carbon-5 is concluded.

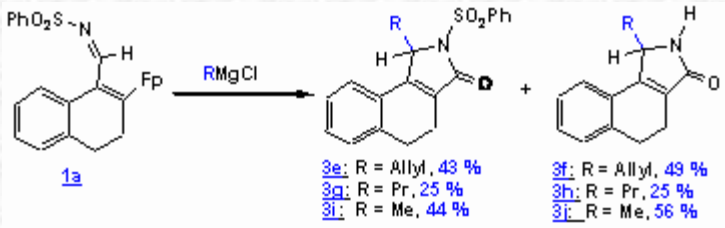


Influence of the temperature on the carbonylation step:

When the cyclohexene-derivative shown below is treated with allyl Grignard reagent at room temperature the *N*-sulfonyl g -lactam is isolated in only 19% yield. However, the yield could be increased by raising the reaction temperature after the initial 1,2-addition for the cyclocarbonylation key step. Thereby, in 1,2-dichloroethane at 50°C complete turnover to the desired product is achieved. The *N*-sulfonyl g -lactam is isolated in 75 % yield after flash chromatography.



Unexpected Deprotection: What role does the iron play in this game?

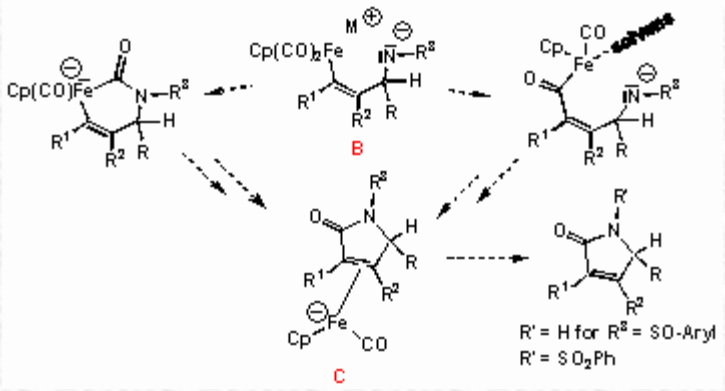


Reactions of compound **1a** with either organolithium or Grignard reagents led to the non-*N*-protected lactams **3f**, **3h, 3j** besides the lactams **3e**, **3g, 3i**. At the current stage the cleavage of the N-S bon is not conclusive. Iron-mediated redox processes my be involved in the formation of the non-*N*-protected g -lactams **3f**, **3h, 3j**.

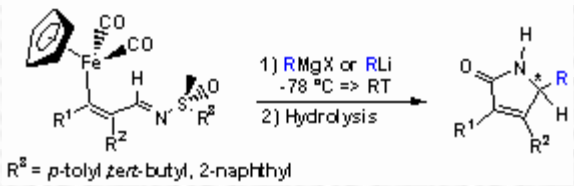
Mechanistic Considerations:

After 1,2-additon of the organometallic reagents to the *N*-sulfonyl azadienes, furnishing the metallated amides (B), the carbonylation steps may proceed via an acyl iron intermediate or a ferrilactam intermediate.[1-4]

For the formation of the allyliron complexes presented above it seems reasonable to propose an anionic p -alkene-iron complex as intermediate (C) being formed after the reductive elimination step leading to the five-membered ring system. In an intramolecular nucleophilic substitution reaction the attack of the iron moiety at the neighboring methylene group could lead to a phenolate prior aqueous work-up yielding the allyliron complexes.



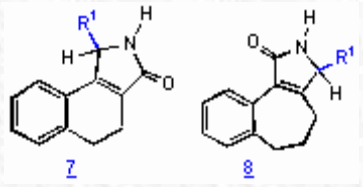
Application of Iron-substituted *N*-Sulfinyl Azadienes:



Chiral sulfinimines react with Grignard- or organolithium reagents to give exclusively non-*N*-protected a,b-unsaturated g-lactams. Only the *N*-*tert*-butyl sulfinyl imines can be treated with organolithiums and alkyl Grignard reagents since

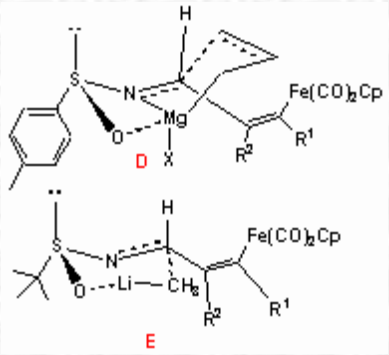
the sulfur atom is effectively shielded by the tert-butyl residue leading to exclusive attack at the imine carbon atom. For the reactions summarized in the Table, the enantioselectivities were determined by shift experiments to range from 10% *ee* up to 62% *ee*.

Iron-mediated redox processes during aqueous work-up seem to be responsible for the N-S bond cleavages observed.



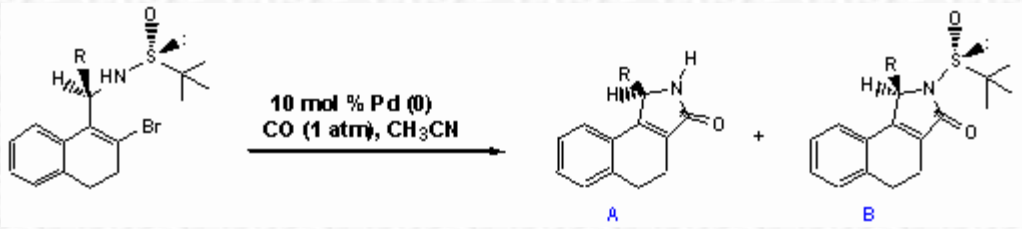
	R^3	Lactam	R^1-M	Yield	*ee (%)*
1	*p*-tolyl	8	AllylMgCl	64 %	40
2	*p*-tolyl	8	BnMgCl	27 %	62
3	2-naphthyl	8	AllylMgCl	63 %	40
4	*tert*-butyl	8	AllylMgCl	45 %	46
5	*p*-tolyl	7	AllylMgCl	66 %	52
6	*p*-tolyl	7	AllylMgBr	27 %	45
7	*tert*-butyl	7	AllylMgCl	55 %	38
8	*tert*-butyl	7	MeLi	91 %	10

For the addition of organolithiums and Grignard reagents to sulfinimines six-membered ring transition state models have been proposed by Davis and Ellman to predict the diastereofacial selectivity. [5,6]



Palladium-catalyzed Cyclocarbonylations:

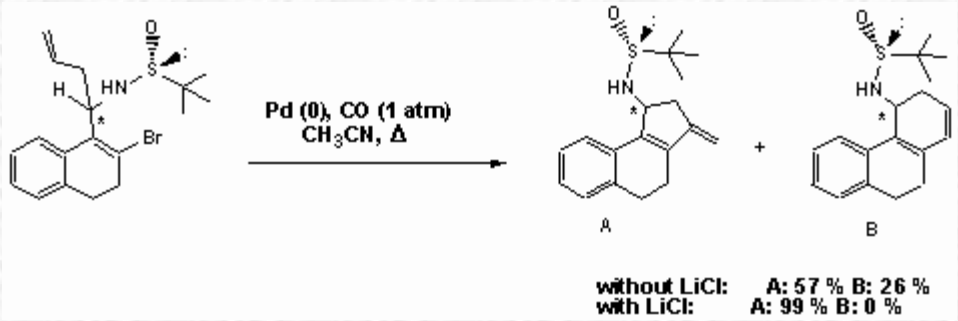
Enantiopure g-lactams **3** are accessible by palladium(0)-catalyzed cyclocarbonylation reactions of chiral sulfinamides. The chiral sulfinyl amides used are synthesized from the corresponding imines by 1,2-addition of organolithium or Grignard-reagents in 50-100 % yield. The diastereoselectivity obtained ranged from 51:49 up to 91:9. Fortunately, the diastereomers are easily separated by chromatography. The absolute configuration of an allyl-substituted and a methyl-substitued optically pure sulfinamide was elucidated by X-ray analysis. In the palladium-catalyzed cyclocarbonylation reactions surprisingly *N*-sulfinyl-substituted (B) and non-*N*-protected derivatives (A) are formed. The reactions are carried out with $Pd(PPh_3)_4$ and *n*-Bu_3N as base in acetonitrile at reflux for 5-28 h. The N-S bond cleavage can be attributed to attack of hydrogen bromide formed from the palladium hydride intermediate within the catalytic cycle.



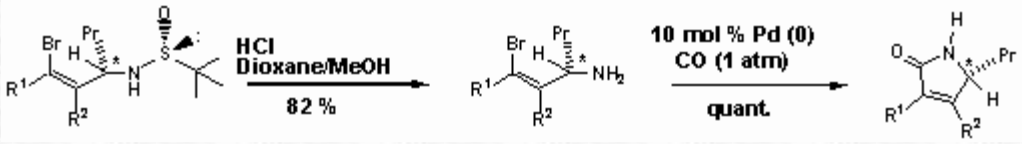
	R	t	A	B
1	Me	5 h	28	37
2	Me	23.5 h	17	56
3	Me[a]	28 h	50	25
4	*n*Pr	22 h	48	40
5	Bn	21.5 h	29	71

[a] $Pd(OAc)_2(PPh_3)_2$

The palladium-catalyzed cyclocarbonylation of allyl-substituted sulfinamides gave the desired lactam derivatives in less than 5% yield. The chiral amines shown below are found to be formed instead by Heck-reaction. In the presence of LiCl compound A is exclusively obtained.



From the optically pure sulfinamide shown below the amine derivative is prepared by treatment with HCl in dioxane/methanol for cyclocarbonylation studies, yielding the non-*N*-protected a , b -unsaturated g -lactam quantitatively.



In summary, 5-substituted a , b -unsaturated g -lactams were obtained in novel reaction cascades starting from iron-substituted *N*-sulfonyl or *N*-sulfinyl azadienes and organometallic reagents. Enantiomerically pure derivatives were prepared from chiral sulfinamides by a palladium-catalyzed cyclocarbonylation strategy starting from b -bromo-substituted *N*-sulfinyl azadienes.

References:

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