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Platinum(II) Chloride-Catalyzed Stereoselective Domino Enyne Isomerization/Diels−Alder Reaction

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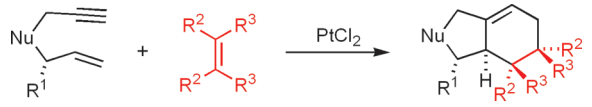
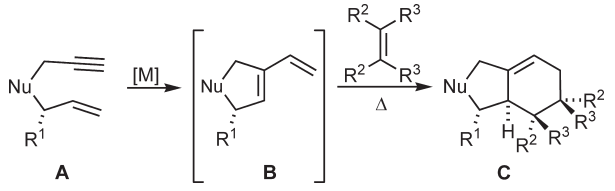


Chiral 1,6-enynes were prepared via Ir-catalyzed allylic substitutions. Their platinum(II) chloride-catalyzed domino enyne isomerization/Diels−Alder reaction provided stereoselective access to complex heterocycles. Very high diastereoselectivity was induced by a chirality center of the enyne.

Isomerization reactions of 1,6-enynes, readily inducible by transition metal complexes, offer access to a broad range of dienes.[1] The reaction course varies with the transition metal catalyst and the substituents of the 1,6-enyne. Our objective was a chemoselective enyne isomerization leading to a 1,3-diene in the presence of a dienophile in order to achieve a stereoselective Diels−Alder reaction in domino[2] fashion (Scheme 1).

SCHEME 1. Domino Enyne Isomerization/Diels−Alder Reaction



Consecutive sequences of enyne metathesis, using Grubbs-type catalysts, and Diels−Alder reaction have been reported.[3] Gênet et al. accomplished interesting substrate-controlled diastereoselective reactions in a sequential one pot, not a domino manner,[3a] i.e. by addition of the dienophile after complete formation of the diene. Domino sequences were accomplished by Bentz and Laschat[3b] for Diels−Alder reactions at room temperature in the presence of stoichiometric amounts of BCl_3. We wondered whether the domino sequence could be accomplished for thermal Diels−Alder reactions, which would often require temperatures not tolerated by Grubbs-type catalysts. We have now found that this is possible with platinum(II) chloride as a thermally stable catalyst. Thermal Diels−Alder reactions could be carried out at 110 °C (refluxing toluene) with a high degree of diastereoselectivity. In addition, we herein describe the synthesis of a new class of chiral, 5-substituted enynes that allows diastereoselective Diels−Alder reactions to give complex tricyclic heterocycles of potential interest for medicinal chemistry.

In the exploratory work, the chiral 1,6-enynes **3a**[4] and **3b** were chosen as substrates. These compounds were prepared from cinnamyl methyl carbonate (**1**) with high enantiomeric purity (97.5−98.5% ee) by asymmetric Ir-catalyzed allylic substitution and subsequent alkylation with propargyl bromide (Scheme 2).[5] Then catalysts for the enyne isomerization were screened using **3a** as substrate (Table 1).

Despite phenomenologically similar reactivity toward 1,6-enynes, the catalysts differ in substrate specificity, reaction mechanism, and required reaction conditions.[1b] The Grubbs catalysts I and II did not lead to complete conversion of enyne **3a** to diene **4**. This has previously been observed for other monosubstituted alkynes.[6] Better results were obtained with $PtCl_2$,[7] $FeCl_3$,[8] and $[Au(PPh_3)Cl]/AgSbF_6$[9] as catalysts. The catalyst $Ph_3PAuCl/AgSbF_6$, displaying the highest activity, was not compatible with dienophiles at high temperatures, i.e. product mixtures were formed. As best suited catalyst, $PtCl_2$ was identified, which induced high yields and is thermally stable as is necessary for most Diels−Alder reactions. This catalyst had already found application as an enyne isomerization catalyst in total synthesis.[7,10]

For the domino reaction to yield cycloadducts **5**, a solution of the enyne, a dienophile and $PtCl_2$ in toluene was heated at reflux (Table 2). A single diastereoisomer was obtained in all cases. HPLC analysis of the crude products showed complete conservation of enantiomeric purity.

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(2) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.

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(10) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305–8314.

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SCHEME 2. Ir-Catalyzed Allylic Substitution−Propargylation Sequence

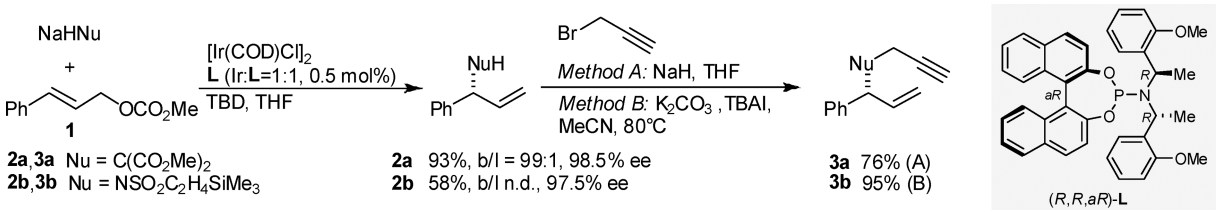
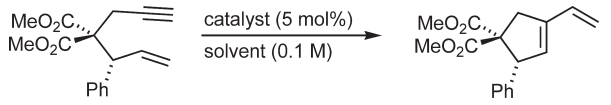


TABLE 1. Catalyst Screening for the Enyne Isomerization of 3a



entry[a]	catalyst	solvent	temp. (°C)	conversion/ time	yield (%)
1	Grubbs′ I	CH_2Cl_2	rflx	14%,[b] 2 d	
2	Grubbs′ II	CH_2Cl_2	rflx	33%,[b] 2 d	
3	$PtCl_2$	toluene	80	full,[c] 3 h	90
4	$Ph_3PAuCl/AgSbF_6$	CH_2Cl_2	rt	full,[c] < 1 h	74
5	$FeCl_3$	toluene	80	incomplete,[c] 26 h	66

[a]All reactions were carried out under an argon atmosphere on a 0.5 mmol scale. [b]Determined by GC. [c]Determined by TLC.

Isolated yields were good with *N*-phenylmaleimide and tetracyanoethylene as dienophiles and moderate otherwise. Considering the complexity of this multistep transformation, even yields on the order of 40% are satisfactory.

The relative configurations of the products were determined for **5a**, **5d**, and **5e** by crystal structure analyses.[11] Accordingly, the Diels−Alder reaction proceeded via *endo* addition at the less hindered face of the diene moiety (Figure 1).

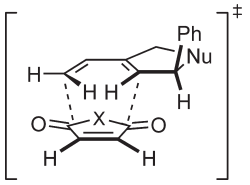


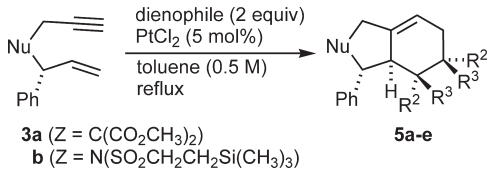
FIGURE 1. *Endo* [4πs + 2πs] transition state.

In conclusion, we are reporting a $PtCl_2$-catalyzed domino enyne isomerization/Diels−Alder reaction that offers access to highly enantioenriched complex heterocycles.

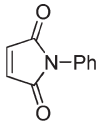
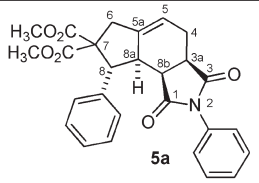
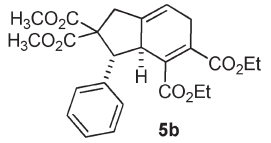
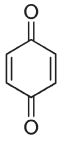
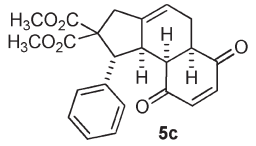
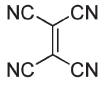
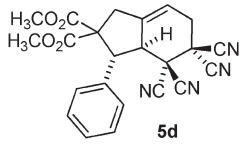
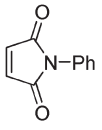
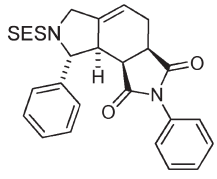
Experimental Section

General Procedure for the $PtCl_2$−Catalyzed Enyne Isomerization Diels−Alder Reaction: (−)-Dimethyl (3a*R*,8*R*,8a*R*,8b*S*)-1,3-Dioxo-2,8-diphenyl-2,3,3a,4,6,8,8a,8b-octahydrocyclopenta[*e*]isoindole-7,7(1*H*) Dicarboxylate (5a). A solution of (-)-(*R*)-**3a** (97.5%ee, 286 mg, 1.0 mmol) and *N*-phenylmaleimide (346 mg, 2.0 mmol) in toluene (2 mL) was treated with $PtCl_2$ (13.3 mg, 50 μmol), and the resulting solution was heated at reflux until after 2 h TLC control [petroleum ether/ethyl acetate, 3:1, R_f(**3a**) = 0.37, R_f(**5a**) = 0.10, $KMnO_4$] indicated complete consumption of **3a**. The reaction mixture was filtered through Celite, and this was washed with CH_2Cl_2 (50 mL). The solvent was removed, and the

TABLE 2. Platium(II) Chloride-Catalyzed Domino Enyne Isomerization/Diels−Alder Reaction



3a (Z = $C(CO_2CH_3)_2$)
b (Z = $N(SO_2CH_2CH_2Si(CH_3)_3)$

entry	enyne	dienophile	yield (%)	product
1	**3a**		62[a]	 **5a**
2	**3a**		44	 **5b**
3	**3a**		49	 **5c**
4	**3a**		70	 **5d**
5	**3b**		36	 **5e** (SES = $SO_2(CH_2)_2Si(CH_3)_3$)

[a]The yield of **5a** upon use of isolated, pure **4** was 69%.

(11) CCDC-756790 (**5a**), CCDC-765791 (**5d**), and CCDC-765792 (**5e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

residue was subjected to flash chromatography on silica gel (30 g, petroleum ether/ethyl acetate, 3:1) to yield **5a** as a slightly yellow foam, which was dissolved in hot ethanol (10 mL). Upon cooling to room temperature, crystallization occurred. After washing of the crystals with cold *n*-hexane (−)-(3a*R*,8*R*,8a*R*,8b*S*)-**5a** (283 mg, 62%) was obtained as colorless and analytically pure needles (mp 165−167 °C). The structure of the compound was confirmed by X-ray crystal structure analysis. $[\alpha]_D^{20} = -148$, ($c = 0.42$, MeOH, 97.5% ee according to starting material); ^{1}H NMR ($CDCl_3$, 300.13 MHz) $\delta = 2.32-2.43$ (m, 1 H), 2.70−2.80 (m, 1 H), 2.89 (dd, $J = 15.5$ Hz, $J = 7.1$ Hz, 1 H), 3.11−3.29 (m, 4 H), 3.47, 3.66 (2 s, 6 H), 4.74 (d, $J = 11.9$ Hz, 1 H), 5.81−5.86 (m, 1 H), 7.17−7.42 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75.48 MHz) $\delta = 22.6$ (t), 40.1 (t), 40.5, 41.1, 44.7 (3 d), 50.8 (d), 52.1, 52.5 (2 q), 64.2 (s), 117.1 (d), 126.6, 127.7, 128.2, 128.8, 129.2 (5 d), 132.0, 137.5, 142.2 (3 s), 171.1 (s), 171.4 (s), 176.7, 178.9 (2 s); HR-MS (EI) *m*/*z* calcd for $C_{27}H_{25}NO_6$ [M^+] 459.1683, found 459.1661; elemental analysis calcd for $C_{27}H_{25}NO_6$ C 70.58 H 5.48 N 3.05, found C 70.66 H 5.51 N 3.07.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds and crystallographic information for **5a**, **5d**, and **5e**. This material is available free of charge via the Internet at http://pubs.acs.org.