Asymmetric Catalysis

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Enantioselective Ficini Reaction: Ruthenium/PNNP-Catalyzed [2+2] Cycloaddition of Ynamides with Cyclic Enones**

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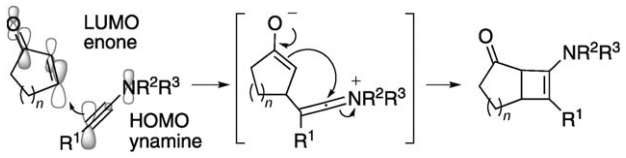
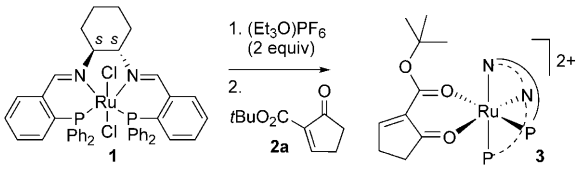
Recent synthetic advances have turned ynamides into broadly available substrates whose reactivity can be finely tuned.[1] In particular, the cross-coupling of amides with alkynyl bromides gives broad access to widely substituted ynamides.[2] Thus, the last few years have witnessed a surge of their use as nitrogen-containing building blocks in organic chemistry that undergo addition at the α or β positions, oxidative or reductive coupling, oxidation, ring-closing metathesis, cycloisomerization, and cycloaddition reactions.[1] Although a vast number of new transformations have been reported, stereoselective reactions with ynamides, and in particular enantioselective ones, are still rare.[3] A straightforward application of ynamides is the Ficini reaction, whose original version is a thermally driven, stepwise [2+2] cycloaddition of an ynamine with a cyclic enone (Scheme 1).[4]



Scheme 1. The original Ficini reaction with ynamines.

The advantage of using ynamides in the Ficini reaction instead on ynamines is that the electron-withdrawing group decreases the reactivity of the triple bond. This decrease in reactivity inhibits the thermal reaction and allows for a catalytic approach, and in particular for enantioselective reactions. Despite this being a straightforward development, the first example of a catalytic reaction of ynamides with enones was reported only very recently.[5] The performance of these combined Ag^{I}/Cu^{II} catalysts is modest, though, and an ynamide bearing a chiral auxiliary on the nitrogen atom gave 1:1 diastereomeric mixture. In general, [2+2] cycloaddition reactions with ynamides are rare, and chiral auxiliaries on the nitrogen canter gave low diastereoselectivity.[6] To the best of our knowledge, no enantioselective reaction has been reported yet. Therefore, a catalytic approach to the problem seems more efficient and in dire need.

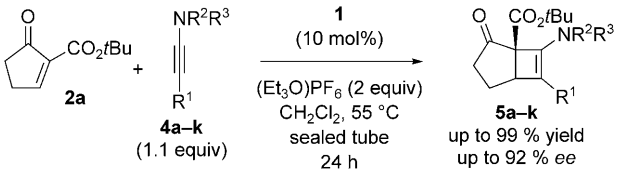
Our research group has recently reported that the dicationic ruthenium/PNNP complex **1**, upon activation with $(Et_3O)PF_6$ (Scheme 2),[7] catalyzes the asymmetric Diels–



Scheme 2. Substrate coordination to the ruthenium/PNNP fragment. PNNP = (1*S*,2*S*)-*N*,*N*′-bis{*o*-(diphenylphosphino)benzylidene}cyclohexane-1,2-diamine.

Alder reaction of α-methylene β-keto ester **2a** with a number of dienes.[8] This [2+4] cycloaddition reaction is the first asymmetric synthesis of alkoxycarbonyltetrahydro-1-indanones and gives access to enantiomerically pure estrone derivatives. More generally, this is a relatively rare example of the use of unsaturated β-keto esters in a cycloaddition reaction.[9]

As an extension to this approach, we report herein the first enantioselective Ficini reaction between ynamides **4** and the unsaturated β-keto ester **2a** to give the corresponding amidocyclobutenes **5a–k** with high yield and enantioselectivity (Scheme 3). A preliminary screening of ynamides showed that the substrates of choice contain an electron-donating substitutent (R^2) and an electron-withdrawing substitutent (R^3), respectively, whose appropriate combination imparts good reactivity to the ynamide in catalysis, but still low enough to inhibit the uncatalyzed background reaction at elevated temperatures.



R^1 is *c*-C_6H_{11}, Ph, *n*-C_6H_{13}, CH_2OBn, or $(CH_2)_2OSiMe_2tBu$, R^2 is Bn or Me, R^3 is Ts, Ms, or Mbs, see Table 1

Scheme 3. Enantioselective Ficini reaction. Bn = benzyl, Mbs = 4-methoxybenzenesulfonyl, Ms = methanesulfonyl, Ts = 4-toluenesulfonyl.

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[**] We thank Mr. Raphael Aardoom (ETH Zürich) for the X-ray analysis and the ETH Zürich for financial support to C.S. (grant no. TH-08 07-1). PNNP = (1*S*,2*S*)-*N*,*N*′-bis{*o*-[diphenylphosphino)benzylidene}cyclohexane-1,2-diamine.

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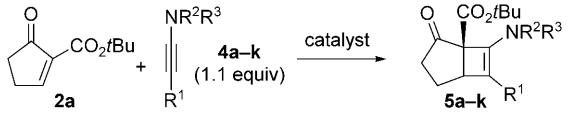
Table 1: Enantioselective Ficini reaction.[a]

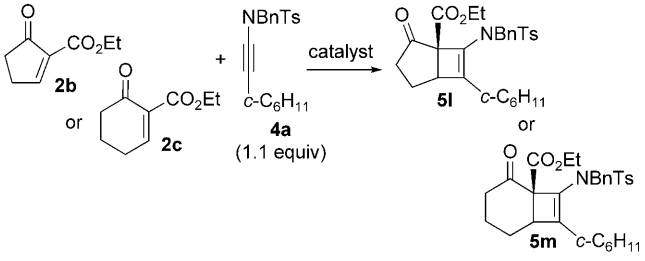


Entry	Product	R^1	R^2	R^3	Yield [%]	*ee* [%]
1	**5a**	*c*-C_6H_{11}	Bn	Ts	97 (75)[b]	90 (>99.5)[b]
2	**5b**	*c*-C_6H_{11}	Me	Ts	88	92
3	**5c**	Ph	Bn	Ts	72	90
4[c]	**5c**	Ph	Bn	Ts	66	92
5	**5d**	Ph	Me	Ts	64	87
6	**5e**	Ph	Me	Ms	69	83
7	**5f**	Ph	Me	Mbs	75	61
8	**5g**	*n*-C_6H_{13}	Bn	Ts	99	78
9	**5h**	*n*-C_6H_{13}	Me	Ms	94	70
10	**5i**	*n*-C_6H_{13}	Me	Mbs	99	78
11	**5j**	CH_2OBn	Me	Ts	60	70
12	**5k**	$(CH_2)_2OSiMe_2tBu$	Bn	Ts	86	76
13[d]	**5l**	*c*-C_6H_{11}	Bn	Ts	97	53
14[d]	**5m**	*c*-C_6H_{11}	Bn	Ts	84	57

[a] Reaction conditions: See the Experimental Section. [b] After a single recrystallization from *n*-hexane. [c] At room temperature. [d] See Scheme 4.

The catalysis results are summarized in Table 1. By and large, bulky substituents at the α position of the ynamide (R^1 = *c*-C_6H_{11} or Ph) are required for high enantioselectivity (entries 1–7), whereas high yields are achieved when R^1 is a good electron donor (entries 1, 2, and 8–10). The cyclohexyl-substituted ynamides **4a** and **4b** give the best combination of very high yield and enantioselectivity up to 92% *ee* (entries 1 and 2). Product **5a** was obtained as a single enantiomer by recrystallization from *n*-hexane. It should be noted that various functional groups (entries 11 and 12) are also tolerated by the protocol. In all reactions, a nearly stoichiometric amount of the alkyne is used (1.1 equiv), and high yields are obtained. This is notable for a reaction that forms an all-carbon stereogenic center at the bridgehead position of a highly strained unsaturated [3.2.0] bicycle.

The smaller ethyl esters **2b** and **2c** gave lower enantioselectivity (entries 13, 14 and Scheme 4), which confirms that a bulky ester group is pivotal, as observed in the Diels–Alder reaction[8] and with the saturated analogues.[7,10] Interestingly, the cyclohexenone derivative **2c** performs similarly to **2b**, and thus suggests an analogous optimization potential for six-membered unsaturated β-keto esters.



Scheme 4. Scope of the β-keto ester. Reaction conditions as in Scheme 3.

An X-ray study of enantiomerically pure *tert*-butyl-7-[*N*-benzyl-4-methylphenylsulfonamido]-6-cyclohexyl-2-oxobicyclo[3.2.0]hept-6-ene-1-carboxylate (**5a**) shows the 1*R*,5*S* absolute configuration (Figure 1),[11] and is in agreement with an attack of the ynamide from the upper enantioface of the coordinated enone (Figure 2). The shielding by one phenyl

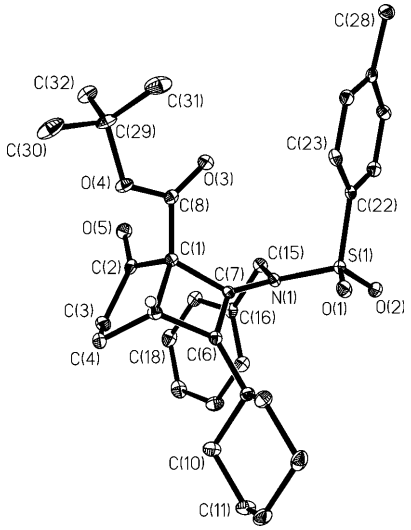


Figure 1. ORTEP plot of **5a**. Hydrogen atoms are omitted for clarity and the ellipsoids are drawn at 30% probability

ring of the PNNP ligand ensures high enantiofacial selectivity, as we have shown for the Diels–Alder reactions with **2a** and catalyst **1**/(Et_3O)PF_6 (2 equiv),[8] as well as for the analogous saturated β-keto esters. The latter substrates undergo Michael addition,[7b,c] hydroxylation,[12] as well as electrophilic fluorination reactions,[10] with high enantioselectivity in the presence of the same ruthenium/PNNP catalyst.

Although formally a [2+2] cycloaddition, the reaction between the ynamide and the enone is likely to occur stepwise

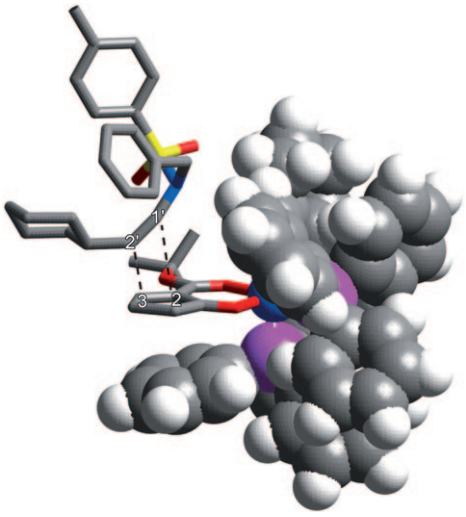


Figure 2. Calculated (MM) model for the approach of ynamide **4a** to complex **3**. Light blue N, dark blue Ru, magenta P, red O, yellow S.

by nucleophilic attack of the β-carbon atom of the ynamide onto the electrophilic position of the enone, as Ficini originally suggested for enamines (Scheme 1).[4] The electronic demand requires that the nitrogen atoms, and therefore its R^1 and R^2 substituents point toward the complex. Molecular modeling (MM) calculations show that the bulky R^1 and R^2 groups fold away from the PNNP backbone as ynamide **4a** approaches the coordinated enone in the open chiral space of complex **3**, and this minimizes the steric interactions in the transition state (Figure 2).[13]

We speculate that the ruthenium/PNNP fragment is particularly effective in stabilizing the intermediate enolate by virtue of its double positive charge. Therefore, the dicationic nature of **3** is possibly the key feature needed to ensure catalytic activity. To the best of our knowledge, this is the first asymmetric [2+2] cycloaddition of ynamides to an enone (Ficini reaction). The catalyst system based on **1**/$(Et_3O)PF_6$ (2 equiv) is highly efficient in terms of yield and enantioselectivity, and the scope of the reaction is promising. The coordination of the unsaturated β-keto ester to the chiral, oxophilic ruthenium/PNNP fragment is a more efficient strategy for enantioselection than introducing a chiral auxiliary at the ynamide nitrogen atom,[5,6] which is remote from the triple bond. Besides using ynamides, the reaction is a further, but still rare example of the use of an unsaturated β-keto ester as the substrate for a cycloaddition reaction.

Experimental Section

Typical procedure: $[RuCl_2(PNNP)]$ (**1**; 10 mg, 0.012 mmol, 0.1 equiv) and $(Et_3O)PF_6$ (6 mg, 0.024 mmol, 0.20 equiv) were stirred in CH_2Cl_2 (1 mL) in a Young Schlenk tube at room temperature overnight. A color change from red to brown indicated the formation of the catalytically active complex. Then a solution of unsaturated β-keto ester (**2a–c**; 0.12 mmol, 1 equiv) in CH_2Cl_2 (1 mL) was added. After 10 min, the ynamide (**4a–k**; 0.13 mmol, 1.1 equiv) was added. The Young Schlenk tube was closed and the mixture was heated to 55 °C. After 24 h, the solvent was evaporated under reduced pressure, and the oily residue was subject to flash chromatography on silica. See the Supporting Information for detailed procedures of substrate synthesis and product characterization.

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[3] To the best of our knowledge, two enantioselective reactions with ynamides have been reported: a) R. K. Friedman, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 10775 – 10782; b) K. Tanaka, K. Takeishi, K. Noguchi, *J. Am. Chem. Soc.* **2006**, *128*, 4586 – 4587; for an application of the same protocol, see: c) J. Oppenheimer, W. Johnson, R. Figueroa, R. Hayashi, R. Hsung, *Tetrahedron* **2009**, *65*, 5001 – 5012.

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[6] Selected papers: a) N. Riddell, K. Villeneuve, W. Tam, *Org. Lett.* **2005**, *7*, 3681 – 3684; b) K. Villeneuve, N. Riddell, W. Tam, *Tetrahedron* **2006**, *62*, 3823 – 3836; for a related enantioselective [2+2+2] cycloaddition, see reference [3a].

[7] a) $(Et_3O)PF_6$ (2 equiv) abstracts both chloro ligands as EtCl from complex **1** and the resulting Et_2O molecules bind to the oxophilic ruthenium/PNNP fragment, see: b) F. Santoro, M. Althaus, C. Bonaccorsi, S. Gischig, A. Mezzetti, *Organometallics* **2008**, *27*, 3866 – 3878; c) M. Althaus, C. Bonaccorsi, A. Mezzetti, F. Santoro, *Organometallics* **2006**, *25*, 3108 – 3110; d) C. Bonaccorsi, M. Althaus, C. Becker, A. Togni, A. Mezzetti, *Pure Appl. Chem.* **2006**, *78*, 391 – 396.

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[11] The value of the Flack parameter in dicates that the absolute configuration is 1*R*,5*S*. This assignment has been confirmed by reduction of the carbonyl function of **5a** and esterification of the resulting alcohol with (−)-camphanic acid chloride to give **6**. See the Supporting Information for synthetic details and X-ray structures. CCDC 802191 (**6**) and 802192 (**5a**) 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.

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[13] The transition state (TS) in Figure 2 has been modeled starting from the X-ray data of **3** and imposing a bond length of 2.0 Å between the C1 atom of the ynamide and C3 atom of the enone. Interestingly, a C1′-C2′-C3-C2 torsion angle of 0° is obtained for the TS without imposing any additional constraint. See the Supporting Information for the details of MM calculations.

