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Desymmetrization of *meso*-dienyne by asymmetric Pauson–Khand type reaction catalysts†

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Desymmetrization of the *meso* dienynes, such as propargyl 1-vinylallyl *N*-tosylamides (1a–c) and propargyl 1-vinylallyl ethers (1d–e), by asymmetric Pauson–Khand type reaction catalysts was studied. The corresponding vinyl substituted bicyclic pentenones (2 and 3) were obtained with high diastereoselectivity and enantioselectivity.

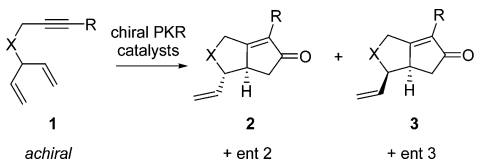
Desymmetrization of *meso* compounds by chiral catalysts leading to optically enriched or pure products is among the most efficient strategies to generate new stereogenic centers from prochiral substrates.[1] Interesting recent reports in this line[2] include desymmetrization by asymmetric ring-closing metathesis (ARMC) catalysts.[3] We have recently developed the asymmetric Pauson–Khand reaction (APKR hereafter) employing a cationic chiral Rh(I) catalyst.[4] A neutral (tol)BINAP-Ir(I) catalyst, and a neutral BINAP-Rh(I) catalyst coupled with aldehydes as the CO source were also reported to effect APKR afterwards.[5] Meantime, we envisioned that it would be attractive to employ these catalysts for the preparation of optically pure bicyclic compounds from prochiral *meso*-dienyne substrates by desymmetrization.

This desymmetrization of dienynes (**1**) by chiral PKR catalysts would generate two stereogenic centers at the same time. Thus it would lead to a mixture of diastereomers as well as enantiomers (Scheme 1).

Here we report our preliminary study on diastereoselectivity and enantioselectivity during the course of desymmetrization by APKR catalysts.

We began our study with the substrate **1a**.[6] Three different conditions reported to date were examined to figure out the characteristics of the reaction and to find the optimum conditions.

As illustrated by entry 1 of Table 1, methyl-substituted substrate **1a** was first subjected to the cationic Rh(I)-(*R*)-BINAP catalyst, which was prepared *in situ* by mixing 3 mol% of $[RhCl(CO)_2]_2$, 9 mol% of (*R*)-BINAP and 12 mol% of AgOTf prior to the addition of **1a** in THF. The reaction mixture was refluxed under 1 atm of CO. The reaction proceeded to completion in 0.5 h to give a mixture of **2a** and **3a** in 9% and 57% yield,[7] respectively. The diastereoselectivity observed here is the opposite to the previously known analogy.[8] The enantiomeric excesses were determined to give 51% for the minor **2a** and 77% for the major **3a**, respectively. Subsequently, **1a** was allowed to react by neutral Rh(I)-(*R*)-BINAP in cinnamoylaldehyde under argon. Cinnamoylaldehyde served as both solvent and CO source at the same time. It was observed that there were substantial improvements in overall chemical yield as well as diastereoselectivity (1 : 8 in entry 5 from 1 : 6 in entry 1) at the cost of enantioselectivity. Enantioselectivity diminished from 77% to 71% for **3a**. However, the general trend of the reaction remained unchanged.

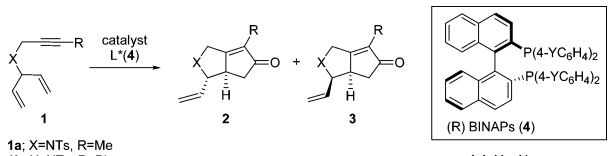


Scheme 1 Desymmetrization of *meso*-dienynes by asymmetric PKR.

On the other hand, when **1a** was subjected to neutral Ir(I)-(*R*)-BINAP catalyst, which was prepared by mixing 15 mol% of $[IrCl(COD)]_2$ and 30 mol% of (*R*)-BINAP in toluene, a couple of interesting things were observed. The reaction became much slower. A mixture of **1a** and iridium catalyst in toluene was refluxed under 1 atm of CO, and the reaction required 36 h for completion. But, the overall chemical yield of this reaction was still as high as those of rhodium catalyzed reactions.

More significant differences of this iridium catalyzed reaction from the previous reactions were the reversal of diastereoselectivity and much better enantioselectivity. **2a** was obtained as a major product in this case. It was obtained in 60% yield with satisfactory

Table 1 Desymmetrization of *meso*-dienynes by asymmetric PKR catalysts



1a; X=NTs, R=Me
1b; X=NTs, R=Ph
1c; X=NTs, R=H
1d; X=O, R=Me
1e; X=O, R=Ph

4-1; Y = H
4-2; Y = CH_3
4-3; Y = OMe
4-4; Y = CF_3

entry	sub	cat[a]	lig	*t*/h	yield (%)[b] (ee (%)[c]) **2**	yield (%)[b] (ee (%)[c]) **3**	dr[e] (**2** : **3**)
1	**1a**	**A**	**4–1**	0.5	9 (51)	57 (77)	1 : 6
2	**1a**	**A**	**4–2**	0.5	11 (52)	61 (80)	1 : 6
3	**1a**	**A**	**4–3**	0.5	8 (52)	57 (73)	1 : 7
4	**1a**	**A**	**4–4**	0.5	14 (33)	54 (53)	1 : 4
5	**1a**	**B**	**4–1**	3	9 (51)	73 (71)	1 : 8
6	**1a**	**B**	**4–2**	2	10 (52)	74 (74)	1 : 7
7	**1a**	**B**	**4–3**	3	7 (52)	74 (71)	1 : 11
8	**1a**	**B**	**4–4**	3	16 (33)	70 (44)	1 : 4.
9	**1a**	**C**	**4–1**	36	60 (93)	5 (67)	12 : 1
10	**1a**	**C**	**4–2**	36	61 (92)	8 (65)	8 : 1
11	**1a**	**C**	**4–3**	24	75 (96)	1 (33)	75 : 1
12	**1a**	**C**	**4–4**	36	64 (85)	5 (45)	13 : 1
13	**1b**	**A**	**4–3**	1.5	22 (5)	64 (60)	1 : 3
14	**1b**	**B**	**4–2**	4	12 (34)	81 (63)	1 : 7
15	**1b**	**C**	**4–3**	36	60 (90)	11 (9)	6 : 1
16	**1c**	**A**	**4–2**	1	24 (50)	35 (67)	1 : 2
17	**1c**	**B**	**4–2**	2	14 (41)	46 (50)	1 : 3
18	**1c**	**C**	**4–3**	18	30 (32)	31 (30)	1 : 1
19	**1d**	**A**	**4–1**	0.1	51 (90)	[d]	
20	**1d**	**B**	**4–3**	2	65 (87)	14 (84)	5 : 1
21	**1d**	**C**	**4–2**	12	62 (92)	[d]	
22	**1e**	**A**	**4–2**	2.5	60 (86)	[d]	
23	**1e**	**B**	**4–2**	4	84 (80)	6 (72)	14 : 1
24	**1e**	**C**	**4–3**	18	80 (90)	[d]	

[a] **A**: $[Rh(CO)_2Cl]_2$ (3 mol%), ligand (9 mol%), AgOTf (12 mol%) in THF at 90 °C under CO (1atm), **B**: $[Rh(cod)Cl]_2$ (5 mol%), ligand (10 mol%), cinnamaldehyde (20 eq) at 120 °C under Ar (1atm), **C**: $[Ir(cod)Cl]_2$ (15 mol%), ligand (30 mol%) in toluene at 130 °C under CO (1atm). [b] Isolated yields. [c] The ees were determined by chiral HPLC. [d] Only trace amounts of this isomer were detected by tlc analysis. [e] Diastereomeric ratio.

† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b4/b401288g/

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enantiomeric excess (93%), while **3a** was obtained in only 5% yield with somewhat inferior enantioselectivity (67% ee).

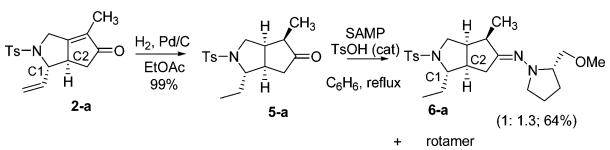
There was a hint that σ-withdrawer ligands significantly slowed down the reaction rate and gave poorer stereoselectivity. When substrate **1a** was reacted with a cationic rhodium(I) catalyst coupled with **4–2** or **4–3**, it did not provide much change in chemical yield and stereoselectivity of **2** and **3** (entries 2 and 3). But, a catalyst coupled with electron withdrawer **4–4** diminished the stereoselectivity substantially (entry 4). Neutral rhodium catalyst did not respond to the electronic character of the ligands as sensitively as cationic rhodium. Instead, beneficial effects of better σ-donors became more evident in case of the iridium(I) catalyst. Almost exclusive formation of **2a** was realized with highest enantiomeric excess (96%) (entry 11). In spite of these facts, it is hard to withdraw the generalized correlation at the moment between stereoselectivities and electronic character of the ligands. Only the best combinations in our hands are listed in Table 1 for the rest of the examples.

Aryl substituted substrates **1b**, which are known to give poorer stereoselctivity than alkyl substituted substrates,[4] were subjected to the same conditions. Generally speaking, most outcomes including the stereoselectivities still exhibited the same trend, but the numbers obtained for **1b** were uniformly lower than **1a**. Treatment of **1b** with the cationic Rh(I) catalyst bearing **4–3** provided **3b** as a major (64%, 60% ee) and **2b** as a minor product (22%, 5% ee). Neutral Rh(I) with **4–2** also provided 81% (63% ee) of **3b** and 12% (34% ee) of **2b**. Again, neutral Ir(I) provided the opposite diastereoselectivity to give **2b** in 60% yield with excellent enantioselectivity (90% ee) together with **3b** in 11% yield (9% ee). Terminal alkyne substrate **1c** was also tested, but the diastereoselectivity and enantioselectivity became much poorer (entries 16–18 in Table 1). Interestingly, a cationic Rh(I) catalyst gave the best results in this specific example.

Next, we turned our attention to the oxygen-tethered substrates. Several things are worth mentioning. 1) Both neutral Rh(I) and Ir(I) provided better chemical yield than cationic Rh(I) did. This might be attributed to the sensitivity of the oxygen functionality to the more acidic catalyst. The differences are more exaggerated in aryl substituted **1–e** (entries 22–24) than alkyl substituted **1–d**. 2) In contrast to substrate **1a–c**, diastereomers **2** were obtained almost exclusively in all cases regardless of the catalyst employed. 3) Diastereoselectivities (exclusive formation of **2** in most cases) and enantioselectivities (> 90%) for the products from **1d–e** are uniformly higher than those of **1a–c**.

The absolute configuration of **2a** obtained by using (*R*)-(4-$CH_3OC_6H_4$)-BINAP-Ir(I) catalyst (from entry 11 in Table 1) was determined unambiguously by a single crystal structure determination after chemical modifications. **2a** was hydrogenated doubly by Pd/C under hydrogen pressure to give **5a**., which was coupled with SAMP[9] to yield a hydrazone **6a** and its rotamer. Single crystal structure determination of **6a** by X-ray crystallography‡ revealed the absolute stereochemistry as (C_1: *S*, C_2: *R*) (Scheme 2 and Fig. 1).

In conclusion, we have demonstrated that the desymmetrization of *meso*-dieneynes by APKR catalysts is a useful tool for the preparation of optically active bicyclic[3,3,0]octanes. Diastereoselectivities and enantioselectivities are good to excellent and



Scheme 2 Derivatization of PKR products for the determination of absolute configuration.

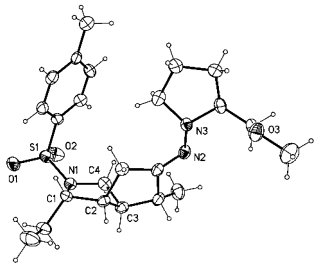


Fig. 1 ORTEP drawing of **6a**.

shown to be dependent on the substrates and catalysts. The origin of the diastereoselectivity will be clarified in due course. Further application to natural products synthesis starting from desymmetrization products is under investigation as well.

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Notes and references

‡ Crystal data: **2a**: $C_{17}H_{19}NO_3S$, M = 317.39, orthorhombic, $P2_12_12_1$ (no. 19), a = 5.794(8), b = 14.0776(12), c = 19.4686(13) Å, U = 1588(2) Å^3, Z = 4, D_c = 1.327 Mg m^{-3}, μ(Mo-K$_\alpha$) = 2.16 mm^{-1}, 1064 reflections measured, 1064 unique (R_{int} = 0.000) which were used in all calculations. The final $R(F^2)$ was 0.0490 using 1002 reflections with $I > 2\sigma(I)$ and $wR(F^2)$ was 0.1298 (all data). **6a**: $C_{23}H_{35}N_3O_3S$, M = 433.60, monoclinic, $P2_1$ (no. 4), a = 11.130(2), b = 7.964(2), c = 13.859(2) Å, β = 106.16(2)°, U = 1179.9(4) Å^3, Z = 2, D_c = 1.220 Mg m^{-3}, μ(Mo-K$_\alpha$) = 1.65 mm^{-1}, 1318 reflections measured, 1252 unique (R_{int} = 0.039) which were used in all calculations. The final $R(F^2)$ was 0.0482 using 1172 reflections with $I > 2\sigma(I)$ and $wR(F^2)$ was 0.1024 (all data) with absolute structure parameter, −0.1(2). CCDC 230163 and 230164. See http://www.rsc.org/suppdata/cc/b4/b401288g/

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6 Details for the preparation of substrates **1a-1e** are described in ESI†.

7 Characterization and stereochemical assignment of products **2–3** were carried out by spectroscopic methods including NOE experiments and single crystal structure determination. Full details can be found in ESI†.

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